IMPACT OF A MULTIPLE BIRTH ON MATERNAL MENTAL HEALTH AND EARLY MOTHER - INFANT INTERACTIONS: IMPLICATIONS FOR INFORMATION PROVISION IN IVF TREATMENT

Charlotte Emma Beer, BSc.

Thesis submitted to the University of Nottingham
for the degree of
Doctor of Philosophy

July 2008

ABSTRACT

One in four IVF pregnancies is a twin birth. This research explored the impact of a multiple IVF birth on maternal mental health and examined whether twin status conferred additional risk for poor mother-infant interaction and parenting stress following a premature birth. It further surveyed factors which had influenced couples' decisions regarding embryo transfer.

A prospective study of 175 mothers conceiving after IVF found mothers of multiples (n=56) had a three-fold risk of scoring above the threshold for depression in the postpartum period. Unsettled and irregular infant behaviour was another independent risk factor. Theme analysis revealed mothers of multiples were more likely to express negative themes such as 'tiredness'. More mothers of singletons described 'feeling wonderful'.

Mothers of premature twins (n=17) were closely matched with mothers of premature singletons and compared using the Nursing Child Assessment Teaching Scale (NCATS), Home Observation for Measurement of the Environment (HOME) Responsivity subscale and the Parenting Stress Index. There were no differences in maternal NCATS scores but twin infants were less responsive and provided less clear cues. Mothers of twins were less responsive in an everyday setting and 25% (versus 0%) reported extreme levels of parenting stress. Singleton mothers had significantly lower scores for the parent child dysfunctional interaction subscale.

None of the couples surveyed (n=68) had chosen to transfer a single embryo (eSET). Only 19.1% rated desire for twins as an important factor in their decision. Most important was desire to increase the chance of pregnancy (92.6%). Couples perceived eSET as reducing the chance of

pregnancy. Most couples found the decision about number of embryos to transfer easy and rated medical advice as very important suggesting a need for more support for this complex decision.

This thesis established that a single birth offers important psychosocial advantages for both mother and baby, findings which could promote informed decisions regarding embryo transfer.

Acknowledgements

The journey towards this thesis began in the 1970's when on hearing two psychologists speak the course of my life changed and I began a career in Psychology. I wish to pay tribute to all the people who have helped, inspired and guided me, and in particular David Sheard, Alan Clarke Michael Herbert and Paul Garrud who persuaded me to start the journey, and Sara Cox whose research was the foundation of this thesis.

I would like to acknowledge the skills and help of the many staff and health professionals involved whose expertise made the research possible and whose support is greatly valued, the staff at CARE and NURTURE and especially George Ndukwe, also Margaret Oates as advising Psychiatrist, and Jane Mischenko who trained me to use the NCATS. My heartfelt thanks and admiration go to the couples who took part in this research, without their courage, honesty and willingness to share their experiences this research would not have happened.

Thank you to my colleagues past and present for their help, support and friendship over the years, especially Susan Hull. My greatest thanks must go to my supervisor Cris Glazebrook, not only has she been a friend and role model but her learning and academic rigour have kept me inspired, motivated and enjoying the last six years so that I can say they have been some of the happiest in my life.

Finally I must thank my family and friends for their help and support and for forgiving my neglect over the last few months. Special thanks to my husband Chris in honour of whom I shall ask for my doctorate to be awarded in my married name Beer.

To my sons and daughters it is never too late to study.

To my husband Chris, thank-you for being my soul mate.

Contents

LIST OF TABLES AND FIGURES

CHAPTER ONE - Introduction

Twins have been celebrated throughout human evolution. They appear in every aspect of our culture from their central role in mythology with the foundation of Rome by Romulus and Remus, the Gemini twins in astrology, the biblical description of Rebekah giving birth to Esau and Jacob in Genesis and as central characters in Twelfth Night and The Comedy of Errors, inspired by the birth of Shakespeare's own twin daughters. Our fascination seems to stem from wonder at nature being able to duplicate itself, as so beautifully put by Antonio in Twelfth Night, "How have you made a division of yourself? An apple, cleft in two, is not more twin than these two creatures. Which is Sebastian?" (Twelfth Night act 5, sc. 1, l. 223-4.). We should perhaps not be surprised then that this glorification of twins has entered even the sphere of infertility with what Bryan describes as "the common belief that twins bring unqualified joy from conception onwards" (page 241) (Bryan 2002). A belief we see reflected in research reporting couples' apparent strong desire for a twin birth from the frequently quoted study by Gleicher and colleagues (Gleicher, Campbell et al. 1995) to a very recent study reporting that 45% of women rate a twin pregnancy as very or extremely desirable (Newton and McBride 2005).

1.1 The increase in the number of multiple births

Until the latter decades of the 20th century twins were relatively rare with only 7.44 per 1,000 births in the UK in 1938, the first year distinguishing maternities with multiple births, while higher order births were even rarer with only 54 triplets recorded (National Statistics 2006). The number of multiple births has increased greatly over the decades. An international

study looking at twin and triplet births during the 1980s and 1990s in Canada, England and Wales, France and the United States reports an increase in the rate of twins from 1981 to 1997 of between 28% to 45% in these countries (Blondel, Kogan et al. 2002). The most recent statistics available from the United States show the twin birth rate rising by 2% in 2004 to 32.2 per 1,000 total births. Although triplet and higher order rates have declined by 6% numbers had soared during the 1980s and 1990s and the current rate is still 1.8 per 1,000 total births (Hamilton, Minino et al. 2007). Rates for the United Kingdom (UK) are considerably lower with the rate of twins only 10.5 per 1,000 births for 2005 (TAMBA 2007), however the rate of multiples continues to rise here too, from a reported 14.1 per 1,000 births in 1995 to 14.9 in 2005 (National Statistics 2005). The introduction to this thesis will explore some of the reasons for this increase and whether it should be seen as a cause for concern.

1.2 Why has there been an increase in the number of multiple births?

One reason for the increase in multiple births is as a result of mothers delaying conceiving until they are older. Paradoxically, although ageing is related to a decline in fecundity, ageing has been found to relate to increased prevalence of natural multiple follicle growth during natural cycles so making dizygotic twins more likely (Beemsterboer, Homburg et al. 2006). This phenomenon is clearly seen in the most recent statistics for multiple delivery rates in the UK where for mothers aged 25-29 the multiple delivery rate was 13.5 per 1,000 births compared to 21.1 for mothers aged 40-44 (National Statistics 2005). A study by Tough and colleagues exploring the impact of delaying childbearing on multiple delivery rates in Alberta Canada concluded that 14% of the 15% increase

in twin births from 1990 to 1996 could be accounted for by delaying childbearing to after 34 years old (Tough, Greene et al. 2000).

However, treatment for infertility has been well documented as the major cause of the increase in multiple births across the world. Infertility described by the BMJ as trying for a baby for at least a year without success is relatively common with approximately one in seven couples seeking help to conceive, partly because natural fertility in humans is low with the chance of pregnancy per menstrual cycle only 33% even in the most fertile couples (Cahill and Wardle 2002). Increasing numbers of couples are therefore seeking to conceive using Assisted Reproductive Technologies (ART) these include In Vitro Fertilisation (IVF) where human eggs and sperm are mixed outside the human body in a laboratory and Intra-Cytoplasmic Sperm Injection (ICSI) where sperm is injected directly into the egg. The number of pregnancies achieved with the help of ART increases each year, with 10,242 children born in the UK after IVF from April 2003 to March 2004 (HFEA 2006).

This increase in ART births has been accompanied by an increase in the number of multiple births. The European Society of Human Reproduction and Embryology (ESHRE) report a total multiple delivery rate of 23.1% in Europe after ART for 2003, the latest figures available (Andersen, Goossens et al. 2007). While in the United States the figures are even higher, in 2004 of the 49,376 infants born after ART 45% were twins and the total multiple birth rate was 50.9% (Wright, Chang et al. 2007). Moreover, infants conceived after ART in the United States accounted for 18% of the multiple births nationwide (Wright, Chang et al. 2007). This is in contrast to the chance of a multiple pregnancy after natural conception of between one and two percent (Braude 2006).

1.3 The problem of zygosity with a multiple birth

Typically twins after IVF occur as a result of multiple ovulations, with two ova fertilising and successfully implanting in the womb, this results in non-identical or dizygotic twins. However, twins can also occur after a single ovum is fertilised and then splits this results in identical twins who share the same genes, called monozygotic twins. For some monozygotic twins if cell division does not occur early enough there will be only one shared outer sac or membrane called the chorion and the two embryos will also share the same placenta, these are called monochorionic twins. Monochorionic twins are at greater risk of death and severe morbidity than dichorionic twins (Pharoah 2002), one reason being because of the additional dangers of sharing a gestational sac such as umbilical cord entanglement (Abusheika, Salha et al. 2000). There is some evidence that the rate of monozygotic as well as dizygotic twins is raised after IVF. One review of published studies found the rate of monozygotic twins was three times higher after fertility treatment (Schachter, Raziel et al. 2001) and twice as high in the authors own study (Tarlatzis, Qublan et al. 2002) irrespective of treatment modality or micromanipulation. A recent study looking at data from the East Flanders Prospective Twin Survey found a greater ratio of monochorionic to dichorionic pairs in iatrogenic twins compared to spontaneous twins (Derom, Leroy et al. 2006).

1.4 The vanishing twin

The true rate of twins is very hard to establish because of the problem of the vanishing twin, if one twin is lost before any scans or tests are carried out then the pregnancy will never have been documented as a twin pregnancy. If clinics typically replace more than one embryo, a proportion

of singleton births are likely to have originated from a twin pregnancy. One study in Denmark found that 1 in 10 singleton deliveries had originated from a twin pregnancy. The authors suggest that one of the causes of higher risks of adverse obstetric outcome for IVF singletons is the spontaneous reduction of a multiple birth after 8 weeks gestation (Pinborg, Lidegaard et al. 2005). This may explain the finding that the birth weight of singletons born after single embryo transfer is higher than singletons born after double embryo transfer and may also explain why IVF singletons have a poorer neonatal outcome than naturally conceived singletons (De Sutter, Delbaere et al. 2006; Kjellberg, Carlsson et al. 2006).

1.5 The impact of multiple births on the rates of premature births

The main danger of a multiple birth for the well-being of the baby is the increased likelihood of being born prematurely and of low birth weight (Gardner, Goldenberg et al. 1995; Alexander, Kogan et al. 1998; ESHRE 2000; Tough, Greene et al. 2000; Blondel, Kogan et al. 2002; Koivurova, Hartikainen et al. 2002; Schieve, Meikle et al. 2002). Blondel and colleagues reported on preterm delivery rates of babies in France, the UK, Canada and the USA and found while singleton preterm delivery rates were 10% in 1995 to 1997 the rate for twins was nearly 50% (Blondel, Kogan et al. 2002). The risk is even greater for triplets with over 40% born very preterm (<33 weeks) and over 30% of very low birth weight (< 1,500g) (Keith and Oleszczuk 2002).

1.6 Risk of a multiple birth to the baby

The fundamental risk to very low birth weight (<1500g) infants is that of perinatal death. A recent study of trends in neonatal morbidity and

mortality in America reports that only 85% of these infants will survive and this figure goes down to 70% for survival without major neonatal morbidity (Fanaroff, Stoll et al. 2007). Figures such as these lead the ESHRE Capri workshop group on multiple pregnancies to conclude that low birth weight and prematurity together had accounted for the high 4.5 increased risk of perinatal mortality for twins and 9 fold increased risk compared to singletons (ESHRE 2000). Marlow's review of early neuro-cognitive outcomes after very preterm birth identified the most common problem as cerebral palsy with studies reporting rates of 8-10% in very low birth weight (VLBW) infants (Marlow, Wolke et al. 2005). More recently a Danish cohort study of all live born singletons and twins born between 1995 and 2000 assessing the incidence of cerebral palsy found preterm delivery was strongly associated with the risk of cerebral palsy (Hvidtjorn, Grove et al. 2006). Any effect of IVF vanished when both preterm delivery and multiplicity were controlled for. The risk of cerebral palsy has been found to increase exponentially with the number of foetuses (Blickstein 2002). There is also evidence of a 46% increased risk for birth defects such as anencephalus for multiple births compared to singletons even after adjusting for variables such as mother's age, race and education (Tang, Ma et al. 2006).

Research suggests that prematurity and low birth weight will also lead to problems with the infant's cognitive and social development. Wolke after reviewing the evidence regarding the dangers to psychological development of very low birth weight (VLBW) infants concluded that a quarter of VLBW infants will have severe or multiple psychological problems and another quarter moderate to mild. These problems included lowered IQ, attention deficit and schooling problems (Wolke 1998). An early study by Crnic and colleagues (1983) compared 37 mother pre-term

(<38 weeks gestation and <1,801g birth weight) and 42 mother full-term dyads during their first year (Crnic, Ragozin et al. 1983). Significant differences were found between the babies for cognitive and language development. The premature babies scored significantly lower on the Bayley Scales of Infant Development motor and cognitive scales. Their scores were within the normal range, however, which was probably a reflection of the fact they were not ill or particularly disadvantaged. The premature babies also vocalised less and performed worse on measures of early language expression.

Studies following up premature infants until school age have found these poorer outcomes persist. For example, The Bavarian longitudinal study followed up a large sample of 264 very premature children (<32 weeks gestation) and 264 full-term controls matched for socioeconomic status, mother's age and marital status until they were 6 years old (Wolke 1998). Compared to their matched peers the premature children scored significantly lower on all measures of cognitive and language abilities. A meta-analysis of studies of cognitive and behavioural outcomes of school aged children born preterm (born at less than 37 weeks) concluded that children born preterm were at risk for reduced cognitive test scores at school age and this was proportional to their immaturity at birth. They also showed an increase in attention-deficit/hyperactivity disorder (ADHD) and other behavioural problems (Bhutta, Cleves et al. 2002).

Given the problems associated with prematurity and low birth weight it is inevitable that twins will be greatly affected by these risks. The March of Dimes Multicentre Prematurity and Prevention Study of 33,873 women delivering from 1982-1986 found that although twins represented only 1.3% of the total population they comprised 12.2% of the total preterm

births (Gardner, Goldenberg et al. 1995). It is therefore not surprising that population studies have shown twins to be at increased risk for foetal death, neonatal death and cerebral palsy compared to singletons (Scher, Petterson et al. 2002). The only contradictory finding has been that preterm twins appear to have lower perinatal mortality rates than singletons of the same birth weight and gestational age, and this was explored in a large study of all births in Ontario during the odd years from 1979 to 1985 (Payne, Campbell et al. 2002). The authors found that although the proportion of births <37 weeks gestation was eight times greater for twins than singletons, the preterm twins had a lower mortality rate. This was not found to be because twins were more likely to be born in a tertiary care hospital (a hospital offering a higher level of care) as hypothesised by the authors. However, the authors did find that the advantage disappeared after standardising for gestational age, so that if gestational age was less than two standard deviations below the mean for their group, twins were actually at a higher risk. The authors suggest this may be because twins are further along their gestational course than singletons of the same age so giving them some advantage over singletons when born between 31 and 36 weeks. However, below 28 weeks they report studies finding twins as disadvantaged as singletons by their premature birth.

Similar results have been found when comparing twin and singleton infants conceived using ART. Pinborg and colleagues in their study of the neonatal outcome of all Danish IVF/ICSI births between 1995 and 2000 found twins had a 10-fold increased age and parity adjusted risk of delivery before 37 weeks than singletons and a 12-fold increased risk of birth weight less than 2500g (Pinborg, Loft et al. 2004)[a]. Findings such as these have lead one systematic review of controlled studies to conclude that "virtually all

perinatal and infant morbidity occurs more frequently in twins than in singletons" (page 264) (Helmerhorst, Perquin et al. 2004).

Differences in developmental outcomes between twins and singletons have also been found. Rutter and colleagues made use of the Avon Longitudinal Study of Parents and Children to explore differences in twin and closely spaced singletons' language in children born after at least 33 weeks gestation. They found that the twins were 3.1 months behind singletons in their language development at three years and their verbal cognitive score was about half a standard deviation lower. These differences were not associated with any of the obstetric or perinatal features they explored (Rutter, Thorpe et al. 2003)[a].

Studies comparing IVF/ICSI twins and singletons have also found significant differences in longer term outcomes. A study of families recruited from a national organisation in France created to follow-up children conceived by assisted reproduction compared IVF/ICSI two to five year old twins with matched singletons (Olivennes, Golombok et al. 2005). The study found no significant differences in the level of emotional or behavioural problems shown by twins and singletons as assessed by the Strengths and Difficulties Questionnaire (SDQ). However, twins showed delayed cognitive development compared to singletons as measured by the Denver Developmental Questionnaire. Analysis of individual item scores showed that twins scored significantly lower on seven items of which four were language items, two fine motor items and one a personal social item. These are areas we might have expected to see differences in given other research findings for twins showing poorer language and motor skills.

Considering the findings for twins it is hardly surprising that triplets have also been found to be at risk for example, Albrecht and Tomich reported in their review of triplet births in the early 1990s a high rate of maternal complications and a perinatal mortality rate of 41 per 1000 (Albrecht and Tomich 1996). Keith and colleagues concluded that all triplet pregnancies should be seen as high risk, with over 40% born very preterm (<33 weeks) and over 30% of very low birth weight (< 1,500g) (Keith and Oleszczuk 2002). As with twins these risks also extend to the infant's cognitive development a recent study by Feldman and Eidelman has shown that triplets are at an increased risk for cognitive delays in the first two years of their life compared to twins and singletons even when matched for birth weight, gestational age, medical risk and family demographic features (Feldman and Eidelman 2005). The study also provides further evidence of the problems of low birth weight as they found that a triplet with a birth weight more than 15% discordant from its siblings had the poorest outcomes. The authors do not give any details about how many, if any, infants were conceived using ART so it is not possible to determine whether this might have been an additional factor.

A further study by French researchers of the families recruited as part of the study to follow-up children conceived by assisted reproduction looked particularly at triplets (Freeman, Golombok et al. 2007). At the time of the study the authors identified 13 families with triplets on the data base and recruited 10 to the study, these families were matched to 15 families of twins and 30 of singletons on gender and age of children, age and educational level of the parents and number of other siblings. Mothers of multiples had higher levels of stress as measured by the Parenting Stress Index– short form (PSI-SF), however triplet mothers did not score

significantly higher than mothers of twins. Triplets were not found to score significantly lower on measures of cognitive development, motor skills or personal/social skills. Triplets did show some delays in language development although this did not differ significantly from the twins' development.

1.7 Additional risk of a multiple IVF birth to the baby

Influenced by the findings discussed in the previous section that singletons conceived after IVF are at increased risk for many perinatal outcomes compared to naturally conceived singletons many researchers have expected and looked for increased risks for twins and multiples conceived after IVF compared to those conceived naturally. These studies have found some conflicting and contradictory results. A national cohort study of all twins born in Denmark in 1997 found that the physical health of IVF/ICSI twins was comparable to that of non IVF/ICSI twins (Pinborg, Loft et al. 2003)[a]. While a case control study of all ART pregnancies in Dutch speaking Belgium from 1992 to 1995 concluded that although singleton IVF babies have a worse perinatal outcome than matched controls IVF twins do not (Dhont, De Sutter et al. 1999). This finding was confirmed by the previously mentioned systematic review of controlled studies in the BMJ which concluded that although singleton pregnancies from ART have a worse perinatal outcome than naturally conceived singletons this was not so for twin pregnancies, and indeed compared to matched controls they may actually be at an advantage (Helmerhorst, Perquin et al. 2004). A study of multiple pregnancies in Norfolk, America found that although the twins, triplets and quadruplets in their study had increased obstetric and neonatal complications these were comparable to those seen in naturally conceived multiples (Seoud, Toner et al. 1992).

However, these studies can give an overly optimistic impression about the risks of a twin IVF birth. Pinborg and colleagues point out with regard to their study in view of the fact the IVF/ICSI twins were more likely to be dichorionic we might have actually expected lower rates of morbidity (Pinborg, Loft et al. 2003)[a]. A later study of this cohort looked at the number of hospital admissions and surgical interventions among IVF twins, spontaneously conceived twins and IVF singletons born between 1995 and 2000, they found that even when restricted to term infants the IVF twins were more likely to be admitted to hospital than singletons were (Pinborg, Loft et al. 2004)[b]. A further report on this cohort concluded that although a similar obstetric outcome was observed for IVF and spontaneously conceived twins the IVF twins were more likely to be admitted to the NICU (Pinborg, Loft et al. 2004)[c]. Again the authors point out that due to a lower proportion of MZ twins one might have expected lower rather than comparable obstetric risks for the IVF twins.

Another point to bear in mind is that although many differences in birth weight and prematurity disappear after controlling for maternal age and parity the mothers of IVF twins will be older and are more likely to be primiparous. Further worrying evidence is provided by Daniel and colleagues who reviewed the perinatal outcome of all twin deliveries at their centre in Israel between 1996 and 1997 and found that nulliparae women who conceived by ART had the worst outcome with only 20% delivering two healthy newborns weighing more than 2500g, with an Apgar score greater than 7 at 5 minutes, no perinatal complications and not admitted to the NICU; compared to 34% of the spontaneous mothers of twins. They conclude by saying that ART conceived pregnancies are 'in

"double-jeopardy" as a twin pregnancy and an ART-conceived pregnancy' (page 688) (Daniel, Ochshorn et al. 2000).

Other studies have also found evidence of poorer outcomes for IVF twins and concluded that twins conceived by IVF were at greater risk for prematurity and had a poorer neonatal prognosis when compared to naturally conceived twins (Moise, Laor et al. 1998; Daniel, Ochshorn et al. 2000). One study carefully matched the IVF twins and naturally conceived twins on all maternal variables and concluded that the IVF twins had a significantly lower average birth weight, this despite the control group having a larger proportion of monozygotic twins, which is usually predictive of a less favourable outcome (Koudstaal, Bruinse et al. 2000).

When debating the outcome of IVF/ICSI twins it is essential to take into consideration some of the special factors associated with their conception, birth and the characteristics of their mother. For example an IVF pregnancy is more likely to be intensively managed and so the babies will be born early as a result of induction or a caesarean delivery. An analysis of trends in twin birth outcomes and prenatal care utilisation in the USA from 1981-1997 found that although twins were accounting for a larger proportion of all low birth weight and preterm births in the USA the mortality rate for twins of mothers who received more prenatal care was lower (Kogan, Alexander et al. 2000), a finding likely to apply to mothers of IVF/ICSI twins. For example, Bernasko and colleagues found significantly higher rates of elective caesarean delivery for mothers of twins conceiving after assisted conception compared to mothers conceiving spontaneously (Bernasko, Lynch et al. 1997). A study of Australian birth records of infants conceived after ART from 1996 to 2000 found the likelihood of preterm birth and low birth weight for twins varied according

to mother's parity and cause of infertility with nulliparity and female factor infertility associated with both. Low birth weight in twins was more prevalent if the mothers were nulliparous and less than 29 or older than 45. The authors suggest that it is the physiological characteristics of the women associated with the cause of infertility such as female factor infertility rather than the particular features of the ART procedure which contribute to a more adverse birth outcome (Wang, Sullivan et al. 2005).

This argument was also put forward by Luke and colleagues whose study of 2,142 mothers of spontaneous and 424 mothers of assisted conception twins argued that assisted conception was not a risk factor for adverse outcome. The study did not control for zygosity however, the authors argued that rather than assisted conception being a risk factor it was other risk factors more common among these pregnancies such as nulliparity and foetal reduction which had increased the risks of an adverse outcome (Luke, Brown et al. 2004). Lambalk and van Hooff attempted to control for zygosity by looking at only primiparous mothers who conceived dizygotic twins. They found a less optimal obstetric outcome for the assisted reproduction babies when comparing the 613 naturally conceived pregnancies with the 480 pregnancies conceived after assisted reproduction. They concluded that not only did twinning contribute to the high rate of premature deliveries but that characteristics of the mother in terms of her being a sub-fertile patient undertaking treatment also made a contribution (Lambalk and van Hooff 2001).

A more recent population based study in East Flanders compared gestational length and preterm birth rates between naturally conceived twins and twins born after ovarian stimulation and after IVF or ICSI, while controlling for both zygosity and chorionicity (Verstraelen, Goetgeluk et al.

2005). The study found that compared to naturally conceived twins, twins conceived after treatment for sub-fertility had a decreased gestational age at birth, and had an increased risk of being born premature the adjusted odds ratio was 1.6 after controlling for birth year, maternal age, parity, foetal sex, caesarean section, zygosity and chorionicity. However this increased risk was only for mild preterm birth (34-36 weeks). They found that the risk was mainly caused by a first birth effect among the sub-fertile couples, but was reduced by the protective effect of dizygotic twinning (Verstraelen, Goetgeluk et al. 2005).

In 2005 two excellent and comprehensive reviews of twin pregnancies were published (McDonald, Murphy et al. 2005; Pinborg 2005). McDonald and colleagues conducted a systematic review and meta-analyses of studies exploring perinatal outcomes of IVF twins. They concluded that when IVF/ICSI twins were compared to naturally conceived twins in studies which matched or controlled for maternal age there was an increased risk of a preterm birth between 32 and 36 weeks, an increased risk of preterm birth <37 weeks if parity was also matched for, and an increased rate of caesarean delivery. However there were no significant differences in the number of perinatal deaths, low birth weight infants or congenital malformations. As in a previous study, the authors make the point that one might have expected better outcomes as there are a lower proportion of monochorionic twins among IVF/ICSI conceived twins and that their mothers are less likely to smoke and to have higher socioeconomic status. Pinborg reviewed all studies of IVF/ICSI twins published after the first IVF birth in 1978 until 2004. Results are reported from those studies which matched for maternal age and parity with sample sizes of at least 400 infants included. The review reports similar adjusted risks of prematurity and low birth weight for the IVF/ICSI twins and naturally conceived twins,

and no increased risk for major malformations although few matched studies with more than 400 infants investigated this issue. Perinatal mortality rates were similar or even lower for IVF/ICSI than naturally conceived twins. However IVF/ICSI twins were more likely to be born by caesarean section and to be admitted to the NICU.

In conclusion, as discussed above, there are a number of reasons why IVF/ICSI twins may have poorer outcomes, but there are also some reasons to actually expect better outcomes than for naturally conceived twins. When studies match infants and mothers appropriately there is some evidence of poorer outcomes compared to naturally conceived twins and unequivocal evidence of a poorer outcome compared to singleton IVF/ICSI infants.

1.8 The risks of a multiple IVF birth to the mother's physical health

There is conclusive evidence about the dangers of a multiple birth to the mother's physical well-being (ESHRE 2000), as well as an estimated threefold elevated risk of maternal mortality (Senat, Ancel et al. 1998). The Avon Longitudinal Study of Pregnancy and Childhood found mothers of twins were significantly more likely to report ill health and were three times more likely to be admitted to hospital during pregnancy than mothers of singletons (Thorpe, Greenwood et al. 1995). A Scottish study reviewed the risks of all twin pregnancies to women living in the Grampian region from 1976 to 1999 and compared them to singleton pregnancies (Campbell and Templeton 2004). The study found a two to three fold increase in obstetric complications such as pre-eclampsia for twin pregnancies.

Mothers of IVF multiples seem to be at even greater risk than mothers who spontaneously conceive multiples. For example, Smithers and colleagues in their carefully matched study of IVF and naturally conceiving mothers of dizygotic twins found that, placenta previa and antepartum haemorrhage occurred more frequently in the IVF mothers even after matching for maternal age and parity (Smithers, Halliday et al. 2003). A recent review of the effects of IVF on maternal and perinatal outcomes concluded that both risks were higher after an IVF pregnancy (Mukhopadhaya and Arulkumaran 2007). Also concerning is the finding reported by Lynch and colleagues that after adjusting for maternal age and parity women conceiving multiples after ART were twice as likely to develop pre-eclampsia as women conceiving spontaneously (Lynch, McDuffie et al. 2002). Pre-eclampsia is not only dangerous for the mother but may also seriously impact on the health of the infant as it frequently leads to restricted growth and preterm delivery. A study investigating the risk factors for adverse outcomes, in assisted conception twins compared to spontaneously conceived twins found that for the assisted conception mothers of twins nulliparity was associated with both an increased risk for pre-eclampsia and very low birth weight, a worrying finding as women seeking assisted conception are more likely to be nulliparous (Luke, Brown et al. 2004). Not surprisingly triplet and quadruplet IVF pregnancies have even greater risks for obstetric and neonatal complications with mothers of triplets being significantly more likely to experience premature onset of labour, pregnancy induced hypertension and gestational diabetes (Seoud, Toner et al. 1992).

This introduction has explored why the number of multiple births has increased over the past decades and suggested some of the reasons why this should be seen as a cause for concern. These include findings of

poorer perinatal outcomes for the infants and increased obstetric complications for the mothers. However, if twin and multiple infants are highly valued and desired should we seek to interfere with either nature or prospective parents' preferences? Artificial reproductive technologies are, though, a manipulation of nature and in many instances will involve a decision at some point in the process which will determine whether a multiple birth will be the outcome.

For many couples this decision will be in association with them deciding how many embryos should be transferred. Typically women undergoing ART have multifollicular ovarian stimulation which results in multiple embryos and a decision has to be reached about how many to replace. The transfer of more than one embryo substantially increases the risk of a multiple birth. Research has shown that reducing the number of embryos transferred from three to two does not lower the ongoing pregnancy rate but does reduce the number of multiples (Westergaard, Johansen et al. 2000). In order to significantly reduce the number of twins it would be necessary to transfer only one embryo (elective single embryo transfer)[1] and this has been hotly debated. Some studies have shown very positive outcomes with reduced multiple birth rates and even better outcomes for singleton babies after elective single embryo transfer (eSET) compared to double embryo transfer (DET) as already mentioned (De Sutter, Delbaere et al. 2006). However, as will be discussed in more depth in chapter three to achieve comparable pregnancy rates to DET women will often need a second cycle of eSET with a frozen embryo (Lukassen, D.Braat et al. 2005; Pandian, Templeton et al. 2005).

[1] e(SET) will be used in this thesis to refer to the elective transfer of a single embryo when more than one is available

To help prospective parents and clinicians with the very difficult decisions they face about the number of embryos to transfer they need to have as much information as possible about the possible impact of a multiple birth. Parenting one infant can represent a challenge and a multiple birth will inevitably be associated with greater physical and arguably emotional demands. However, couples undergoing infertility treatment are typically older and more secure, both financially and in terms of the length of their relationship. The extent to which potentially protective factors may mitigate against the negative outcomes associated with a multiple birth is unclear, particularly where the infants are very premature. There is, therefore, a need to go further with research and explore what, if any, impact a multiple birth will have on maternal mental health following a multiple IVF birth and the implications of a very premature twin birth for the mother-infant relationship. These areas will be explored in the following two chapters. The third chapter will then go on to consider the element of choice regarding a multiple birth which is inherent in all ART pregnancies. Only by a full consideration of whether decisions about the number of embryos to be transferred are truly informed and actually reflect what prospective couples want will we achieve a resolution to the current conflict between calls by the HFEA for fewer multiple births and prospective parents' apparent desire for a multiple birth.

1.9 Introduction to psychological theories and models of behaviour explored in this thesis

This thesis, as described above, will focus on three separate studies. One will explore the impact of a multiple IVF birth on maternal mental health, the second the impact of a premature multiple birth on early mother-infant interaction and the final study will explore factors involved in prospective IVF parents' decision about how many embryos to transfer. The three studies were not undertaken to explore any one psychological theory or

model of behaviour, but rather to extend our knowledge of the impact of multiple births, explore how couples make decisions about embryo transfer and consider the implications for the provision of information in IVF treatment. However, psychological theories and models of behaviour do underpin each separate study and these will be briefly outlined here and then discussed in more depth in relation to each of the studies in the following chapters.

Research on the impact of a multiple birth on maternal mental health has traditionally focused on whether such a birth increases the likelihood of post-natal depression. One conceptual model of depression, provided by Champion and Power (1995) suggests why such a birth may be more likely to result in post-natal depression for the mother (Champion and Power 1995). In contrast to other theories, which have tended to focus on either the individual's cognitive vulnerability or social context, the authors argue that an interaction between the individual's perceived cognitive vulnerability and the social context in which they are living contributes to the likelihood of experiencing depression. Arguably women who present for fertility treatment have already demonstrated how highly they value the role of motherhood and the goal of pregnancy. The model suggests that the more emphasis the woman places on the role of motherhood, and the greater her neglect of other goals, the more vulnerable to depression she will be if an event threatens this role. By including the social context in the model the social pressures the woman experiences (both internal and external) to become a mother can also be explored. The more pressure the woman feels to fulfil her goal of motherhood the more likely she is to become depressed if this goal is threatened by, for example, the birth of premature multiples who may be difficult and unrewarding to care for. The

first study will use both quantitative and qualitative data to explore these issues and review how the findings fit with this theory of depression.

The second study in this thesis will explore how mothers interact with their premature infants and whether twin status has an additional impact. The choice of outcome measures in the study was informed by attachment theory (Bowlby 1969). Inge Bretherton in her comprehensive review of the origins of attachment theory describes how it originated from the work of John Bowlby and Mary Ainsworth (Bretherton 1992). Bowlby, she maintains, argued that in order to grow up mentally healthy, children need to experience an intimate and mutually rewarding relationship with a mother or mother substitute. Ainsworth contributed the notion of the attachment figure as a base from which the child could explore the world. She also introduced the concept of the importance of the mother's sensitivity to the infant's signals and how important this was to the future development of mother-infant interactions.

Bee and Boyd (2002) describe how variations in quality of attachment are now typically assessed using Ainsworth's categories and Strange Situation. The Strange Situation is a standardised laboratory procedure during which children between 12 and 18 months old are observed in the following situations: with the mother, with the mother and a stranger, alone with the stranger, completely alone for a few minutes, reunited with the mother, alone again, with the stranger again, and finally reunited with the mother (Bee and Boyd 2002). On the basis of the pattern of the child's reactions in all these situations their attachment is described as secure, insecure avoidant attachment, or insecure ambivalent attachment. Some researchers use an additional category of insecure disorganised attachment

however, the most important distinction is made between secure and insecure attachment.

A review of the implications of attachment theory and research for the journal Developmental and Behavioural Paediatrics defines attachment as the special emotional bond infants develop with their caregivers during their first year of life (Carlson, Sampson et al. 2003). The authors point out that this is a relationship which develops over time and is dependent on interactions between the caregiver and the infant. However, infants have a propensity to develop these interactions and will do so even in the first few months of life although such interaction will be reflexive rather than intentional. Bee and Boyd suggest that in the early months this attachment is dependent on the development of synchrony which they describe as the mutually reinforcing and interlocking behaviours which develop between infant and caregiver (Bee and Boyd 2002).

Carlson and colleagues outline in their review article the two hypotheses derived from Bowlby's developmental view of attachment which have driven empirical research. These are that 1) differences in quality of care will lead to differences in attachment and 2) differences in patterns of attachment will influence later self-regulation (Carlson, Sampson et al. 2003). These hypotheses suggest infant factors such as prematurity might affect the development of synchrony and that multiple birth status could further impact on infant caregiver interaction. The third chapter will explore these ideas in relation to current literature in this area and the empirical study reported will include measures of mother child interaction in the outcome measures.

The health belief model (HBM) Abraham and Sheeran explain arose from the desire to develop health education that could predict preventative health behaviour and use of services (Abraham and Sheeran 2007). Beliefs were seen as the ideal target because they influence individual behaviour and are modifiable. The model focuses on two aspects, firstly the individual's perception of threat in terms of their perceived susceptibility to the illness or health problems and the anticipated severity of the consequences. Secondly, the model focuses on how the individual evaluates the consequences in terms of the benefits as well as the costs or barriers. In addition the model incorporates cues to action which may activate behaviour. Cues to action have been widely interpreted and may range from how an individual perceives their own symptoms to a public health campaign. Later developments of the model also included the individual's health motivation, arguing that how motivated or concerned the individual was about health matters was also of importance (Ogden 2004).

This model provides a useful framework for exploring how couples decide on how many embryos to transfer. The survey of factors influencing this decision in chapter four should provide useful insight into how couples evaluate the threat of a multiple birth as well as how they perceive the potential costs and benefits of their decision. The chapter will review the literature in relation to the model and what is known about how couples make this often very difficult decision. The HBM also allows scope for influencing the provision of more effective information about this decision in the future (Bellamy 2004) and this will be explored in the final chapter.

CHAPTER TWO - Study I: The impact of a multiple birth on maternal mental health

2.1 BACKGROUND

The research findings discussed in the introduction to this thesis should make it no surprise to discover that the Human Fertilisation and Embryology Authority (HFEA), the United Kingdom's independent regulator of fertility treatment and embryo research, have identified a multiple birth as the biggest risk from IVF. Moreover, the most recent figures available show 23.6% of all IVF births in the UK are twin or triplet (HFEA 2006). Despite the continuing debate about what if any additional negative contribution IVF might make to the outcome of a twin birth as discussed in the introduction there is clear evidence that a twin IVF baby is at significantly greater risk of neonatal morbidity and mortality than a singleton (ESHRE 2001; Wimalasundera, Trew et al. 2003; Pinborg, Loft et al. 2004[d]). There are also well documented dangers of a multiple pregnancy to the mother's physical health (ESHRE 2000) with mothers of IVF multiples at possibly even greater risk than mothers spontaneously conceiving multiples (Smithers, Halliday et al. 2003). One might expect that a multiple pregnancy would also place a greater burden on the mother's emotional well-being.

This chapter will first review the evidence in the literature about the impact of a naturally conceived multiple birth on the mother's emotional well-being. The possible additional impact of an IVF conceived, multiple birth will be explored from a number of perspectives. Firstly the impact of an IVF conception will be explored by comparing differences in the mother's emotional well-being after conceiving a singleton naturally or by assisted

conception and then comparing the impact of naturally conceived or assisted conception twins on emotional well–being. A further perspective will be to explore the impact of parenting a baby possibly more difficult to care for because of a premature birth, low birth weight or a more difficult temperament. Finally Champion and Power's social cognitive theory of depression (Champion and Power 1995) will be explored particularly in relation to expectations of motherhood. The chapter will then go on to present the findings from a study designed to explore these issues which compared the postpartum well-being and mental health of IVF mothers of singletons and multiples.

2.1-i Risks of a naturally conceived multiple birth to the mother's mental health and emotional well-being

The Avon Longitudinal Study of Pregnancy and Childhood found no evidence of poorer emotional well-being, as measured by the Edinburgh Postnatal Depression Scale, in mothers expecting twins, although they did experience poorer physical well-being (Thorpe, Greenwood et al. 1995). The Avon study was a prospective study of all women expecting a baby between 1991 and 1992 and resident in three southwest region health districts in Avon. Of the 11208 women taking part 147 (1.3%) were expecting twins however, no information is given as to how the babies were conceived or on the mother's parity. The authors suggest that a number of factors including the special status of a twin pregnancy, the additional social support and modified expectations of health may have protected these women from the association between poor health and emotional well-being found in the population as a whole. The nature of conception and the mother's parity may also have influenced the impact of a twin pregnancy on the mother's emotional well-being.

Despite there being no evidence of a multiple pregnancy adversely affecting the mother's emotional health caring for multiples after birth seems likely to place a greater strain on a mother's emotional resources and well-being. Indeed just such a strain can be seen encapsulated in Linda Dell'Avvocato's letter to the editor of Health Visitor in which she says "The permanent dilemma of which to pick up first takes on a more stressful tone when they are both ill together, which is usually the case!" (Page 37) (Dell'Avvocato 1998). Research looking at the effects of spontaneously conceived multiples suggests that multiples do place an extra strain on the mother. One study in the early 1980's by Groothuis and colleagues found twin status was even predictive of subsequent child abuse. Forty-eight families with twins were matched with 124 single birth families for maternal age, race and socio-economic status as well as birth date and hospital of delivery; the authors found the greatest predictor of subsequent abuse was twin status. Regression analysis showed that twin status had a greater impact than parity, length of nursery stay, birth weight or Apgar score although these also influenced outcome (Groothuis, Altemeier et al. 1982).

Haigh and Wilkinson found that mothers of twins were more likely to be depressed compared to random and matched singleton controls, with a small group of mothers showing clinical levels of depression and anxiety (Haigh and Wilkinson 1989). The authors suggested that the increased stress experienced by the mothers of twins was a result of the increased physical and emotional requirements of an extra baby rather than a particular factor related to caring for a twin. Thorpe and colleagues also found that mothers of twins were more likely to experience depression than mothers of singletons and that this was independent of social and demographic factors and the presence of disability in the child (Thorpe,

Golding et al. 1991). However, they argued that it was not just the extra burden of caring for another baby that was the problem but the close age spacing between the children as mothers of closely spaced siblings were also at greater risk of depression independent of the number of children. In a study to explore the pre and postnatal determinants of stress in mothers of one year old twins Colpin and colleagues found parenting stress as measured by the Parenting Stress Index (PSI) was significantly predicted by pre and post natal personal well-being and marital support but not by social support or the presence of other children (Colpin, De-Munter et al. 2000).

2.1-ii Coping with a triad

One of the fundamental problems of caring for multiples was identified by Rowland as the problem of coping with a triad (Rowland 1991). This means that not only must the mother try to bond with two babies simultaneously and research suggests that mothers usually bond more quickly and easily with one twin, often the heaviest (Spillman 1987); but that the babies will spend more time with each other than anyone else whereas a singleton baby spends more time alone with its mother than with anyone else (Rowland 1991). Robin and colleagues examined the ways French mothers interact with their twins during early childhood looking particularly at the burden of care and responsibilities and the ways mothers adapt to a triadic situation in a series of studies (Robin, Josse et al. 1988).

A survey of 150 families of twins found when the babies were 2 months old a great burden of care was falling on the mothers with 54% of mothers feeding at night and providing 10 hours of care within each 24 hours, not surprisingly 44% of the mothers reported feelings of fatigue. Twenty

families of one year old twins were later observed and interviewed to explore the triadic situation. Mothers are reported as interacting with the twins along a continuum from early twinship where the twins were treated as a single unit with minimum dyadic relationships between the mother and babies, to a desire for dyadic relationships where the mothers attempted to have as personalised and individual a relationship with each child as she could manage. The authors suggest these findings may explain some of the differences in twin and singleton early verbal communication (Robin, Josse et al. 1988).

2.1-iii Evidence from qualitative studies about the risks of a multiple birth to the mother's emotional well-being

The qualitative literature has also provided evidence about the strain of a multiple birth on the mother. A survey of 41 Australian mothers of twins found mothers reporting problems regarding the emotional strain of a twin birth, with 34% saying the twins were an emotional strain, 37% that they had put a great strain on their marriage and 19% that they could not give each twin individual attention (Hay, Gleeson et al. 1990). A study looking at parental interactions with and perceptions of multiple births identified three themes in interviews with the parents of 7 sets of twins, one set of triplets and 49 parents of singletons. These themes were, the positive and negative specialness of multiples, the difficulties involved in managing more than one infant and attachment issues (Holditch-Davis, Roberts et al. 1999).

In a review of the qualitative literature on mothers of multiples Beck reported the main findings to be the physical and psychological challenges facing the mothers (Beck 2002)[a]. She identified the need for a grounded theory study to explore the problems mothers went through during the first year, and went on to conduct such a study: interviewing 16 American

mothers of twins. These interviews revealed that 'life on hold' was the basic psychological problem experienced, and 'releasing the pause button' was the social psychological process of mothering twins during the first year of life (Beck 2002)[b]. This study included mothers who had conceived after assisted and natural conception and both primiparous and multiparous mothers. Although this was an integral part of the study design so that issues such as mothers wondering what life would have been like if they had had a singleton could be addressed it makes it hard to explore the interaction between such issues as first time motherhood, assisted conception and coping with a multiple birth.

More recently Ellison and Hall conducted focus groups with 43 mothers of multiple and singleton children in order to determine the quality of life domains most impacted by multiple births. Qualitative data analysis identified what they described as eight core domains of quality of life most impacted by multiple births these were: social stigma, pregnancy and neonatal losses, marital satisfaction, children's health, meeting family needs, parenting stress, maternal depression and the infertility treatment experience (Ellison and Hall 2003). Two of these domains were new: social stigma and compound losses. Another unexpected finding was that while mothers of multiples described how caring for multiples placed great strain on their marriages for some this caused their relationship to deteriorate, while others actually became stronger when forced to work as a team in order to cope. With regard to parenting stress the most common complaint was sleep deprivation, also important though was the necessity to manage the routines of family life. Although the study identified some new areas of concern, in particular social stigma with mothers finding that the birth of multiples left them open to unwanted questions and scrutiny about their fertility; the focus groups were small and combined first time

mothers, mothers with children already, mothers of both singletons and multiples and mothers of multiples conceiving spontaneously or after ART.

2.1-iv The impact of higher order multiples on the mother

The mothering of higher order multiples has, not surprisingly, been found to be even more stressful for the mother. A study by Goshen-Gottstein was one of the first to use observational methods to explore the problems faced by mothers of multiples in Israel (Goshen-Gottstein 1980). Fourteen families, four with twins, six with triplets and four with quadruplets were visited and observed at home by two researchers every month from when the babies were five months old to two years and then bimonthly. The author was particularly interested in how the mother was observed as behaving and how she said she behaved towards her children. The author describes how although the mothers claimed to love all their children equally they were often observed leaving one child out or coping by getting someone else to care for one child. Some mothers resorted to treating their babies as a unit in an attempt to treat all equally, so for example all would be woken to feed at the same time. The author concludes by calling for both practical and psychological help for these mothers to cope with the demands of a multiple birth. Mothers of higher order multiples were more ambivalent towards their babies and appeared more depressed by their birth (Goshen-Gottstein 1980). The study gives no details about how the babies were conceived, combining both spontaneous and assisted conceptions however it was one of the first studies to give an in-depth insight into the difficulties of mothering multiples.

More evidence is provided by Robin and colleagues study of 14 mothers of French triplets, 5 of which were natural and 9 artificially induced although only one was IVF (Robin, Bydlowski et al. 1991). Mothers were

interviewed at home when their babies were 4 months and 1 year old. Forty percent of the mothers were depressed and expressed tiredness and discouragement at 4 months and even at one year postpartum 30% of the mothers still showed depressive tendencies. Observational data revealed that in 60% of the families there were no obvious signs of enjoyment in their interactions with the infants at 4 months and this was still true of 20% of the families at one year old.

Garel and colleagues have carried out further work looking at the psychological effects of the birth of triplets. They followed up 12 French mothers of triplets in France (Garel and Blondel 1992). Despite these being apparently much wanted babies with all but one baby being conceived after ART, semi-structured interviews with the mothers one year postpartum revealed the majority were suffering from social isolation, most said the triplets had placed a strain on their marriage and they struggled to give adequate attention to three children at once. Most importantly the mothers' emotional well-being was seriously affected with 3 being treated for major depressive disorders and 6 experiencing severe psychological difficulties.

Eleven of the mothers were followed up when their children were four years old with the authors expecting many of the problems to have resolved by this time, however, they found that 4 mothers had high levels of depression as measured by the Centre for Epidemiologic Studies – Depression Scale and were being treated with psychotropic medication. Four mothers spontaneously expressed regrets about having triplets with one saying "I have regretted having three children. I thought for the first time that it was a high price to pay" (Page 1164) (Garel, Salobir et al. 1997). However, as the authors point out some of the characteristics of

the mothers themselves may have contributed to their difficulties in that they were older than naturally conceiving mothers typically are, and all but one had no previous children. Moreover the mothers reported feeling unable to ask for help and this coupled with feelings of uncertainty about how to cope with the babies may have made them feel they were failing.

2.1-v The impact of an IVF twin birth

Increasing debate in the media about regulations regarding fertility treatment has lead to journalists entering the debate about the merits of twins. Joanna Moorhead in a recent article in the Guardian questioned whether prospective IVF parents knew what they were letting themselves in for by requesting twins and included a quote from a mother of twins who described what the reality of premature twins meant for her "Coming home with two tiny babies was very traumatic- I had no friends, no support network, and here I was looking after two babies who had had a whole paediatric team the week before. It was very stressful, very demanding and very lonely" (page 14) (Moorhead 2005).

A study looking at family functioning in IVF parents of twins and singletons aged 2 to 5 years old in France mentioned in section 1.6, as finding lower levels of cognitive functioning in twins but no differences in emotional and behavioural problems also looked at maternal well-being (Olivennes, Golombok et al. 2005). The 344 families of twins recruited from the 488 IVF/ICSI twins born between July 1998 and June 2001 were matched according to the child's age and gender to a singleton family recruited from the same data base. The mothers were sent a questionnaire booklet to complete when their child was between 2 and 5 years old (mean age 3.45). The booklet included the short form of the Parenting Stress Index (PSI-SF)

to assess parenting stress, the Edinburgh Postnatal Depression Scale (EPDS) to assess depression and the Golombok Rust Inventory of Marital State to assess the quality of the marital relationship and some structured questions about the family. The authors found significantly higher levels of parenting stress with higher total scores and higher scores on the parental distress subscale although not for the parent child dysfunctional interaction or the difficult child subscale. Mothers of twins were also found to experience significantly higher levels of depression (mean= 7.52) compared to mothers of singletons (mean= 6.94). The only significant difference in marital satisfaction was that mothers of twins reported having sexual intercourse less frequently. With regard to experience of motherhood significantly fewer mothers of twins were in paid employment (59%) than were mothers of singletons (77%). Mothers of twins were also significantly more likely to say they found parenting difficult, were less likely to obtain pleasure from their child with only 76% reporting feelings of enormous pleasure compared to 89% of the mothers of singletons and to desire more children 32% compared to 48% of mothers of singletons.

A very recent extension to this study, as mentioned in section 1.6 looked at mothers of triplets as a separate group (Freeman, Golombok et al. 2007). Although mothers of triplets were not found to experience significantly higher levels of parenting stress than the mothers of twins as a combined group the mothers of multiples scored higher than the mothers of singletons. There were no significant differences in levels of depression between the three groups of mothers: mothers of triplets (n=10) mothers of twins (n=15) and mothers of singletons (n=30), however mothers of triplets were more likely to report finding parenting difficult, and there was a trend for them to be less likely to report experiencing enormous pleasure from parenting their triplets (60%) than mothers of twins (87%) or

singletons (90%) did. The authors of these studies conclude that these greater difficulties in parenting experienced by families of twins and triplets should be used to inform couples' and clinicians' decision making about ART. The studies were not prospective and did not explore the possibility of the twins' cognitive development interacting with parenting stress and depression. These studies were not able to determine the contribution IVF status makes and whether it interacts with multiplicity because they did not include a naturally conceived group of twins. One way of exploring the impact of IVF status further is to look at studies of IVF and naturally conceived singletons.

2.1-vi The effect of a singleton birth on a mother's well-being after conceiving spontaneously or after IVF

A number of studies have found little evidence of any detriment to a mother's emotional well-being after an assisted conception. For example Colpin and colleagues found no significant differences in mother's psychological functioning between IVF mothers and naturally conceiving mothers of singletons (Colpin, Demyttenaere et al. 1995). A prospective French study also found no significant differences in rates of depression assessed by interview or observation in mothers conceiving naturally, after IVF or after ovarian stimulation (Raoul-Duval, Bertrand-Servais et al. 1994). Moreover, a cross-sectional European study found mothers of assisted conception children reported greater warmth towards their child, were more emotionally involved and actually reported less stress associated with parenting than mothers who conceived naturally (Golombok, Brewaeys et al. 1996). While Weaver and colleagues found that parents conceiving after ART gave higher positive ratings for their feelings about their babies and for feelings of freedom than parents conceiving spontaneously (Weaver, Clifford et al. 1993).

Hahn and DiPietro also report positive findings for IVF parents: their cross-sectional survey of IVF and matched control mother child pairs in Taiwan found IVF mothers reported a greater level of protectiveness towards their children than control mothers and that teachers reported them as displaying greater warmth towards their children and the children as having fewer behavioural problems (Hahn and DiPietro 2001). Moreover, IVF mothers of singletons perceived less parental stress than control mothers of singletons did. Although IVF mothers reported less satisfaction with some aspects of family functioning the authors suggest this may be because of cultural factors. Interestingly mothers within the IVF group with one child reported less parenting stress than mothers with more than one child this could be seen as evidence that caring for more than one child causes greater stress, but does not allow us to separate out the issue of first time parenthood.

A prospective Finnish study of couples conceiving a singleton spontaneously or after ART also found no evidence of ART predicting mental health problems in couples during the transition to parenthood and one year postpartum. However, for all women worry over the child at two months, being an older mother and having more children were all associated with a higher level of depressive symptoms. These findings although reassuring about the possible effects of ART on depressive symptoms could be interpreted as suggesting mothers of multiples whose babies are likely to be less healthy may be more vulnerable to depressive symptoms (Repokari, Punamaki et al. 2005).

However, a study of 65 primiparous IVF mothers and 62 age matched naturally conceiving mothers found at 4 months postpartum the IVF mothers reported lower self-esteem, lower self-efficacy and rated their

babies as more difficult (McMahon, Ungerer et al. 1997)[a]. A follow-up at one year postpartum of these mothers and children revealed that IVF mothers rated their children as more difficult in terms of behaviour than control mothers did. The authors suggest that the results demonstrate the IVF mothers experience some uncertainty in their role as a parent (Gibson, Ungerer et al. 1998).

Studies seem to indicate few psychological problems for mothers of singleton IVF children with Hahn in his review of this area concluding that his findings were positive and reassuring for IVF parents, although none as he pointed out had looked at parents of multiples (Hahn 2001). Multiple births conceived as a result of assisted conception are much wanted babies; moreover as will be discussed in detail in chapter four these parents are often eager, for all sorts of reasons, to have a multiple birth (Leiblum, Kemmann et al. 1990; Gleicher, Campbell et al. 1995; Goldfarb, Kinzer et al. 1996; Murdoch 1997; Grobman, Milad et al. 2001; Kalra, Milad et al. 2003; Child, Henderson et al. 2004; Ryan, Zhang et al. 2004; Ryan, Maassen et al. 2005). Further research is needed to see whether these factors can be sufficient to protect IVF parents from the strains of a twin birth which have been found cross-culturally in the previously mentioned studies in Australia, France and America and have also been found in a study of Taiwanese twins with 41% of mothers reporting mood fluctuations and 28% disturbance to their marriage when the twins were 3 months old (Chang 1990).

One issue may be the level of multiplicity, a recent German study asked couples what they considered the ideal number of children to be and found 53% wished to have two (Stobel-Richter, Beutel et al. 2005); prospective IVF parents have been found to be less eager for triplets or beyond but see

twins as completing the ideal family in one pregnancy (Child, AM et al. 2004). Of interest here is a recent study by Ellison and colleagues in which they used the domains of interest revealed in their earlier focus group study (Ellison and Hall 2003), to construct a survey questionnaire sent to mothers of at least one year old singletons (128), twins (111) and triplets (10) conceived after ART (Ellison, Hotamisligil et al. 2005). Using multivariate logistic regression models they were able to clearly demonstrate that for each additional multiple birth child the odds of having difficulty meeting material needs tripled, while the odds of lower quality of life and increased social stigma doubled. There was also an increased risk of maternal depression for each increase in multiplicity. The fact that IVF multiples are usually born to first-time inexperienced mothers may make them particularly vulnerable to stress, although in Colpin and colleagues study of naturally conceived twins presence of other children was not a significant predictor of parental stress (Colpin, De-Munter et al. 2000).

2.1-vii The effect of a twin birth on a mother's emotional well-being after conceiving spontaneously or after IVF

In order to better evaluate the impact of an IVF twin birth on the psychological well-being of the mother some studies have made comparisons with mothers of naturally conceived twins. Cook and colleagues compared 12 families of twins conceived by IVF with 14 families of naturally conceived twins (Cook, Bradley et al. 1998). Parents of IVF twins reported significantly higher levels of stress as measured by the PSI. Mothers of IVF and naturally conceiving twins obtained similar scores on measures of quality of parenting however Golombok and colleagues' study had found mothers of IVF singletons expressed greater warmth to their children and shared greater emotional involvement with them than mothers of naturally conceived singletons (Golombok, Brewaeys et al.

1996). There were however, a number of problems with this study by Cook and colleagues firstly the sample size was small and the return rate for some questionnaires was poor, most importantly though the majority of the IVF twins were first born. The increased stress experienced by the IVF parents may as the authors point out have been due to the increased demands and expectations twins placed on the IVF parents, or have reflected the greater parental experience of the naturally conceiving parents. Another issue is the fact that mothers of naturally conceived twins are likely to be older with increasing maternal age associated with an increase in dizygotic twinning rates (Beemsterboer, Homburg et al. 2006), whereas IVF mothers of multiples are likely to be younger (Templeton and Morris 1998); even if first time parenthood is controlled for parents' age may have an additional impact.

In an attempt to unravel these issues Munro and colleagues carried out a larger comparative study of parents of pre-school twins including, 40 IVF, 25 spontaneously conceiving and 15 parents who attended for an infertility workup (Munro, Ironside et al. 1990). All parents were matched according to the twin's age (within 3 months), birth order, presence of younger or older siblings and zygosity. They found that IVF parents of twins had the same degree of psychiatric morbidity as measured by probable caseness on the General Health Questionnaire (GHQ) as did naturally conceiving parents. Parents conceiving after attending for an infertility workup were found to have lower scores than the controls or IVF parents. The authors suggest this may be because this latter group would have been most prepared for the possibility of a twin birth.

A later study reported results for these same couples from the Interview Schedule for Social Interaction (ISSSI) (Munro, Ironside et al. 1992).

Results showed that IVF parents reported deficient social relationships compared to non-IVF parents in terms of numerical size and affective quality of available relationships. The authors suggest a number of reasons for this increased social isolation among the IVF parents including of most relevance to this research that the couple may feel unable to complain about family matters after experiencing such difficulties conceiving. Mothers reported less adequate and available social relationships than fathers with many saying they had no time for their own interests. The study suggests a twin birth may have a negative effect on IVF parents. Although this study matched the twins for presence of siblings it did not control for first time parenthood which may have interacted with some of these issues.

Colpin and colleagues controlled for the presence of older children in their comparative study of families of 1 year old twins (54 had conceived spontaneously, 25 had conceived after hormonal treatment and 24 after IVF or artificial insemination) (Colpin, Munter et al. 1999). First time mothers with a history of infertility had scores on the 'sense of competence' and 'parent health' scales of the Parenting Stress Index and on the GHQ-30 indicating significantly higher stress related to competence and health and lower psychosocial well-being. The authors conclude that their findings support those of Gibson and colleagues that first-time motherhood of twins is a risk factor for parenting stress and well-being (Gibson, Ungerer et al. 1998). They suggest that infertile parents may have unrealistic expectations of their child and so find coping with the realities of a twin birth particularly hard to cope with. The role of expectations in the psychological well-being of mothers needs to be further explored.

Recent research by Tully and colleagues however, has failed to support these findings (Tully, Moffitt et al. 2003). This study which the authors claimed to be the largest study on IVF or ovulation induction (OI) twins compared a population based sample of IVF/OI families of twins with a control group. The groups were carefully matched on potentially confounding family and child variables including zygosity, ethnicity, number of children in the family and whether the twins were first born to the mother, or not. They found no significant differences between the IVF/OI and control families on measures of parental adjustment or parent and teacher ratings of the twins' behaviour at age five. The authors wonder whether the IVF/OI parents' more positive attitude towards twins and the experience of fertility treatment acted as a protective factor for coping with their twins. They also speculate that the reason they found no evidence of the increased warmth IVF parents have been found to display towards their singletons (Golombok, Brewaeys et al. 1996), was because in the case of twins this warmth had to be shared between two children.

Another recent prospective study which looked at parenting stress in first time mothers found IVF mothers of multiples were more likely to have scores on the PSI-SF indicating severe parenting stress than IVF mothers of singletons or mothers of naturally conceived singletons (Glazebrook, Sheard et al. 2004). Mothers of multiple children were not found to have poorer mental health as measured by the GHQ-12, but were more likely to report having felt depressed since the birth than IVF mothers of singletons. The authors point out that the study highlights the demands of parenting multiples on inexperienced mothers, especially considering the multiple babies were more likely to be premature, of lower birth weight and have more medical complications.

2.1-viii The impact of caring for a premature, low birth weight or difficult to care for baby on a mother' emotional well-being

Given the increased likelihood of a multiple birth baby to be born prematurely and to have more medical complications well documented by for example (ESHRE 2000) it is essential to explore the possible effects on a mother's emotional well-being of trying to raise such a baby. It is interesting to note here that a study by Pinborg and colleagues exploring mothers of twins attitudes towards twins and single embryo transfer (SET) found that delivery of a child with a very low birth weight (>1500g) (VLBW) was predictive of a high acceptance of SET (Pinborg, Loft et al. 2003)[b]. A recent study in Australia of the impact of a very premature birth (>32 weeks) on the psychological health of 62 mothers found a high percentage: 40% of mothers reported significant depressive symptoms on the EDPS, logistic regression analysis showed that high maternal stress resulted in an increased likelihood of depressive symptoms (OR 1.15 CI 1.04-1.26, P<0.01) (Davis, Edwards et al. 2003). These findings one could argue are only to be expected but they need to be taken into consideration as IVF mothers of multiples are likely to experience very high levels of stress. However, the authors did find higher levels of maternal education and increased perception of support from nursing staff resulted in decreased likelihood of depressive symptoms; both protective factors likely to be true of IVF mothers.

Singer and colleagues looked at the effects of a VLBW baby on the mother. This study compared maternal psychological distress and parenting stress in 122 mothers of VLBW babies at high risk: diagnosed as having bronchopulmonary dysplasia, 84 mothers of VLBW babies at low risk: not diagnosed as having bronchopulmonary dysplasia, and 123 mothers of term babies (Singer, Salvator et al. 1999). They found mothers of high

risk VLBW babies reported higher levels of psychological distress, especially depression, anxiety and obsessive compulsive behaviours as measured by the Brief Symptom Inventory (BSI) than mothers of low risk VLBW or term babies, over the three years they were followed. Mothers of high risk VLBW babies had scores on the Parenting Stress Index child domain indicating they found their child more distractable, hyperactive and demanding at one and three years old than mothers of term infants did. However the parent domain scores did not differ significantly for any of the groups indicating the mothers did not feel less supported nor had lower feelings of parental competence.

The authors also looked at the added effect of a multiple birth however they report no evidence of greater maternal stress on any of the dimensions measured for multiple births. They conclude that in general mothers had adapted positively by three years after the birth to a VLBW baby, however they did find that nearly a third of mothers of VLBW babies had clinically meaningful levels of depression and anxiety a finding which should not be ignored. The finding that multiple birth status did not have a significant effect may as the authors suggest be due to small numbers, the majority of the multiple births fell in the low risk category as one might expect as the multiple status will have caused the VLBW. These findings suggest that the birth of a VLBW baby does contribute to psychological distress and parenting stress in mothers. One might speculate that IVF mothers may be particularly vulnerable to such distress and stress.

More recently a qualitative study in France looked at the consequences for the family of a very preterm birth (>33 weeks) (Garel, Bahuaud et al. 2004). Themes emerging from the semi-structured interviews were mothers' feelings of anxiety and depression. The mothers' difficulties were

not linked to the degree of prematurity or length of stay in the neonatal unit but with the baby's present health, re-admittances to hospital and to maternal characteristics such as isolation, lack of support and loss of earlier babies.

Veddovi and colleagues detailed study looked at the ways maternal psychological well-being, maternal competencies, infant development and mother-infant relationships all interact with the birth of a preterm baby (Veddovi, Gibson et al. 2004). They found having a first born infant who was more sleepy or drowsy was associated with higher maternal parental stress at one year corrected age. The authors suggest there are problems in how representative the sample was as the babies were not high risk, the mothers were from a relatively affluent metropolitan area and the participation rate of 67% suggests those mothers most stressed may have refused to participate. However the mothers are probably quite typical of IVF first time mothers of multiples.

Pridham and colleagues looked at factors associated with mothers' evaluation of their care giving for premature (N=54) and full-term infants (N=49) at one, four, eight and 12 months post-term (Pridham, Lin et al. 2001). Mothers' evaluated their care giving using a subscale of the self-report instrument "What being the parent of a baby is like" which includes items assessing how well the mother believes she is meeting expectations for her care-giving practice and performance. Mothers' evaluations became more positive over time and evaluations at one month were significantly lower than later evaluations. This suggests mothers may feel particularly vulnerable in the first weeks after birth about looking after their baby. Although regression analyses showed mothers' care giving evaluation was not associated with the infant's maturity at birth or the

health of their lungs the authors suggest this may be because the mothers still felt better able to care for their infants than they thought others could. However care giving evaluation was positively associated with the infant's positive feeding behaviour and their responsiveness. Moreover the mothers' care-giving evaluation was negatively associated with symptoms of depression as measured by the 20-item Centre for Epidemiologic Study-Depression Scale (CES-D). This study provides some support for the idea of an interaction between the mother's well-being and how she experiences caring for her baby (Pridham, Lin et al. 2001).

A community based survey of Australian middle-class mothers attending maternal and child health care centres found 15% of mothers had scores on the EPDS above 12 indicating probable clinical depression and 46% of mothers reported their infant's sleep to be a problem (Hiscock and Wake 2001). Even after controlling for possible confounders the authors report that maternal report of an infant sleep problem was a significant predictor of an EPDS score over 12. The authors recognise that because the study was cross-sectional they cannot prove causality however they argue that depressed mothers perceive their infant's sleep patterns differently to non depressed mothers. These findings have implications for the mothers of multiples as we might expect their babies to have greater sleep problems not least because the chance of any problem is doubled with twins.

2.1-ix The impact of the baby's temperament on how a mother feels

Studies have also found evidence of the contribution infant factors, in terms of their temperament, may make to how the mother feels. Early work in the 1980's by Cutrona and Troutman explored the hypothesis that giving birth to a temperamentally difficult infant would be a significant risk

factor for depressive symptoms (Cutrona and Troutman 1986). Fifty five women were recruited during pregnancy to the study and of these 20% were found to show levels of depression on Beck's depression inventory showing evidence of some depression (BDI $\geq$ 9), path analysis showed that infant temperamental difficulty was related to the mothers' level of postpartum depression and was able to account for 30% of the variance in these scores. Further analyses revealed that infant temperamental difficulty also indirectly influenced feelings of depression postpartum through the mediation of parenting self-efficacy.

Beck carried out a meta-analysis of 17 studies published between 1974 and 1993 looking at the relationship between postpartum depression and infant temperament which included Cutrona and Troutman's study (Beck 1996)[a]. She concluded that there was a significant moderate correlation between postpartum depression and infant temperament which was true whether studies were weighted by sample size, un-weighted or weighted by an assigned quality score. However, both increased sample size and later year of publication were significantly negatively correlated with the effect size. One criticism Beck makes of many of the studies is that temperament ratings were usually based only on maternal report making it hard to determine if these ratings actually reflect the infant's temperament or rather the mother's negative response set. A strength of the Cutrona and Troutman study was that infant temperamental difficulty was assessed by three different methods: by mothers scoring their babies on the dimensions of intensity, mood, withdrawal and adaptability on the revised Infant Temperament Questionnaire, secondly a mean daily crying duration was calculated based on mothers' records of crying duration over a 7 day period, and finally an observer kept a record of the infant's crying during a 60 minute assessment period (Cutrona and Troutman 1986).

Further evidence for the role of infant factors in post-natal depression is provided by a later study by Murray and colleagues (Murray, Stanley et al. 1996). In this study of a group of women selected as being at high or low risk of post-natal depression they found that maternal perceptions of the baby as highly unsettled and irregular in behaviour as measured by The Mother and Baby Scale (MABS) was predictive of the mother becoming depressed. Poor motor functioning as measured by the Neonatal Behavioural Assessment Scale (NBAS) was also found to be predictive of post-natal depression in the mothers. These findings may be particularly relevant for women with multiple births as their babies are likely to be of lower birth weight and more premature (Blondel, Kogan et al. 2002) and this was shown to correlate with poorer motor functioning.

A more recent Australian study explored further the links between postnatal depression, anxiety and infant behaviours, and is of particular relevance here as the mothers were all older well-educated mothers of singletons and included a control group of mothers with similar demographic, obstetric and perinatal backgrounds (McMahon, Barnett et al. 2001). The study group of mothers had been admitted to a residential care unit due to significant ongoing difficulties with their infants. The study mothers were significantly more likely to score above 12 on the EPDS: 36% compared to only 6% of the control mothers, they also scored significantly higher on both trait and state anxiety measures and 20% of them rated their infant as 'difficult' using the Short Temperament Scale for Infants compared to only 5% of the control mothers. Significant moderate correlations were found between EPDS scores and both state and trait anxiety scores for all the mothers and there were strong correlations between the study mothers' state and trait anxiety scores and how difficult

they rated their infant. However there was no significant correlation between the study mothers' EPDS scores and how difficult they rated their infant. Although the authors acknowledge the study does not clarify the direction of causality between infant behaviour and psychological well-being in the mother it provides further evidence of their close association.

The association between infant temperament and maternal well-being was also explored in another Australian study of women referred to a mother and baby unit after diagnosis of infant feeding or settling problems (Fisher, Feekery et al. 2002). The study found what it describes as an incremental association between severity of maternal distress and self-reported difficulty in comforting the baby and anxiety about infant care. Women classified as being in the 'probably depressed group' were significantly more likely to say they were unable to settle their baby than women classified as 'fatigued' or 'fatigued and depressed'. Findings such as these have lead to the speculation that an unsettled or difficult baby may be particularly detrimental to the mental-health of a mother of multiples (Fisher and Stocky 2003).

2.1-x A multiple birth as a risk factor for postnatal depression and depressive symptoms

Studies exploring risk factors for postnatal depression have not included multiplicity or IVF status as separate variables; however, some factors identified suggest IVF mothers of multiples may be at greater risk while others would suggest these mothers may be at less risk. Warner and colleagues' study of 2375 women in Manchester found four variables associated with a high score on the EPDS (>12): not being able to breast feed, an unplanned pregnancy, and unemployment in the mother or head of household (Warner, Appleby et al. 1996). Mothers undergoing fertility

treatment have planned their pregnancy and they and their partners are unlikely to be unemployed in view of the fact IVF treatment is rarely available on the National Health Service (NHS). Further evidence of the possibility of a reduced risk for postpartum depression comes from O'Hara and Swain's review and meta-analysis of studies of non-psychotic postpartum depression (O'Hara and Swain 1996). This study concluded that the strongest predictors were: past history of psychopathology and psychological disturbance during pregnancy, poor marital relationship and low social support, and stressful life events; while indicators of low social status showed a small but significant predictive relation. These findings suggest that IVF mothers may have a degree of protection from some of these risk factors by their entry onto an IVF program as all couples are expected to be in a stable relationship and will have financial security.

However, other factors which have been identified as predictors of postpartum depression may be more likely to apply to women undergoing treatment for infertility, or having a multiple birth. For example, Beck carried out a meta-analysis of 44 studies looking at the predictors of postpartum depression with effect sizes calculated in three ways: un-weighted, weighted by sample size and weighted by an assigned quality score (Beck 1996)[b]. The author found what she described as moderate significant effect sizes for the variables: child care stress, life stress, social support, prenatal anxiety, maternity blues, marital satisfaction, history of previous depression and a large significant effect size for prenatal depression. All these predictors; except marital satisfaction as couples usually have to be in a long term relationship before they are accepted for treatment, may apply to IVF mothers. A later study by Bergant and colleagues found other predictors of depressed mood, as indicated by scores of $\geq$ 10 on the EPDS, which may be likely to apply to IVF mothers'

of multiples. Using multiple logistic regression analysis they found the highest risk associated with a high EPDS score was high childbirth burden, followed by high trait anxiety, low life satisfaction, low professional occupation and low birth weight (Bergant, Heim et al. 1999); as already discussed mothers' of multiples are more likely to have babies of low birth weight and to have had a difficult birth.

Forman and colleagues carried out a large study of 5252 women giving birth from 1994 to 1995 at a hospital in Denmark (Forman, Videbech et al. 2000). Four months after delivery 5.5% of the women were defined as having postpartum depression based on a score of 13 or above on the EPDS. Risk factors identified by multivariate logistic regression were found to be psychological distress in late pregnancy, perceived social isolation during pregnancy, high parity and a history of pre-pregnancy psychiatric disease. However, they found no association with pregnancy or delivery complications. Of particular interest is their finding that psychological distress in late pregnancy was a predictor of postpartum distress and this is in accord with O'Hara and Swain, Beck and Bergant's findings with regard to prenatal anxiety (Beck 1996[b]; O'Hara and Swain 1996; Bergant, Heim et al. 1999); moreover mothers of IVF multiples were found by Glazebrook and colleagues to be significantly more anxious at 18 and 28 weeks pregnant than IVF mothers of singletons or control mothers (Glazebrook, Cox et al. 2000).

An Australian study also found higher levels of anxiety on pregnancy specific anxiety measures in IVF mothers during pregnancy than in control mothers (McMahon, Ungerer et al. 1997)[b]. A further study in Australia revealed that assisted conception was associated with an increased risk of admission to a residential unit for treatment of maternal mood disorder or

infant feeding or sleeping disorders during the first year postpartum (Fisher, Hammarberg et al. 2005). These mothers were also more likely to be older, to have had a caesarean delivery and a multiple births. Mood was assessed using the Edinburgh Postnatal Depression Scale (EPDS). Although the women conceiving after ART did not score significantly higher than those conceiving spontaneously, nor did they score lower, and all the women scored higher than a community sample. One suggestion has been that women who have required medical assistance to conceive might be more likely to seek medical help subsequently, and that this could be the reason for their over representation in such a study. Unfortunately this audit of medical records did not allow the researchers to separate and quantify the contribution made by a multiple birth and having a caesarean. Taken together these findings suggest there may be reason to consider mothers of multiples, and in particular IVF mothers of multiples to be at greater risk of suffering from postpartum depression than first thought.

A further potential source of stress and depression for all parents of multiples is the possibility of death or handicap of one baby; with Blickstein estimating a 3 to 6 fold increased risk of cerebral palsy associated with a multiple birth (Blickstein 2002), and Sher and colleagues reporting twins had a five fold increased risk of stillbirth or neonatal death than singletons (Scher, Petterson et al. 2002). Bryan suggests that IVF parents who have lost one of their multiple conceived babies may find it especially hard to grieve adequately as not only will they be preoccupied with the surviving baby or babies, they will have a constant reminder of the dead baby in the survivor, may have lost a perceived status as a parent of multiples and may have their grief underestimated by others who expect them to be grateful for any survivors (Bryan 2003). These ideas were confirmed by Ellison and Hall's qualitative study which found that six of the ten

previously infertile mothers in their focus groups had experienced a pregnancy or neonatal loss with women frequently reporting these experiences were minimised or even overlooked by others (Ellison and Hall 2003).

Recently Beck carried out a further meta-analysis of 84 studies looking at predictors of postpartum depression in the 1990's (Beck 2001). She found 13 significant predictors of which 10 had moderate effect sizes these included: prenatal depression, child care stress, prenatal anxiety, life stress, social support, marital relationship, history of previous depression, and maternity blues, all of which had been found to have a moderate effect in the 1996 studies except for prenatal depression which had a large effect before and history of depression which increased from a small to moderate effect size. Four new predictor variables were found: self esteem which had a moderate effect and marital status, socioeconomic status and unplanned or unwanted pregnancy which all had small effect sizes. As with the earlier studies of predictors of postnatal depression Beck did not look at multiplicity as a risk factor however the factors: child care stress, prenatal anxiety, life stress and social support may be of particular relevance for IVF mothers of multiples. One interesting finding to emerge from this research was the importance of self-esteem which appears to be a way in which the mother can buffer herself from the negative effects of life events and stressors. Linked to how effectively she is able to do this will be what expectations she has of motherhood and of herself as a mother.

2.1-xi The social cognitive theory of depression

Champion and Power's (1995) social cognitive theory of depression which was outlined in chapter one provides a model of depression which suggests

why post-natal depression may be more likely after the birth of an IVF multiple (Champion and Power 1995). The model argues that an individual's cognitive vulnerability to depression is related to the extent to which they pursue a highly valued goal or pursue one goal to the exclusion of others. As already stated women presenting for infertility treatment have demonstrated the value they place on motherhood by presenting themselves for a treatment which comes with well known high financial and emotional costs. Research studies also provide evidence of just how highly valued this role can be. One qualitative study explored the experiences of 26 infertile Israeli women and describes how "Infertility became a 'master status' for these women, undermining any other merits and achievements they might have" (page 821) with women feeling unable to reject the extensive infertility treatments on offer in Israel a country with a strong pro-natalist ideology (Remennick 2000). An ethnographic qualitative interview study of infertility among low income Latinos in the USA also found evidence of the importance placed on children with both men and women claiming childless marriages were considered a failure (Becker, Castrillo et al. 2006).

For, IVF mothers despite achieving the longed for goal of a baby, the baby or babies may themselves in some way threaten the realisation of this goal. As already outlined in this chapter caring for a premature, low birth weight or temperamentally difficult baby may be harder for the mother. How the mother responds to these pressures may be linked to the perceieved social pressures she feels to achieve this goal. Support for this can be seen in the research showing the role of self-esteem in the development of postpartum depression with Fontaine and Jones finding that self-esteem was a reliable contributing factor to differential susceptibility to depression postpartum (Fontaine and Jones 1997),

Horowitz and colleagues recent finding that a more positive self-evaluation as a parent decreased the likelihood of elevated depression scores (Horowitz, Damato et al. 2005) and Beck's finding that self esteem was a significant predictor of postpartum depression (Beck 2001). Fontaine and Jones argue that a mother's belief in her ability to produce the desired outcome is of most importantance (Fontaine and Jones 1997).

The way, in which the mother perceives her role, as 'mother' is crucial: what does she expect of herself, and for herself? Fowle's study of 136 American women 8-14 weeks after delivery was an attempt to look at the relationship between postpartum depressive symptoms and maternal role attainment with the author suggesting that "The difference between postpartum depression and depression experienced at other times in a woman's life rests in the postpartum mother's feelings of guilt and inadequacy that are centred about being an incompetent and inadequate parent" (page 85) (Fowles 1998). Depressive symptoms were measured using the EPDS and a score of $\geq$13 was considered to be indicative of depression. Role attainment was assessed using three different scales 'My self as a mother' which measure a mother's progress in developing a maternal role, 'My baby scale' which measures the mother's evaluation of her baby and the 'Perceived competence scale' which assesses a mother's perceptions of competence in feeding and infant care tasks. Ten percent of mothers scored $\geq$13 on the EPDS. Scores on the role attainment scales indicated they had strong positive perceptions of themselves as mothers and most felt competent in their feeding and childcare tasks. Significant negative relationships were found between scores on the EPDS and the role attainment scales. Of concern here is whether mothers struggling with more difficult to care for babies may be even more vulnerable.

Further evidence in support of this theory comes from Beck's meta-synthesis of 18 qualitative studies of postpartum depression which found one of four themes reflecting the perspectives involved in postpartum depression was an incongruity between expectations and the reality of motherhood (Beck 2002)[c]. A recent qualitative study by Choi and colleagues further explored how mothers with no previous experience of motherhood talked about motherhood (Choi, Henshaw et al. 2005). In-depth semi-structured interviews were carried out with 24 women a number of years after the birth of their first child. The authors describe how unprepared for motherhood the women were and that their expectations of motherhood were based on myths of motherhood with, for example women describing not knowing what to do for their baby in contrast with the ideology of motherhood as 'coming naturally'. They go on to describe how striking they found women's expectations of themselves as being able to cope, and their fears of being seen as unable to cope by other people. These fears and expectations are likely to be even greater for mothers of multiples, and indeed Ellinson and Hall found mothers of multiples who had had fertility treatment describing in their focus groups how they felt unable to complain of tiredness because they had spent so many years trying to conceive (Ellison and Hall 2003). These expectations may be compounded by the previously mentioned favourable attitudes found by researchers towards a multiple pregnancy in prospective IVF mothers, and by the pressure already noted by Bryan to see twins as an unqualified joy (Bryan 2002).

2.1-xii The need for a further study

Despite many studies of naturally conceived twins and multiples suggesting mothers are more likely to experience poorer emotional well-being after a

multiple birth (e.g. Goshen-Gottstein 1980; Groothuis, Altemeier et al. 1982; Hay, Gleeson et al. 1990; Thorpe, Golding et al. 1991) studies of IVF conceived multiples have shown some conflicting results and raised many questions which require further investigation. One study comparing maternal well-being for mothers of naturally conceived or IVF twins failed to take into account first time parenthood (Cook, Bradley et al. 1998). However, one study which did control for the presence of older children found first-time motherhood of twins was a risk factor for parenting stress (Colin, Munter et al. 1999). A later study failed to replicate these findings (Tully, Moffitt et al. 2003) although it did not find evidence of the greater warmth expressed by parents to their singleton IVF conceived children found by Golombok and colleagues (Golombok, Brewaeys et al. 1996). Future studies of the impact of a multiple IVF birth would need to take account of first time parenthood.

Despite IVF babies being very wanted babies and their mothers usually regarded as well supported emotionally and financially the social cognitive theory of depression provides a model for explaining why mothers who have difficulty realising their high expectations of motherhood and themselves as a mother may be at risk of poorer emotional well-being or even depression after a multiple birth. This assertion is supported by Klock whose review of psychological adjustment to twins after infertility "hypothesised that mothers of twins who have a history of infertility would be at increased risk for depression and marital decline" (page 645) (Klock 2004). Further research is needed to explore these issues.

To date there have been few prospective studies of IVF first-time mothers and very little qualitative work to explore how IVF mothers actually describe their experiences or expectations of motherhood. For example

one study which reported on mothers' experiences of parenting twins and singletons used a structured question with four response options to explore how much pleasure they had from their child (Olivennes, Golombok et al. 2005). Certainly, qualitative researchers would argue that no study of the effects of parenting multiples on the mother could be complete without collecting qualitative as well as quantitative data (Pope and Mays 1995). However, many of the in-depth qualitative studies have included mothers conceiving after a natural or assisted conception (Beck 2002)[b], and first time mothers as well as mothers with children already (Ellison and Hall 2003). Qualitative research exploring the impact of first time motherhood for mothers of twins and singletons is clearly needed.

A large study comparing the experience of pregnancy and motherhood for mothers conceiving naturally and by IVF (Glazebrook, Cox et al. 2000) had asked mothers about their experiences shortly after giving birth. This data offered the unique opportunity to complement quantitative data already obtained about the mothers according to the three ways outlined by Pope and May (1995). Firstly, and at the simplest level the words used by mothers to describe their experiences could be examined, secondly the work could be used to validate and supplement other quantitative data collected to form a process of triangulation and finally areas not previously explored could be searched for (Pope and Mays 1995). However, Yardley has recently argued that this combination of quantitative and qualitative data should be seen as something more than a mixed methods approach, or an attempt to triangulate. Findings from the quantitative and qualitative methodologies can instead be merged, to produce what she terms "a composite analysis" so that the whole can become greater than the sum of its parts and new organic ideas emerge (Yardley and Bishop 2007).

This study aimed to provide insight into the experience of first-time IVF motherhood and the impact of a multiple birth on postpartum mental health using a composite analysis to explore the research questions:

1. Did first-time IVF mothers of twins or triplets have poorer emotional well-being at six weeks postpartum compared to mothers of singletons?
2. What impact did caring for a more unsettled and irregular baby have on postpartum mental health in mothers of twins or triplets?

2.2 METHOD

2.2-i Design

This study was part of a prospective longitudinal study of psychological outcome and adjustment to parenthood in couples conceiving following IVF treatment (Glazebrook, Sheard et al. 2004). Couples were recruited to the study at 18 weeks of pregnancy and were sent postal questionnaires at 18 and 28 weeks of pregnancy and at 6 weeks and 1 year postpartum, in addition a telephone interview was carried out at 6 weeks postpartum. This study focused on data from the 6 week postpartum interview and questionnaires.

2.2-ii Ethics

Signed consent was obtained for follow-up and to access information from medical notes (see appendix one). The study received full ethical approval from the relevant ethics committees.

2.2-iii Participants

Letters were sent to 625 women known to have successfully conceived following treatment for infertility at one research and treatment unit in a United Kingdom hospital inviting them to take part in the study (see appendix two). Inclusion criteria were that participants should be at least 18 weeks pregnant, be resident in the United Kingdom, and English speaking. Of the women approached 242 consented to take part in the research. In addition the present study selected only first time mothers. Only first time mothers were included in this study, as research findings have suggested that first time motherhood of multiples may be a risk factor for parenting stress and poor psychosocial well-being (Gibson, Ungerer et al. 1998; Colpin, Munter et al. 1999; Glazebrook, Sheard et al. 2004). Of the 242 consenting women 207 were first time mothers and interviews were successfully carried out with 175 women.

2.2-iv Measures

The Edinburgh Postnatal Depression Scale (EPDS)

This ten item self-report scale was developed by its authors as a tool for detecting depression in women following childbirth in recognition of the fact existing mental health questionnaires, such as the GHQ contained somatic items which might be influenced by the physiological changes of pregnancy (Cox 1994). Higher total scores indicate greater feelings of depression with women scoring over 12 being most likely to be suffering from a depressive illness. The scale has been shown by the authors to have a high level of specificity and sensitivity, and they report that using a score of above 12/13 achieved a sensitivity of 86%, and a specificity (proportion of non-depressed women who were true negatives) of 78%. The split-half reliability of the scale was found to be 0.88, and the standardised alpha coefficient was 0.87. Most importantly the authors report the scale to be

both easily completed and acceptable to mothers (Cox, Holden et al. 1987). This study treated a score of above 12 as being indicative of depression.

Unsettled and irregular behaviour (UIB)

This is a sub-scale of the Mother and Baby Scale (MABS) developed by St. James-Roberts and Wolke (St. James-Roberts and Wolke 1988). This scale was developed by the authors to explore the idea that some babies are characteristically 'difficult' in their style of behaviour and that this reflects true individual differences. The MABS is a 29 item scale completed by mothers about their baby. The first part of the scale asks mothers to rate 15 specific behaviours on a five point scale, with 0 being 'not at all' and 5 'very often' this forms the sub-scale unsettled and irregular behaviour and scores can range from 0 to 75.

The authors report high internal consistency for this scale as demonstrated by a Cronbach's alpha of 0.92. Mothers of multiples were asked to rate each of their babies. The score describing the most irregular and unsettled baby was used in all analyses.

The telephone Interview

Interviews with the mothers were planned to take the form of a semi-structured taped telephone interview with a researcher. These interviews were intended not only to generate qualitative data but also to build a rapport with the mothers to encourage them to continue to take part in the study. For this reason all mothers were interviewed, although many qualitative researchers may argue such extensive interviewing was unnecessary once new themes had stopped emerging. A small number of women 15 (8.6%) completed a written questionnaire because either,

despite several attempts they were unavailable for interview by phone, or in the case of one mother she felt her written English was better than her spoken and she preferred to complete a written questionnaire. The interviews asked for details about obstetric information including the type of delivery, birth weight, weeks of gestation, infant health complications and time spent in the Special Care Unit; followed by open ended questions these included how the labour went, how the mother was feeling in herself, what impact the birth had had on her relationship with her partner and anything else she would like to add about her experiences. The present study focused on the obstetric information and replies to the question "how are you feeling in yourself at the moment?"

The question "how are you feeling in yourself at the moment?" was asked after details had been obtained about the birth and in some cases this meant a rapport between the mother and the researcher had already been established, particularly if the birth had been difficult and considerable detail and explanation had been given. If, the researcher felt it was necessary women were additionally prompted to consider how they were feeling emotionally as well as physically.

2.2-v Procedure

Demographic information was obtained by questionnaire at 18 weeks of pregnancy. Details of fertility treatments were obtained from medical notes. Mothers were contacted by telephone six weeks postpartum. Mothers who did not wish to complete the interview over the telephone or who were unobtainable were posted the written version of the interview. A few mothers requested that the interview was not taped and so notes were taken during the interview and used instead, these notes were taken routinely and were used in the event of equipment failure. Some

interviews could not take place at around six weeks as discharge home was delayed due to the babies and or the mother being ill after delivery. In these cases the mother was asked to reflect on how she had felt 6 weeks after the birth. The semi-structured interview was carried out first (more detail on the interview procedure is given below) and then the UIB was administered verbally, unless the mother asked to be sent the written version instead. After the interview the mothers were sent the EPDS. All the taped interviews were recorded and then transcribed verbatim. Obstetric details for mothers lost to follow-up were obtained from the medical notes.

2.2-vi The Interview Process

In response to the question "how do you feel in yourself at the moment", the most common response was fine or okay with 70 (40%) of mothers replying in such a way, for example the mother replies

> 'Fine' (1703)

The researcher brought to the interview the desire to explore any feelings of depression and so typically after this response mothers would then be prompted with

> 'Emotionally and physically you felt okay?'

At this stage mothers did one of three things. They either made it clear that this was exactly what they meant by their initial reply and that they wanted to stop this line of questioning for example the above mother replied again

> 'Yeah fine no problems at all' (1703)

or, they expanded on why they felt okay, for example

> 'On the whole yes. I think the normal thing where it actually hits you on lack of sleep etc. But on the whole fine.' (1799)

Some mothers when probed explained how although they felt okay now this had not always been so for example

'Researcher - And emotionally have you felt okay since he was born?

Mother - The first couple of weeks I felt really sad I just had this sad feeling come over me all the time, and I knew that women do have these baby blues but I keep saying to my husband I should not be feeling like this I should be on top of the world I should be really happy because I've got the baby that I always wanted and now I feel so sad and sometimes I just used to start crying. My husband just had to look at me wrong and I just started to cry but after that my midwife and my health visitor were quite good, they were very supportive and I came through it all right.

Researcher - And that's all gone now?

Mother Yes that's all right now I'm fine. (1721)

Some mothers although replying with the usual stoical fine or okay indicated in some way that this might not have always been so for example one mother replied

'Fine, absolutely fine, yeah I feel really good now.' (1785)

Alerted by the word 'now' the researcher prompted further

"And emotionally have you felt okay?"

which produced further information about how the mother had felt earlier

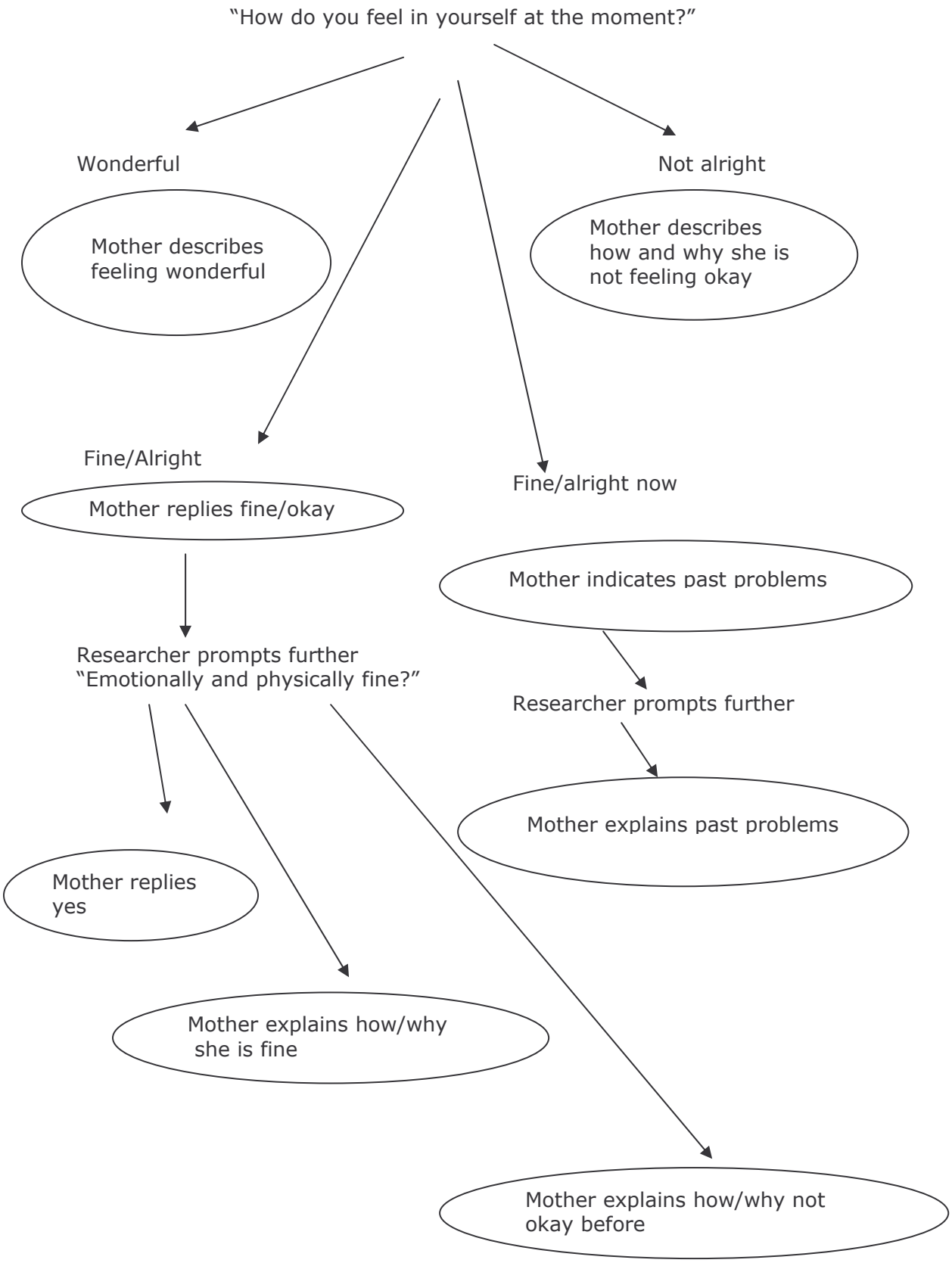
'Yeah. I cried an awful lot about the 3rd day but I felt so awful and I don't think that helped, and he was screaming all the time and really colicky and awful and it was terrible. And the hospital was awful, absolutely awful, the noise, every time you got him to sleep he was woken up and it was just continuous so that really got on top of me. So I cried for oh about 4 or 5 days every time anybody looked at me, but once that passed I've been fine.' (1785)

In some cases the mother indicated immediately that she had not been feeling okay for example one began her answer with

> 'I've had very severe post-natal depression. I was really quite desperate.' (1041)

Figure 1 outlines the progression of the interview.

Figure 1: progression of the interview



2.3-vii Analysis

Quantitative data were analysed using SPSS version 13.0**.** Only scores on the UIB followed a normal distribution and so were analysed using parametric statistics all other analyses were conducted using non-parametric statistics.

Qualitative data were subjected to theme analysis according to the method outlined by Boyatzis (Boyatzis 1998). Thematic analysis was chosen as the preferred method of analysis for both pragmatic and theoretical reasons. Interview transcripts were available for 175 mothers and the researchers were keen to make use of all the data which meant some very labour intensive methods of qualitative analysis such as grounded theory and interpretative phenomenological analysis (IPA) would be inappropriate. For example Smith (2003) describes how a commitment to detailed interpretation is a distinctive feature of IPA and that many researchers recognise this can only be done on very small samples (Smith and Osborn 2003) However, as Braun and Clarke describe, thematic analysis offers other more important advantages over these methods (Braun and Clarke 2006). Both grounded theory and IPA are, they argue, theoretically bounded. Grounded Theory seeks ultimately to produce one theory grounded in the data, whereas theme analysis is flexible enough to allow a theme to emerge from the data itself, while at the same time allowing the researcher to explore pre-existing theories derived from the research literature.

Content analysis could have been used as the method of analysis however it relies solely on the semantic content of the data and does not allow the

researcher to seek for underlying meanings or ideas. Nor does content analysis allow the researcher to explore for patterns or ideas, such as expectations of motherhood, derived from the literature. Theme analysis is not dependent on quantifiable measures and so more important than the theme's prevalence is the fact it captures an important element of the data. However, as Braun and Clarke describe in their list of the advantages of thematic analysis it can summarise key features of a large body of data which can then highlight similarities and differences (Braun and Clarke 2006).

The decision was made to quantify the prevalence of themes in order to explore any significant differences between the accounts of mothers of twins and singletons. This was intended not to replace the importance of a theme emerging from the data but because it was felt that with a large number of transcripts a powerful and memorable example of a theme might make it assume disproportionate importance. This is supported by Boyatzis who argues in his book on theme analysis that themes may usefully be scored and the researcher use numerical representations to check for consistency of judgement and to better communicate their findings to researchers grounded in quantitative methods (Boyatzis 1998).

Many of the qualitative studies described earlier in this chapter used more theoretical methods of analysis with for example Beck identifying the need for a grounded theory study (Beck 2002)[b]. Ellison and Hall's transcripts of their focus groups were analysed for themes but they describe these as being identified using grounded theory procedures of coding (Ellison and Hall 2003).

All the interview transcripts or written interview schedules were read several times to get a feel for the ideas expressed by the women. Each transcript was then explored for codeable moments this resulted in the development of 10 themes which described how the mother was feeling physically or emotionally. Themes were identified at both the manifest and latent level. Themes identified at the manifest level were directly observable in the information. An example of this is the theme 'feeling fine' for this theme these words or close paraphrases of them were easily identified in the transcripts. Latent level themes included those which were generated inductively from the raw information. An example of this is the theme 'emotional well-being linked to easy baby and feelings of confidence as a mother'. Although some mothers made the connection themselves in their reply for others the theme was applied by the researcher based on the mother talking of confidence in her role as mother and evidence of her emotional well-being. These themes were continuously debated, refined and moderated by all the researchers involved in the project.

In addition two latent themes were generated deductively based on past theory and research by the principal researcher: this author. Research by Beck showing that an incongruity between expectations and the reality of motherhood was involved in postpartum depression (Beck 2002)[c] and Champion and Power's social cognitive theory of depression which suggests that women who value motherhood very highly may be vulnerable to depression if this role is threatened (Champion and Power 1995) lead to an exploration of the transcripts for any mention of expectations in relation to how the mother was experiencing motherhood and how she found her baby or babies. As a result of this the theme 'expectations of motherhood or of self as a mother not met' was generated. In order to meet Mays and Pope's exhortation to always look for negative cases in qualitative research

(Mays and Pope 2000) the transcripts were then explored for any evidence of expectations being positively surpassed and the theme 'expectations of motherhood- surpassed' was generated (see table 1 for a full list of themes).

Table 1: **Identified themes**

Theme
Feeling wonderful[a]
Feeling tired[a]
Feeling emotionally labile[a]
Emotional well-being – worry over the baby or babies[b]
Expectations of motherhood surpassed[bc]
Expectations of motherhood or of self as a mother – not met[bc]
Emotional well-being linked to easy baby and feelings of confidence as a mother[b]
Feeling fine[a]
Questioning parenthood[b]
Talk of having experienced 'baby blues'[b]
Feeling down depressed or emotionally stressed now or earlier[a]
Physical health problems or body changes[a]

[a] Manifest level theme
[b] Latent level theme
[c] Theme generated deductively form past research and theory

Once the themes were identified a thematic code for each was developed by the principal researcher which included the five elements identified by Boyatzis as necessary for the development of a good thematic code (Boyatzis 1998). These five elements included establishing a conceptually meaningful label for the theme, a definition of each theme, a description of

how to know when the theme occurs for example any indicators seen as signalling the theme, a description of any qualifications or exclusions to the application of the theme and finally examples of positive and negative instances of the theme taken from the transcripts. The thematic codes for each theme were then put together to form a coding scheme or codebook (see appendix three for a copy of the codebook).

This codebook was used to assess the inter-rater reliability of the thematic codes. The codebook was given to another member of the research team who had not been involved in the development of the thematic codes. This researcher used the codebook to assign themes to a sample of quotes taken from the transcripts. This sample included a maximum of 10% of examples of all the themes and a minimum of 3 examples of each theme this resulted in a sample of 46 quotes. The number of matches of themes: themes identified by both raters, as a proportion of the number of examples of themes was then calculated to give an overall percentage agreement score. Forty of the 46 themes identified by the principal researcher were correctly identified by the second rater giving an overall agreement of 86.96%. However, Boyatzis advises that percentage agreement on presence can also be calculated which takes into account that "the absence of the coded theme does not imply the opposite of presence, or there is not an equal likelihood of observing presence and absence" (page 155) (Boyatzis 1998) both of which premises were important considerations in the themes identified.

The equation is:

$$2 \times \frac{\text{(Number of times both coder A and B saw it)}}{\text{(No. of times coder A saw it + No. of times coder B saw it)}}$$

Accordingly percentage agreement on presence was calculated for each theme as well. This ranged from 60% to 100%, with 10 of the 12 themes achieving above 70% agreement (see table 2).

Table 2: percentage agreement on presence for each theme

Theme	No of quotes containing the theme	Percentage agreement on presence
Feeling wonderful	5	80%
Feeling tired	6	100%
Feeling emotionally labile	3	80%
Emotional well-being – worry over the baby or babies	4	60%
Expectations of motherhood surpassed	3	80%
Expectations of motherhood or of self as a mother – not met	3	66.67%
Emotional well-being linked to easy baby and feelings of confidence as a mother	3	100%
Feeling fine	7	93.33%
Questioning parenthood	3	100%
Talk of having experienced 'baby blues'	3	100%
Feeling down depressed or emotionally stressed now or earlier	3	80%
Physical health problems or body changes	3	100%

Although Boyatzis suggests that "typically, scores of 70% or better are considered necessary in this type of research" (page 156) (Boyatzis 1998) he also discusses the problem of how frequency of occurrence or observation will affect reliability. Few occurrences of the codeable

phenomenon will mean a low denominator in the percentage agreement on presence formula so that a small change in agreement can change the percentage dramatically. The two themes with reliability of less than 70% were both themes occurring only 4 times or less in the sample of quotes and discussion revealed the second rater had often been confused between two themes and had assigned a code which the principal researcher had already assigned to that mother on the basis of earlier data. In view of the fact all disagreements were resolved after discussion the data was coded without further modification of the coding scheme.

Once the themes were established all the transcripts were explored for evidence of each theme. The number of singleton and multiple mothers in whose transcript each theme was identified were then cross tabulated. Two by two tables were created for each theme with multiple birth (multiple birth/singleton birth) cross tabulated by theme (theme identified/theme not identified). Chi square analyses were carried out to look for significant differences with Fisher's Exact Tests used when expected frequencies were less than five.

2.3 RESULTS

Of the 625 women approached by letter, 242 (38.7%) consented to take part in the original study. Of these 207 were first time mothers, 3 mothers were subsequently lost to contact, 3 had neonatal deaths and 26 were not available for interview within the study period; leaving 175 (84.5% of the 207 first time mothers who had consented to take part in the original study) mothers to be interviewed. No significant differences were found between those interviewed and mothers who were not interviewed in

terms of having a multiple birth, a caesarean section, a baby born prematurely before 37 weeks gestation, a baby below 2.5 kg at birth or a baby admitted to the Special Care Unit. However, mothers not interviewed were significantly more likely to have conceived using donor sperm (12.9% vs 2.3%, Fisher's Exact Test p=0.021).

The majority of mothers (119) had a singleton birth, 49 mothers had twins and 7 triplets. The mothers of twins and triplets were combined to form a group of 56 mothers of multiples. N=119 singleton, n=49 twins, n=7 triplets = 56 multiples = 32%.

The mothers ranged in age from 22 to 49 at the time of the study, with a median age of 34. The mothers of multiples were significantly younger than the mothers of singletons with a median age of 33 compared to 34 for the mothers of singletons (Mann Whitney U Test z=-2.497, P=0.013). All the mothers except one mother of a singleton were in a stable relationship at the time of the interview. The mothers had been living with their partner for from 2 to 30 years, with a median of 8 years married or living together. There was no significant difference in the number of years the mothers of multiples and singletons had been together (see table 3). Details were available for 166 mothers on how long it had taken them to conceive. The mothers had taken from 12 to 216 months to conceive their baby with a median time taken of 48 months. There was no significant difference in the number of months taken to conceive between the mothers of multiples and singletons (see table 3).

Table 3: **demographic details of mothers of multiples, singletons and all mothers interviewed**

Mothers	Statistic	Age in years	No. of years with partner	No. of months taken to conceive
Mothers of multiples	**No.**	56	56	53
	Median	33.0*	8.0	48.0
	Interquartile range	30-34	5.1-10	30-72
Mothers of singletons	**No.**	119	118	113
	Median	34*	8.0	48.0
	Interquartile range	31-37	5-11	24-63
All mothers	**No.**	175	174	166
	Median	34	8.0	48.0
	Interquartile range	31-36	5-10.25	24-66

***p=<0.05**

The majority of the mothers came from social class one or two as defined by the Standard Occupational Classification Manual (Office of Population Census 1990). There were no significant differences in the percentage of mothers of singletons and multiples from each social class (see table 4).

Table 4: social class of mothers of multiples, singletons and all mothers interviewed

Social Class	Multiple mothers (N=55)	Singleton mothers (N=118)	All mothers (N=173)
I	5 (9.1%)	13 (11.0%)	18 (10.4%)
II	26 (47.3%)	62 (52.5%)	88 (50.9%)
III Non Manual	17 (30.9%)	28 (23.7%)	45 (26.0%)
III Manual	3 (5.5%)	6 (5.1%)	9 (5.2%)
IV	0 (0%)	3 (2.5%)	3 (1.7%)
Student	0 (0%)	1 (0.8%)	1 (0.6%)
Housewife	4 (7.3%)	5 (4.2%)	9 (5.2%)

The multiple birth mothers were much less likely to have a normal vaginal delivery only 12.5% compared to 40.3% of singletons. The multiple birth mothers were also significantly more likely to have an emergency caesarean, with 42.9% requiring one compared to 22.7 % of singletons (Chi square with continuity correction 6.556 df = 1, P = 0.010). (See table 5 for details).

Table 5: type of delivery for mothers of multiples, singletons and all mothers interviewed

Type of delivery	Multiple mothers (N=56)	Singleton mothers (N=119)	All mothers (N=175)
Normal vaginal	7 (12.5%)	48 (40.3%)	55 (31.4%)
Ventouse	4 (7.1%)	19 (16.0%)	23 (13.1%)
Forceps	5 (8.9%)	7 (5.9%)	12 (6.9%)
Elective Caesarean	16 (28.6%)	18 (15.1%)	34 (19.4%)
Emergency Caesarean	24 (42.9%)**	27 (22.7%)**	51 (29.1%)

** p=<0.01

2.3-i The Babies

The median age of the babies at time of interview was 8.6 weeks. However, the multiple birth babies were significantly older at time of interview median age 11.5 weeks compared to the singletons median age 7.7 weeks (Z = -6.039, P = < 0.001). This reflects the fact that the multiple birth babies were more likely to be born prematurely and to be in hospital longer before they went home and their mothers were contacted for interview. Details regarding prematurity were available for 169 babies, the multiple birth babies were born significantly more days prematurely, median number of days premature 27 compared to singletons median number of days premature 3 (Z = -8.196, P = < 0.001). The multiple birth babies were also significantly more likely to be born very prematurely (less than 32 weeks gestation) with 5 (9.4%) born very prematurely compared

to only 2 (1.7%) of singletons (Fisher's Exact Test p = 0.032). (See table 6 for details).

When comparing the weight of the singleton and multiple babies the weight of the baby with the lowest birth weight in each set of twins or triplets, was taken; as expected the multiple babies weighed significantly less. The multiple birth babies had a median weight of 2,007g compared to a median of 3,300g for singleton babies (Z = -9.216, P = < 0.001). The multiple birth babies were also more likely to be classed as low birth weight babies (less than 2,500g) than the singleton babies with 73.2% being low birth weight compared to only 7.6% of singletons (Chi square with continuity correction 77.238 df = 1, P = <0.001). Moreover they were also significantly more likely to be very low birth weight with 19.6% weighing less than 1,500g compared to 1.7% of the singleton babies (Fisher's Exact Test p=<0.001) (see table 7 for details). The multiple birth babies because of their lower birth weight and greater prematurity stayed in hospital significantly longer than the singleton babies (although one singleton baby was still in hospital at the time of the interview). Multiples stayed in for a median of 9 days compared to a median of 4 for singleton babies (Z = -6.751, P = < 0.001) (see table 7 for details).

Table 6: details about the babies

Mothers	Statistic	Age in weeks at interview	No. of days premature	No. of days in hospital after birth	Weight in g of lightest baby
Mothers of multiples	**No.**	56	53	56	56
	Median	11.46***	27.0***	9.0***	2,070***
	Inter-quartile range	30-34	5.1-10	5-17.8	1,600-2,500
Mothers of singletons	**No.**	119	116	119	119
	Median	7.71***	3.0***	4.0***	3,300***
	Inter-quartile range	6-9.1	0-12	3-6	3,000-3,700
All mothers	**No.**	175	169	175	175
	Median	8.57	11.0	5.0	3,005
	Inter-quartile range	6.7-11.5	0-22.5	3-8	2,300-3,500

*** p=<0.001

Table 7: number and percent of babies born with low or very low birth weight by birth group

Type of delivery	Multiple mothers (N=56)	Singleton mothers (N=119)	All mothers (N=175)
Low birth weight (<2,500g)	41 (73.2%)***	9 (7.6%)***	50 (28.6%)
Very low birth weight (<1.500g)	11 (19.6%)***	2 (1.7%)***	13 (7.4%)

*** p=<0.001

The multiple birth babies were also significantly more likely to have had some complication with their health such as breathing problems, needing

an operation, jaundice etc than the singleton babies, 58.9% compared to 26.1% (Chi square with continuity correction 16.356 df = 1, P = <0.001). Multiple birth babies were significantly more likely to have needed to spend time in the Special Care Unit than singletons, with 27 (48.2%) of multiples having been in the Special Care Unit compared to only 9 (7.6%) of singletons (Chi square with continuity correction 36.065 df = 1, P = <0.001). These results suggest that the multiples may be harder to take care of.

2.3-ii Quantitative measures

The Edinburgh Postnatal Depression Scale (EPDS)

Mothers were told at the time of the telephone interview that they would be sent the EPDS to complete. Subsequently 102 of the 119 mothers of singletons (a response rate of 86%) and 45 of the 56 mothers of multiples (a response rate of 80%) returned the questionnaires. There was a trend for mothers of multiples to have higher EPDS scores (Mann Whitney U test z=-1.482, p=.069 (one tailed)) and to score above 12 indicating the mother was experiencing clinically significant psychological symptoms of depression (Fisher's Exact Test, (one sided) p=0.055) (see table 8).

Table 8: mothers' scores on the EPDS

EPDS	Mothers of multiples (N=45)	Mothers of singletons (N=102)	All mothers (N=147)
Median	6.0	5.0	5.0
Interquartile range	3 – 11	3 – 8	3-9
EPDS >12	15.6%	5.9%	8.8%

The Unsettled and Irregular Baby Scale (UIB)

The UIB scale was completed by 151 of the mothers, some mothers failed to return the questionnaires and some did not complete this scale as their baby was much older by the time we contacted them sometimes because the baby had been in hospital for a prolonged period. Scores on the UIB ranged from 10 to 70 and were normally distributed although the mean UIB score for the multiples was higher this was not statistically significant (Unpaired t test, t=-0.690, df=149, p=0.491 (two tailed)) (see table 9).

Table 9: babies' scores on the Unsettled and Irregular Baby Scale

	Multiples (N=46)	Singletons (N=105)	All babies (N=151)
Mean	36.41	34.75	35.23
Std. Deviation	12.64	14.01	13.59
Range	10-61	10-70	10-70

2.3-iii Results from the qualitative theme analysis

Ten themes were identified at the manifest and latent level, as described in the description of the analysis of the qualitative data. All the interview transcripts were then explored for evidence of these themes. When the mothers were asked how they felt emotionally, as mentioned in the discussion of the progress of the interview the majority of mothers (40%) responded with the culturally socially acceptable response of fine or okay and even if the mother went on to elaborate further this impression was not refuted. However over a quarter of all mothers responded with a very

positive assertion about how happy they were because of the birth of their baby for example-:

> "Wonderful, the best thing that's happened to us, absolutely marvellous." (1807, singleton mother)

> "Really good really happy, over the moon."
> (1127, mother of multiples)

A very small proportion of mothers (7%) did describe how they were feeling depressed or very emotionally stressed at the present time or had done so earlier; for some this was associated with problems with the baby, the mother or other family member for example-:

> (N.B. Baby born very premature under 2LBS and then very ill, transferred to a hospital far from home, interview done at 6 months with the baby still in hospital)
> "And I found it very difficult when I came back. When I came back I think that was the worst time, I don't know why. I just felt I needed a lot of support, and my husband's not one to put his arm round your shoulders and say oh cheer up X because he's just as worried as I am. And I really was stressed out I felt I was so stressed out for about 2 or 3 weeks." (1753, singleton mother)

> (N.B tape not recorded properly so relying on notes.)
> "It was very hard at first. I was breast feeding for 3 weeks and it was too much I got too tired and was not eating well and lost weight and became very low in myself. I felt guilty." (1243, mother of multiples)

Some mothers (13%) talked of how they had experienced what they often termed 'the baby blues', this was clearly identified as something that was transient and had now passed. Examples of this theme are:-

> "I only had one weepy time at all which was about the third day after the baby was born which I think is quite normal and I just burst into tears for no reason the third and fourth day, and after that I was fine." (1825, mother of singleton)

> "Just normal baby blues in hospital." (1045, mother of multiples)

A few mothers (8%) talked of how they had felt emotionally labile experiencing different emotions on different days. For example the mothers describe:-

> "I have my good days and my bad days. Some days I feel as though I'm doing everything wrong and I can't cope other days I feel fine." (1103, mother of singleton)

> "I have good days and I have bad days so it's very variable…." (1375, mother of multiples)

Three themes showed a clear connection between how the mother was feeling emotionally and the impact of the baby on her. One such theme was emotional well-being linked to worry over the baby or babies this could be in terms of the baby's health, crying, feeding or trying to care for two babies at once, and this was seen in 22% of the transcripts, for example:-

> "I just start to enjoy him and not worry when something happens." (1057, mother of singleton)

> "Yes it's probably the worst bit really trying to juggle with them." (1809, mother of multiples)

The reverse to this was seen in the theme mother's well-being linked to seeing her baby as easy, getting into a routine and her feeling confident as a mother. This theme was less common only appearing in 14% of the transcripts. For example:-

> "Mentally very happy – feel that now more in control and am able to understand my baby's daily pattern more."
> (1049, mother of singleton)

> "I've just got to the stage when they do settle in the evenings and I do have the evenings with my husband."
> (1751, mother of multiples)

The last theme showing this connection was the very rare theme questioning parenthood, seen in only 3% of the transcripts, in which the mother questioned her decision about parenthood in terms of becoming a parent or with regard to her decision to have more than one baby. For example:-

> "I thought what have we done here have we done the right thing."
> (1045, mother of multiples)

Two themes relate to how the mother was feeling physically. As might be expected many mothers mention feeling tired, or having been very tired, one might have expected this would have been even higher than the 32% of mothers for whom this theme was identified, however some mothers went on immediately to explain how they were compensating for this

tiredness or to deny that it was affecting them. Examples of the theme are:-

"Tired, still tired. Exhausted to begin with."
(1033, mother of singleton)

"Very tired obviously having two." (1015, mother of multiples)

A small proportion of mothers (15%) mentioned past or present physical health problems or issues about changes to their bodies for example:-

"…. still aware that my pelvic floor muscles require toning up. Almost back to my normal weight (4lbs to lose), although I'm a different shape – my waist seems thicker."
(1109, mother of singleton)

"Physically sort of one problem after another blocked ducts things like that. So that's the only thing physically I'm quite run down."
(1257, mother of multiples)

As mentioned in the description of the analysis of the qualitative data two themes were generated deductively based on past theory and research. The IVF mothers in our study had provided evidence of how valued the role of motherhood was to them by undertaking the emotional, physical and financial costs of the IVF treatment. Champion and Power's social cognitive theory of depression suggests that if this highly valued role is threatened mothers may be more vulnerable to depression (Champion and Power 1995). Mothers might be particularly vulnerable if their babies were low birth weight, premature or ill; all factors recognised as making caring for a new baby harder, and thus threatening the role of motherhood. Moreover Beck's meta-synthesis of qualitative studies had shown that an

incongruity between expectations and the reality of motherhood was involved in postpartum depression (Beck 2002)[c] and so it was essential to explore whether there was any incongruity for these IVF mothers between their expectations and the reality of motherhood. The inductively generated themes 'emotional well-being – worry over the baby or babies' and emotional well-being linked to easy baby and feelings of confidence as a mother had revealed how the baby impacted on the mother's well-being, suggesting this may be a pathway for those expectations not to be met. All the transcripts were therefore explored for any evidence of the mothers' expectations not being met and the theme 'expectations of motherhood or of self as a mother – not met' was generated.

A proportion of the mothers (13%) did make some mention of how the experience of mothering or motherhood had been different from their expectations in a negative way. Mothers talk of their expectations in a number of ways, some talk of how they find motherhood hard work or more difficult than they had expected. For example-:

> "It was a shock, I think just having a baby in general was a shock because I didn't expect all the night feeds and being up and because I was breast feeding it meant I was up every 3 hours, so it was a bit of a shock I don't think I had quite anticipated that, but it was happy though." (1067, mother of singleton)

> "I think the first 6 weeks were bad. I wasn't prepared for the just total 24 hour commitment to somebody else. I don't know if it was my age or just because I hadn't come to terms with it and then suddenly I was faced with them." (1291, mother of multiples)

Others talk of the very high expectations they have of themselves as mothers, for example-:

"I feel mortified if I don't know exactly why he is crying. If I can't bring his wind up I'm traumatised I think I should be able to do it. So it does feel a bit pressured." (1101, mother of singleton)

"The only thing I'm finding hard is not having one to one contact with either of them. Feel like a production line putting one down to deal with the other." (1107, mother of multiples)

Other mothers talk of how the reality of motherhood is different to their expectation, for example-:

"It was not how I expected to feel. I suppose you have a lot of expectations. After been trying to have a baby for 8 years it's hard to show you are feeling a bit down." (1041, mother of singleton)

"I do feel a bit as though we're always going to have these worries because of that I'm not enjoying them as much as I'd hoped I would be." (1301, mother of multiples)

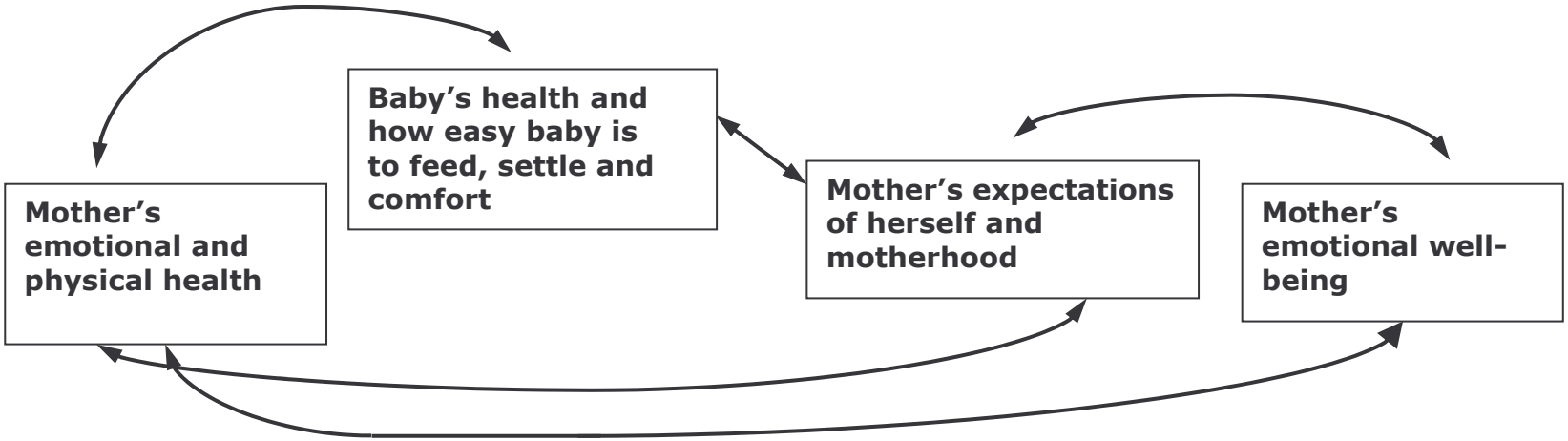
Mays and Pope suggest that one way to improve the validity of qualitative research is to search for alternative explanations and to explore for elements which might contradict any emerging explanation (Mays and Pope 2000). Mothers' accounts of their experiences were therefore also explored for any mention of the experience being better than they had expected. Very few (4.6%) of mothers talked of the experience being better than they had expected, for example:-

"I mean I wanted a child so much anyway and I always had high expectations but it's even better than I thought, I love it."
(1311, mother of singleton)

> "They're a handful, but I knew they would be. Everything that's happened I've expected it to be either worse or the same."
> (1213, mother of multiples)

However, this comment by the mother of multiples does imply that her expectations were quite low to start with. Expectations of mothering ability and of the experience of mothering appear to contribute to the mother's emotional well-being and may be one path to depression if she cannot meet her expectations of herself. These expectations will inevitably interconnect with how the mother feels and how she finds the baby. Figure 2 is a model showing these interconnections.

Figure 2: interconnections between the mother's emotional well-being, her expectations of motherhood, and the baby and mother's health



2.3-iv Themes significantly discriminating between mothers of singletons and multiples

As described in the analysis section 2.3-vii all the transcripts were explored for evidence of each of the twelve themes identified, and the number of singleton and multiple mothers mentioning each theme were cross tabulated, (see table 10 on page 92). Two by two tables were created for each theme with multiple birth (multiple birth/singleton birth) cross tabulated by theme (theme identified/theme not identified). Chi square analyses were carried out to look for significant differences with Fisher's Exact Tests used when expected frequencies were less than five. Previous research had suggested that mothers of multiples might be experiencing poorer emotional well-being and more difficulties parenting (Garel, Salobir et al. 1997; Colpin, Munter et al. 1999; Olivennes, Golombok et al. 2005; Freeman, Golombok et al. 2007), and four themes discriminated significantly between the two groups. One sided tests were used as the differences were in the predicted direction. (See figure 3 and table 10 which follow examples of these themes).

Tiredness

The mothers of multiples (46.4%) were more likely to talk of being tired without explaining how they compensated for this or expanding on how they felt this was not affecting their emotional well-being, than the mothers of singletons (32.8%), for example:-

> "Very, very tired have so many sleepless nights."
>
> (1045, mother of multiples)

> "Tired, still tired. Exhausted to begin with."
>
> (1033, mother of singleton)

(Chi square with continuity correction 6.934, df = 1, p = 0.004)

Worry over the baby or babies

This was talked about by (32.1%) of the mothers of multiples, for example:-

"Mentally I feel good on a good day if they cry a lot I feel bad." (1079, mother of multiples)

In comparison this was only identified in (17.6%) of the mothers of singletons transcripts, for example:-

"At the beginning it was hard the worst time was about 3 weeks after he was born he was crying all the time." (1267, mother of singleton)

(Chi square with continuity correction 3.821 df = 1, p = 0.025)

Emotional well-being – feeling down, depressed or emotionally stressed now or earlier

As already described a small number of mothers had experienced, or were still experiencing feelings of stress and or depression. Although overall the numbers were low the theme was identified significantly more often in the transcripts of the multiple mothers (14.3%), for example:-

"So I'm not so good I think I suffered a bit of post natal afterwards." (1129, mother of multiples)

Compared to (4.2%) of the mothers of singletons, for example:-

"I was suffering from post natal depression about two weeks ago they've given me some drugs for that as well that's helped a lot." (1781, mother of singleton)

(Fisher's Exact Test, p = 0.023)

Questioning parenthood

This theme reflected the mother expressing some doubts about her decision with regard to parenthood or with regard to having a multiple birth. This theme was also identified only rarely but again was significantly more likely in the mothers of multiples (7.1%), for example:-

> "Have my thoughts, do sometimes think if only there was one." (1295, mother of multiples)

Compared to only one mother (0.8%) of a singleton, who explained:-

> "I wouldn't go through IVF again it was our third and last try but worried if I was pregnant naturally. All these years I wanted it to happen, and now I just dread it." 1041, mother of singleton)

(Fisher's Exact Test, p = 0.037)

Two themes were identified significantly more often in the transcripts of the mothers of singletons, as this was unexpected two tailed test of significance were used. (See figure 3 and table 10)

Feeling wonderful

Mothers of singletons were more likely to describe how well they felt emotionally and how delighted they were with their baby (32.8%), for example:-

> "On cloud nine with her." (1025, mother of singleton)

Compared to (16.1%) of mothers of multiples, for example:-

> "Really good really happy, over the moon."
> (1127, mother of multiples)

(Chi square with continuity correction 5.336, df = 1, p = 0.033)

Emotional well-being - talk of having experienced 'baby blues'

The mothers of singletons were also significantly more likely to describe having experienced something often described as the 'baby blues (17.6%) for example:-

"Sometimes I felt a bit tearful a bit emotional at the slightest thing." (1033, mother of singleton)

Evidence of such a transient mental state was much less common for the mothers of multiples (5.4%) for example:-

"I had like blues a bit the first few days after I had them but that soon went it didn't stop long." (1763, mother of multiples)

(Chi square with continuity correction 3.877, df = 1, p = 0.049)

Figure 3: Graph showing themes significantly discriminating between IVF mothers of singles and multiples

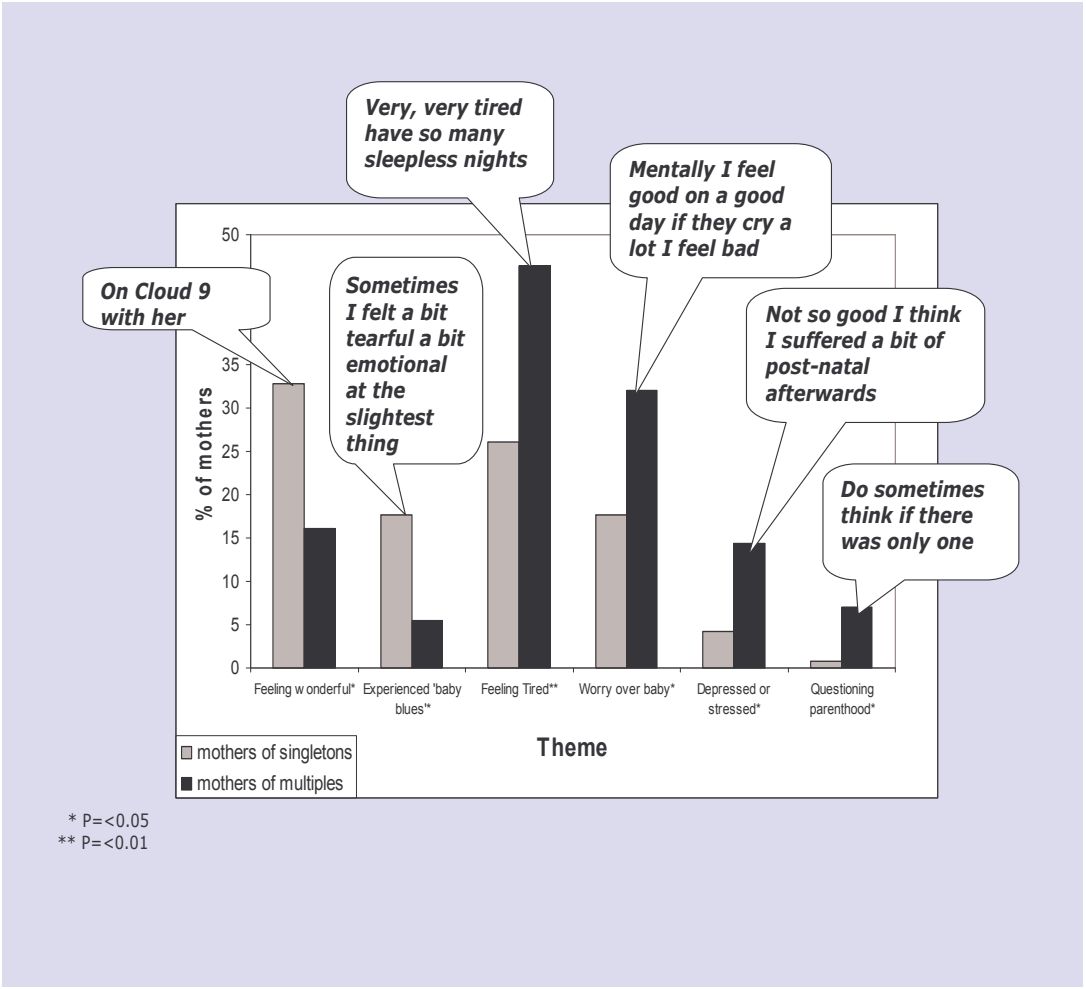


Table 10: percentage of singleton, multiple and all mothers in whose transcripts each theme was identified

Theme	No. and % of singleton mothers	No. and % of multiple mothers	P values
Feeling wonderful[a]	39 32.8%	9 16.1%	<0.05
Feeling tired[a]	31 26.1%	26 46.4%	<0.01
Feeling down depressed or emotionally stressed now or earlier[a]	5 4.2%	8 14.3%	<0.05
Emotional well-being – worry over the baby or babies[b]	21 17.6%	18 32.1%	<0.05
Questioning parenthood[b]	1 0.8%	4 7.1%	<0.05
Talk of having experienced 'baby blues'[b]	21 17.6%	3 5.4%	<0.05
Emotional well-being linked to easy baby and feelings of confidence as a mother[b]	16 13.4%	9 16.1%	NS
Feeling fine[a]	52 43.7%	18 32.1%	NS
Feeling emotionally labile[a]	8 6.7%	6 10.7%	NS
Physical health problems or body changes[a]	16 13.4%	10 17.9%	NS
Expectations of motherhood or of self as a mother – not met[bc]	15 12.6%	8 14.3%	NS
Expectations of motherhood surpassed[bc]	6 5.0%	2 3.6.%	NS

[a] Manifest level theme
[b] Latent level theme
[c] Theme generated deductively form past research and theory

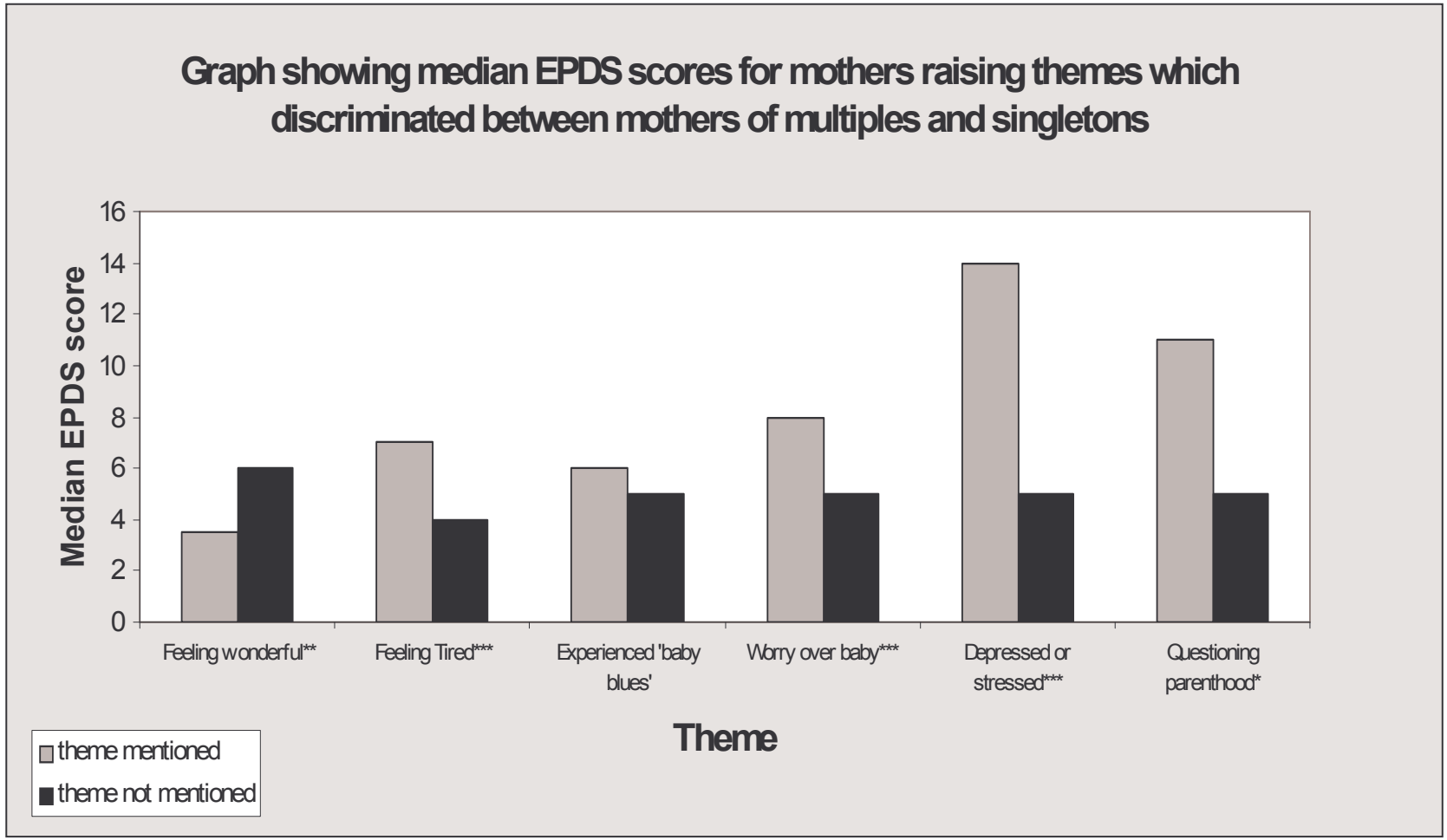
2.3-v Triangulation

An important function of qualitative data as described by Pope and Mays is to support, or triangulate with other data (Pope and Mays 1995), and so further analyses were carried out to explore how the qualitative data triangulated with the quantitative data collected. Six themes had been found to significantly discriminate between mothers of singletons and multiples, the EPDS scores of mothers in whose transcripts these themes had been identified were compared with the EPDS scores of mothers whose transcripts had not provided evidence of the theme. Four themes: 'feeling down depressed or emotionally stressed now or earlier', 'feeling tired', 'questioning parenthood' and 'emotional well-being – worry over the baby or babies' were identified significantly more often in the mothers of multiples replies and could be seen as negative or indicating feelings of low emotional well-being, mothers for whom this theme was identified in their response had significantly higher EPDS scores. (See table 11 and figure 4). The theme 'feeling wonderful' had been found significantly more often in the replies of mothers of singletons and furthermore the EPDS scores of mothers whose replies revealed this theme were significantly lower indicating greater emotional well-being. There was no significant difference in the EPDS sores of mothers in whose replies the theme 'talk of having experienced the 'baby blues' was identified (see table 11 and figure 4).

Table 11: comparison of EPDS scores for themes which significantly discriminated between mothers of multiples and singletons

Theme	Theme identified		Theme not identified		Z value	P
	N	Median & (Inter-quartile range)	N	Median & (Inter-quartile range)		
Feeling tired	57	7 (4–11)	118	4 (3-7)	-3.239	<0.001
Worry over the baby	39	8 (4.5– 12)	136	5 (2.8 –7)	-3.826	<0.001
Feeling depressed or stressed	13	14 (11–16.5)	162	5 (3–8)	-4.077	<0.001
Questioning parenthood	5	11 (6.5–12.5)	170	5 (3–8)	-1.935	<0.05
Experienced 'baby blues'	24	6 (4–10.5)	151	5 (3–8.3)	-1.183	NS
Feeling wonderful	48	3.5 (1.25–7.8)	127	6 (4–9)	-2.504	<0.01

Figure 4: Graph to show median EPDS scores for mothers raising themes which significantly discriminated between mothers of multiples and singletons



*p=<0.05 **p=<0.01 ***p=<0.001

To further explore the impact on the mothers of not having their expectations of motherhood or of themselves as a mother met, EPDS scores of mothers whose transcripts revealed this theme were compared to the EPDS scores of mothers whose transcript did not. Mothers who indicated that their expectations of motherhood or of themselves as a mother had not been met did have significantly higher EPDS scores (n=18, median=10.5) compared to mothers whose transcript did not reveal this theme (n=129, median=5) ($z=-3.839$, $p<0.001$). These mothers were also significantly more likely to score above 12 on the EPDS, indicating they were experiencing clinically significant psychological symptoms of depression. Of the mothers who mentioned their expectations in a negative way 27.8% scored above 12 compared to 6.2% of those who did not mention their expectations in a negative way, (Fisher's Exact Test, (two sided) $p=0.011$).

For some mothers a theme 'emotional well-being linked to worry about the baby' had been identified and we were interested to see how the quantitative measure of finding the baby unsettled and irregular fitted with how the mother felt. Mothers for whom the theme 'emotional well-being linked to worry about the baby' had been identified did rate their baby as significantly more unsettled and irregular (n=32, mean=41.38) compared to mothers for whom this theme was not identified (n=119, mean=33.61), ($t=-2.941$, $df=149$, $p=0.04$ (2 tailed)). Although this theme had been identified significantly more often in the responses of the multiple mothers previous analysis of UIB scores (see table 9 page 79) did not show that mothers of multiples rated their baby as significantly more unsettled and irregular than mothers of singletons .

2.3-vi Further Analyses

The more unsettled and irregular mothers rated their babies the higher they scored on the EPDS indicating lower emotional well-being (Spearman Rho r=0.453, n=139, p<0.001). In order to look at this relationship in more detail while controlling for other factors which might have had an impact on the mothers' well-being but differed significantly between the mothers of singletons and multiples a stepwise regression analysis was performed. Mother's total EPDS score was the dependent variable with the following factors entered into the regression: multiple birth, mother's age, baby's age at the time of the telephone interview, whether the mother had a caesarean delivery, if the baby had been in the Special Care Unit, was born at less than 32 weeks gestation or was very low birth weight (less than 1,500g) and the baby's Unsettled and Irregular Behaviour score (UIB). Only baby's Unsettled and Irregular Behaviour score was significantly associated with mother's total EPDS score, this accounted for 16.5% of the variance (see tables 12 and 13). At this stage after the birth of their baby or babies the most important predictor of a mother's score on the EPDS is how unsettled and irregular she finds her baby's behaviour.

Table 12: stepwise Regression Model Summary Table

Model	R	R Square	Adjusted R Square	SRD Error of the Estimate
1	0.414[a]	0.171	0.165	4.00426

[a] Predictors: (Constant), UIB score

Table 13: coefficients of variables entered

Coefficients[a]

Model	Unstandardised Coefficients		Standardised Coefficients	t	Sig.
	B	Std. Error	Beta		
1 (Constant)	1.315	0.950		1.385	0.168
UIB score	0.131	0.025	0.414	5.258	0.000

[a] Dependent Variable: total EPDS score

In order to explore the effect of a multiple birth on an EPDS score >12 a logistic regression was conducted with EPDS score >12 as the dependent variable and multiple birth (yes /no), maternal age, caesarean delivery, weeks postpartum, and UIB scores as independent variables. Once infant temperament was controlled for a multiple birth created a significant three fold risk of an EPDS score >12 (see table 14).

Table 14: logistic Regression with dependent variable EPDS >12

Variable	Significance	Odds ratio	95% C.I. for Odds ratio	
			Lower	Upper
UIB score (Unsettled and irregular behaviour)	0.006	1.076	1.021	1.134
Multiple birth (yes/no)	0.048	3.457	1.011	11.618

In order to explore further the effect of multiplicity on the mother's emotional well-being, given that Ellison and colleagues had found an increased risk of maternal depression for each increase in multiplicity

(Ellison, Hotamisligil et al. 2005), the logistic regression was repeated as above using number of babies as the independent variable instead of multiple births. Once UIB score was controlled for each additional child doubled the chance of the mother having an EPDS score >12 but this just failed to reach significance (OR=2.2, CI=0.904-5.393, P=0.08).

2.4 DISCUSSION

This study attempted to answer two research questions prompted by the social cognitive theory of depression (Champion and Power 1995) and a review of the research literature exploring the impact of a multiple birth on the mother's emotional well-being. Despite appearing a low risk group for post-natal depression 8.8% of the first time mothers in this study scored above 12 on the EPDS indicating clinically significant psychological symptoms of depression. In answer to the first research question we found a trend towards significance for mothers of multiples to score higher on the EPDS and to score above 12, with 15.6% scoring above 12 compared to only 5.9% of the mothers of singletons. These findings support Klock's suggestion in her review of the psychological adjustment to twins after infertility that mothers of multiples will be more vulnerable to depression (Klock, 2004). These rates were also higher than the 11.8 % found by Warner and colleagues in a large urban sample (Warner, Appleby et al. 1996) or the 12% reported by O'Hara and Swain in their analysis of prevalence of post-natal depression by method of assessment (O'Hara and Swain 1996). Analysis of the qualitative data also suggested a more negative experience and poorer emotional well-being for the mothers of multiples. The mothers of multiples' accounts offered some support for the findings of other researchers that mothers struggle to meet the needs, and

treat as individuals, twins or triplets (Garel and Blondel 1992; Holditch-Davis, Roberts et al. 1999; Beck 2002[a]). The finding that the theme "questioning parenthood" was more common in mothers of multiples might be considered controversial since mothers of singletons could not express doubts about a multiple birth. The theme has been retained because, although rare, it emerged from the data at the manifest level. Theoretically it was quite possible for mothers of singletons to express doubts relating to decisions about parenthood although only one mother did so.

An unexpected finding was that mothers' of singletons were significantly more likely to mention having experienced what was termed 'baby blues'. This appeared to contradict the finding that mother's of singletons were significantly more likely to express euphoric delight in their baby and were significantly less likely to mention more negative themes reflecting their experience of motherhood. However, reflection suggested what was important for these mothers was that their experience of poorer emotional well-being had been identified by themselves and in some cases by health professionals as well; as temporary, clearly passed and was common among new mothers. This was in contrast to the theme 'feeling down, depressed or emotionally stressed now or earlier' which reflected a distress seen as atypical, more disabling and not transitory.

In answer to the second research question, although multiple infants were not rated as significantly more irritable or irregular there was a correlation between mothers' ratings of infants' irritability and irregularity and their EPDS scores. More difficult infant temperament was associated with poorer postpartum mental health. Controlling for infant temperament resulted in a threefold increase in risk of scoring above the EPDS cut-off in mothers of multiples. This suggests that the combination of a difficult infant and a

multiple birth increases the mother's emotional vulnerability. Repeating the regression with number of babies rather than multiples showed support for Ellison and colleagues finding of an increased risk of maternal depression with each increase in multiplicity (Ellison, Hotamisligil et al. 2005), although a trend rather than statistical significance was achieved in our analysis, probably reflecting the lack of power due to the small numbers of mothers with triplets.

The finding of an association between infant temperament and poorer postpartum mental health confirms previous work suggesting infant temperament may combine with other vulnerability factors to increase the risk of depression (Cutrona and Troutman 1986; Murray, Stanley et al. 1996). The social cognitive theory of depression (Champion and Power 1995) suggests that if the highly valued goal of motherhood is threatened mothers are more likely to become depressed. This study found some evidence for this in so much as an association was found between higher scores on the EPDS and ratings of a more unsettled and irregular baby. However, this does assume that finding your baby more difficult to care for will make mothers feel less competent. For mothers of multiples the more infants born may arguably also increase their chance of having an infant with a difficult temperament. St James-Roberts and Wolke's initial study developing the mother and infant behaviour scale reports a mean score of 31.8 for the UIB for the forty, four day old breast fed babies in their sample (St. James-Roberts and Wolke 1988). This score is lower than that found for the singletons in this study and considerably lower than the score for multiples suggesting that the mothers in the present study were finding their babies unsettled and irregular. Although the babies in the present study were rated when they were older, no correlation was found between UIB score and baby's age.

Cutrona and Troutman suggested that one explanation for the link discovered between infant temperamental difficulty and maternal depression in their study was the mothers' feelings of resentment and disappointment that her infant was not as imagined during pregnancy (Cutrona and Troutman 1986); supporting further the link between expectations of motherhood and emotional well-being. The present study did not find that mothers of multiples were more likely to have their expectations of motherhood or of themselves as a mother not met however mothers whose expectations were not met did score significantly higher on the EPDS. This fits with the social cognitive theory of depression (Champion and Power 1995) which would suggest being unable to realise a highly valued goal would increase the risk of depression.

Mothers of multiples may have been protected by lower initial expectations of themselves. We know they were in general well-educated and are likely to have prepared for a multiple birth by talking to other mothers of multiples via support groups. Some support for this idea can be seen in the conclusions of the Avon Longitudinal study. Thorpe and colleagues found that although poor physical health was associated with poor emotional well-being for all pregnant women, and that women expecting twins had poorer physical health they did not have significantly higher scores on the EPDS at 18 or 32 weeks pregnant. The authors suggested that the women may have had lower expectations of health and have adapted their behaviour to adjust for the pregnancy more than women expecting a single child (Thorpe, Greenwood et al. 1995).

Qualitative analysis of the data revealed some of the complex interactions between the mother's emotional well-being, her expectations of

motherhood and how she is actually experiencing motherhood and provide further support for the impact of the baby's behaviour on the mother's emotional well-being. The themes "emotional well-being linked to worry over the baby" and "emotional well-being linked to easy baby and feelings of confidence as a mother" suggest the impact of the baby's health and temperament on the mother's emotional well-being. An observation further supported by the significant correlation ($r = 0.453$, $n = 139$, $p = >0.001$) found between higher scores on the EPDS and mothers rating their baby as more unsettled and irregular. The finding of what Cohen describes as a significant moderate correlation: an $r \geq .30$ (Cohen 1977) is also strengthened by the large sample size ($n = 139$) as Beck had found sample size and effect to be correlated such that the larger the sample size the smaller the effect or relationship between infant temperament and postpartum depression (Beck 1996)[a]. Further support comes from the finding that the variable UIB score entered a logistic regression to estimate the risk of an EPDS diagnosis of depression before multiplicity.

These findings concur with those of other researchers in highlighting the potential protective function of an "easy" baby (Beck 1996[a]; Murray, Stanley et al. 1996). More recently as already mentioned Pridham and colleagues have shown mothers' evaluation of care giving in terms of meeting expectations of herself as a mother were influenced by her infant's positive feeding behaviour and responsiveness (Pridham, Lin et al. 2001).

As expected multiple birth babies were more premature, lower in birth weight and spent more days in hospital before they went home than the singleton babies. These factors are likely to have made caring for these babies harder and to have placed greater strain on their mothers, this was reflected in the qualitative theme 'emotional well-being linked to worry

over the baby' which was identified significantly more often in the transcripts of mothers of multiples rather than singletons. The importance of the baby's present health rather than the degree of prematurity or length of stay in the neonatal unit for the mother's emotional well-being was also noted in a French qualitative study looking at the consequences of a very preterm birth for the family (Garel, Bahuaud et al. 2004). As mentioned in the introduction section 1.7 a study of the Australian birth records of ART conceived babies found that low birth weight and preterm twins were more likely to be born to first time mothers who were younger or older (Wang, Sullivan et al. 2005). This suggests a further cause of concern if potentially more vulnerable mothers will have to cope with these harder to care for babies.

One of the most interesting themes to appear inductively was the theme "feeling wonderful". Exploration of the literature had suggested that mothers of multiples might experience poorer emotional well-being after the birth however this theme revealed a more subtle shift in emotions with mothers of multiples merely expressing less delight than the mothers of singletons. This reflects the finding by Olivennes and colleagues that fewer mothers of twins (76%) than singletons (89%) in their study reported feelings of enormous pleasure (Olivennes, Golombok et al. 2005).

2.4-i Limitations of the study

The initial response to the invitation to participate in the study was low. Women were being asked to commit to a longitudinal study while still in the early stages of pregnancy and van Balen and colleagues have suggested a response rate of around 40% for this type of research is to be expected (van Balen, Naaktgeboren et al. 1996). Once recruited to the

study a high retention rate was achieved (87%). Whilst the low initial response rate may limit the generalisabilty of the findings, women accepting the invitation to participate in the study were found to be representative of a random sample of 100 women receiving treatment at the same clinic at the time of the study (Glazebrook, Cox et al. 2000). The women taking part in the study were a particular sample in that they were older: mean age of 33.8 years, than the mean age of 26.9 reported by the ESRC for first time mothers in the UK (ESRC 2005). Just over 70% of mothers were categorised as social class I or II as defined by the Standard Occupational Classification Manual (Office of Population Census. 1990). However, this demographic profile is typical of women seeking IVF treatment and other researchers have reported similar mean ages and high educational achievement suggesting superior social status (Leiblum, Kemmann et al. 1990; Goldfarb, Kinzer et al. 1996; Kalra, Milad et al. 2003). The only factor which impacted significantly on both the initial response rate (Glazebrook, Cox et al. 2000), and participation in the postpartum interview was conception using donor sperm. This may reflect a desire by the mother to ensure privacy and protect her partner.

The rate of multiples (32%) is higher than current national rates (23.6%) (HFEA 2006) because the study was carried out before the introduction of the HFEA guidelines restricting the number of embryos transferred to no more than two except in exceptional circumstances. This study did not include a control group of naturally conceived singletons or multiples and this could be seen as a limitation. However, the aim was to explore the impact of a multiple birth on a first time IVF mother, rather than to compare or contrast the experience of a multiple birth for mothers conceiving naturally or after IVF. Moreover including a naturally conceived control group of multiples would be difficult if mothers were to be matched

for age. Naturally conceived multiples are more common in older mothers, with 21.2 per 1,000 maternities being multiple births for women aged 35 to 39 in 2004 compared to 13.0 per 1,000 in women aged 25 to 29 (National Statistics 2005), whereas IVF conceived multiples are more common in younger women, reflecting their increased likelihood of a live birth regardless of the number of embryos transferred (Schieve, Peterson et al. 1999)

While scoring above 12 on the EPDS cannot be seen as indicating that a mother is experiencing post-natal depression it is a useful tool for detecting feelings of depression and poor emotional well-being and cut-off scores are widely used to indicate mothers are experiencing clinically significant psychological symptoms. Murray and Carothers have demonstrated the acceptability of the EPDS to a large representative community sample, with a response rate of 97.3% to a postal questionnaire; and report that using a cut-off point of above 12 they were able to correctly identify over 80% of mothers with major depression and 50% of those with minor depression (Murray and Carothers 1990). In addition McMahon and colleagues found in their study of older better educated mothers of singletons that a cut-off of above 12 for the EPDS gave high specificity (94%) and positive predictive validity (93%); however the sensitivity was low at only 52% but they suggest this was because the EPDS was completed at a different time point and asked about symptoms only during the preceding week whereas the diagnostic interviews were conducted when the babies were older and asked about all episodes of depression since the baby was born (McMahon, Barnett et al. 2001).

2.4-ii Strengths of the study

This study was prospective and with the exception of maternal age and number of week's postpartum at follow-up, the groups were well matched. Maternal age and week's postpartum were both controlled for in the quantitative analyses. During the interviews, mothers were requested to reflect on how they had felt at 6 weeks when collecting the qualitative data. Mothers of multiples tended to talk of how they were now in more of a routine and had been more tired previously, although potentially they could have been influenced by a greater number of sleepless nights. The comparable response rates for mothers of multiples and singletons also strengthened this study. Women were not more likely to reply if they had multiples, motivated by a desire to record a negative experience. Limitations of the study by Ellison and colleagues were the inclusion of mothers who were not first time mothers and the higher response rate from mothers of multiples (76%) than singletons (52%) (Ellison, Hotamisligil et al. 2005).

The major advantage of this study was the collection of both qualitative and quantitative data which enabled the production of not only a thick description of the experience of first time motherhood of an IVF baby/babies as advocated by Holliday (Holliday 2002); but also a composite analysis of the experience of motherhood after IVF. Yardley suggests that such a composite analysis goes beyond just bringing together qualitative and quantitative methodologies so that new organic ideas can emerge from a combining of all the data (Yardley and Bishop 2007). In this study the theme analysis of the qualitative data revealed some of the complex interactions between the mother's well-being, her expectations of herself and how she experiences her baby; thus explaining

some of the findings from the quantitative data. However, most importantly it revealed the emergence of the theme "feeling wonderful" which illustrates the advantages of a composite approach. Although both the qualitative and quantitative data found evidence of poorer emotional well-being and postpartum mental health this unexpected theme enables the emphasis to move from the disadvantages of a multiple birth to the positive impact of a singleton birth showing that for a third of mothers of singletons it was a very positive emotional experience.

2.5 CONCLUSIONS

This composite analysis found some support for the predictions, based on the social cognitive theory of depression (Champion and Power 1995), that mothers of multiples would have poorer post-partum mental health than mothers of singletons and caring for a more unsettled and irregular baby would impact on emotional well-being. These predictions generated the research questions explored in this chapter. Mothers of multiples scored higher on the EPDS than mothers of singletons indicating poorer emotional well-being and although this did not quite reach significance if infant temperament was controlled for a significant impact of a multiple birth was found. This suggests an additional impact of a harder to care for baby on a mother's mental health already made more vulnerable by a multiple birth. As suggested by the social cognitive theory of depression, there was an association between higher scores on the EPDS and mothers rating their baby as more irregular and unsettled. Multiple babies, although more likely to be premature and of low birth weight, were not significantly more likely to be rated as more unsettled and irregular than singletons.

However, if they were, the combination of a difficult infant and a multiple birth increased the mother's emotional vulnerability.

The qualitative data suggests a complex interconnection between the mothers' emotional well-being, her expectations of her mothering skills, her experience of motherhood, and the baby's health and temperament. Some significant differences were found between themes identified in the transcripts of mothers of singletons and multiples with the experience appearing to be more positive for the mothers of singletons. These mothers were only a few months postpartum and research suggests that the emotional consequences are likely to continue.

Demand for ART continues to increase. The new NICE guidelines recommend that 3 cycles of IVF should be offered to couples paid for by the NHS, in cases where the woman is between 23 and 39, there is an identified cause of the fertility problem or unexplained infertility for at least 3 years (NICE 2004). IVF treatment could therefore become available to women with fewer resources and who may be at greater risk of a multiple birth. Moreover, there is a danger that with women often waiting to start a family until they are in their thirties they may feel pressured to resort to IVF treatment earlier.

Prospective IVF parents are usually involved in the decision about how many embryos to implant and their decision will directly affect their chances of a multiple birth. This study confirms that couples not only need information about the physical risks of a multiple birth but also about the emotional consequences with mothers of multiples shown to be at increased risk of poorer mental health.

Analysis of the mothers' reflections on their early experience of motherhood revealed that mother's of singletons reported the experience as even more positive than mothers of multiples. One way to promote single embryo transfer may be to reframe the information for parents concerning decisions about the number of embryos to transfer, focusing not on the risks associated with a multiple birth but on the benefits of a singleton birth.

Mothers of multiples often have to care for and interact with infants who are premature and low birth weight factors which may well affect not only maternal mental health but also the way the mother interacts with her baby. Research studies discussed in the introduction to this thesis section 1.6 have shown that twins and higher order multiples are more likely to have cognitive and behavioural problems as they get older than singletons and this may be because of differences in the mother child interaction. The next chapter will explore what, if any, impact a multiple premature birth may have on early mother-infant interaction.

CHAPTER THREE - Study II: Impact of a multiple birth on early mother-infant interactions

3.1 BACKGROUND

The results of the previous chapter add to the growing body of evidence that a multiple birth will have a negative impact on the mother's emotional well-being. Mothers of multiples have an increased likelihood of experiencing depression (Haigh and Wilkinson 1989; Thorpe, Golding et al. 1991; Ellison, Hotamisligil et al. 2005) and have higher levels of parenting stress (Garel, Salobir et al. 1997; Colpin, Munter et al. 1999; Glazebrook, Sheard et al. 2004; Olivennes, Golombok et al. 2005; Freeman, Golombok et al. 2007). Since affective disorders can compromise maternal interactions with the child (Field 1995; Murray, Stanley et al. 1996; Cooper and Murray 1998), this clearly represents a further disadvantage for twin infants and, indeed Groothuis and colleagues found that twin status was predictive of subsequent child abuse (Groothuis, Altemeier et al. 1982). Of particular concern is that this psychological and social disadvantage is in addition to the established health risks for twins discussed in chapter two.

Multiple birth babies are significantly more likely to be born prematurely (born before 37 weeks gestation), with figures suggesting that half of all twins and most triplets will be born prematurely (Gardner, Goldenberg et al. 1995). The impact of this increase in twin births can be seen in the fact that for the United States, France and Canada 10% to 19% of all preterm births were attributable to twins (Blondel, Kogan et al. 2002). Moreover American researchers report that multiple births accounted for 26% of very low birth weight babies (<1,500g) in 1997-2002 compared to 19% in the early 1990s (Fanaroff, Stoll et al. 2007). This makes it difficult to study

the impact of a twin birth on the mother-infant relationship, since outcomes may be confounded by the negative effects of prematurity both on infant development and maternal interactions.

Twin studies which exclude premature infants neglect the potential additive disadvantages faced by a premature twin infant. Moreover, attachment theory as outlined in the introduction section 1.9 would predict that any disruption to early mother-infant interaction is likely to disturb secure attachment which may have long lasting consequences for the infant's cognitive and social development. This chapter will first consider the impact of a premature birth on maternal mental health and mother-infant interaction and attachment, and go on to debate possible reasons for this. The chapter will then explore the impact of a multiple birth on mother infant-interactions and discuss why these might be affected. Research looking at the contribution of attachment theory, birth status, social risk, mother-infant interaction and developmental outcomes, and whether interaction can compensate for early disadvantage will then be explored. Finally, the chapter will review the evidence suggesting a twin premature birth will constitute an additional disadvantage and then describe a study which examines this issue.

3.1-i The effect of a premature birth on maternal mental-health

Miles and Holditch-Davis in a review and summary of research on parenting the prematurely born child conclude mothers have intense emotional responses to the birth of a baby so premature it requires admittance to the Neonatal Intensive Care Unit (NICU) (Miles and Holditch-Davis 1997). These responses include anxiety, helplessness, fear, and loss of control, with some mothers also reporting feelings of guilt and shame. Such

responses stem from the stress experienced by mothers as they try to cope with their worries about the infant's health and possibly even survival, while dealing with being physically separated from their infant and distanced emotionally by their fragile appearance (Miles and Holditch-Davis 1997). Many studies describe how such stress impacts on maternal well-being. As already discussed in chapter one a study by Singer and colleagues found that mothers of very low birth weight babies were more likely to report symptoms of distress than mothers of full-term babies and that the impact varied according to the infant's age and health status with lower levels of distress for mothers of older infants and medically lower risk infants (Singer, Salvator et al. 1999). Davis and colleagues' study also previously described in chapter one found 40% of mothers of babies born at less than 32 weeks gestation had a score of 12 or above on the EPDS one month after their baby was admitted to the neonatal unit and higher scores on the Stress subscale of the Depression Anxiety Stress Scales were correlated with higher scores on the EPDS (Davis, Edwards et al. 2003).

Holditch-Davis and colleagues as part of their extensive research on premature infants and their mothers carried out semi-structured interviews with a convenience sample of 30 mothers 6 months after the expected date of delivery of their premature infants (Holditch-Davis, Bartlett et al. 2003). These interviews were analysed to identify three symptoms related to posttraumatic stress disorder: re-experiencing, avoidance, and increased arousal. All the mothers were found to have at least one symptom and more than half had all three; moreover number of symptoms was significantly correlated with higher scores on the Centre for Epidemiological Studies Depression Scale (CESD) indicating more depressive symptoms at enrolment to the study, and greater maternal stress about the NICU as measured by the Parental Stressor Scale- NICU.

3.1-ii Will a premature birth impact on early mother-infant interaction?

Given the findings of the influence of a premature birth on maternal well-being we might expect a premature birth to also impact on the mother-infant interaction. Evidence of such an impact will be explored in this section. Some early studies suggested mothers of premature infants worked harder and interacted more with their infants. For example, Beckwith and Cohen observed 123 premature babies ($\leq$ 37 weeks gestation and <2500g) from a range of racial and ethnic backgrounds in their own homes at 1 month corrected age (Beckwith and Cohen 1978). The authors found that the more obstetric and postnatal complications the babies were rated as having the more interaction they received from their primary caregiver independent of the duration of feeding. The authors suggest this increased interaction may help compensate for their poor start in life.

A study by Crnic and colleagues also found evidence of mothers interacting more during early interactions with their premature babies (Crnic, Ragozin et al. 1983). Mother-infant interactions were assessed by means of observation of unstructured play sessions and a standardised assessment: the Nursing Child Assessment Teaching Scale (NCATS). Observation measures of mothers of premature infants found them to be more active and stimulating, while their infants were less active, less responsive and both smiled and vocalised less than full-term babies. Both premature infants and their mothers appeared to be less positive and enjoy interacting less than full-term babies and their mothers. Significant differences were also found on the NCATS however, these showed mothers

of premature infants were less effective and less sensitive in their maternal behaviour as shown by lower scores on the sensitivity to child's cues, the social emotional growth fostering and the cognitive growth fostering subscales. Further evidence of the mother working harder during interactions with her premature infant is provided by Greene and colleagues. They found mothers of premature babies were more vocally responsive, and overall more responsive to their infants, when their infants were three months corrected age than mothers of full-term babies (Greene, Fox et al. 1983).

Jarvis and colleagues also investigated mother-infant interaction but included three groups of premature infants: healthy premature babies (< 37 wks gestation, < 2500g and no major medical complications) severely ill premature babies (< 37 wks gestation, < 2500g and bronchopulmonary dysplasia) and moderately ill premature babies (< 37 wks gestation, < 2500g with respiratory distress symptoms requiring mechanical ventilation for at least 3 days) (Jarvis, Myers et al. 1989). This study found degree of illness in the premature babies did impact on mother-infant interactions when the infants were four and eight months corrected age. Mothers of the sickest premature babies had lower scores on the NCATS, they were found to be less sensitive to their baby's cues, showed less response to their baby's distress and scored lower on the social-emotional growth fostering sub-scale than mothers of healthy and moderately ill premature babies. Moreover their scores on these sub-scales declined from four to eight months. However, there were no significant differences between the groups for the NCATS child sub-scale scores. Of interest in this study was the finding that the mother and moderately ill infant dyads scored higher on the NCATS than the healthy preterm group the authors suggest this may have been because these mothers visited their babies more while in

hospital although there is no data on this. If these differences in mother child interaction extend beyond eight months this may go some way to explaining the differences in developmental outcome found between groups of premature infants as already discussed in the introduction to this thesis.

Differences in the quality of interaction between mainly middle-class parents and their premature or term infants were explored by Harrison and Magill-Evans (Harrison and Magill-Evans 1996). This study of 54 term and 49 healthy preterm (mean gestational age 34.1 weeks) infants also used the NCATS as well as measures of parenting stress and support. The study found parents of preterm infants had significantly lower scores on the NCATS subscales response to distress, social emotional growth fostering and cognitive growth fostering as well as the total score. However, they found no significant differences in the infants' scores. Parents' scores decreased over time with significantly lower scores reported for social emotional growth fostering and response to distress at 12 months compared to 3 months. The authors found no significant interactions between group and time and so offer no simple explanation for why the parents of premature babies had lower scores. Levels of parenting stress as measured by the PSI were not correlated with NCATS scores nor did they find any evidence that the differences between the groups were due to differences in level of stress. One suggestion the authors make for the differences between the groups is that it may be to do with parents of premature infants having lower expectations of their infants this idea will be further explored in a later section of this chapter.

The inter-relationship between the effect of a premature baby on the mother and the effect this has on her subsequent interaction with her baby has been explored by a recent German study (Schmucker, Brisch et al.

2005). The study looked at mother-infant interactions for mothers with premature very low birth weight (<1,500g), and full-term babies at three months old. The premature babies were more vocally responsive but they and their mothers were less facially responsive than the full-term babies. Higher levels of maternal anxiety were associated with infants being less facially responsive; however neurobiological risk was also a factor as higher risk infants were less facially responsive.

An interesting study by Wijnroks looked at the interaction of 52 mothers and their premature (<37 weeks gestation) infants while playing at six months corrected age, mothers were divided into a high and low anxious group based on their recollections of their experiences surrounding their infant's hospitalisation (Wijnroks 1999). Mothers in the high anxious group were more active and intrusive during interactions with their infants than mothers in the low anxious group. Not surprisingly recollected anxiety was moderately correlated with the infants' biological risk factor, however it was not related to the infants current developmental status and the influence of recollected anxiety was described by the authors as being "relatively independent of the infant's current interactive behaviour" (page 404). The study cannot, however answer the question whether the mother's style of interaction will have an adverse effect on the baby's development.

In contrast a study of 46 low income immigrant Latina mothers and their very low birth weight ($\leq$1,750 g) babies found no significant differences in either the mother or baby's interaction between mothers defined as depressed (scored above 16 on the Centre for Epidemiologic Studies Depression Scale) or not (Ruttenberg, Finello et al. 1997). The authors had expected to find that depression would exaggerate interaction

difficulties, and debate whether their findings reflect the fact the scale used to measure depression was not sensitive for these mothers, or whether as mothers of premature babies they were all working much harder at the interaction so protecting the infant from any adverse effects of their depression.

A study by Murray and colleagues exploring the role of infant factors in postnatal depression and mother-infant interaction also found no clear relationship between neonatal functioning and the quality of mother-infant interactions when the infants were eight weeks old (Murray, Stanley et al. 1996). The infants were not premature in this study and were only recruited if over 38 weeks gestation and singleton births, however neonatal functioning as assessed by the Neonatal Behavioural Assessment Scale showed that poor motor scores and high irritability were predictive of the onset of maternal depression and were weakly but significantly correlated with less optimal ratings of face to face mother-infant interactions. The authors suggest that the vulnerability to depression in terms of psychosocial risk factors and the depression itself will impair maternal interaction and so over ride any impact of individual infant differences. The finding of the importance of motor functioning to the mother's emotional well-being is of particular relevance to any study of premature babies as they are highly likely to have poor motor functioning which the authors suggest will limit the opportunities for satisfying psychological engagement.

3.1-iii Will a premature birth impact on later mother-infant interaction?

An early longitudinal study by Crawford attempted to look at the influence of a premature birth on mother-infant interaction at a later stage (Crawford 1982). This study of 16 premature (<33 weeks gestation and <1,850g), and 17 full-term mother infant dyads over 14 months found mothers of

premature babies displayed more care-taking and affectionate behaviour towards their babies than mothers of term babies. The study provides few details about the sample or how they were selected although the groups were matched for maternal age, parity and social class. Unlike many studies however, the infants chronological ages were used meaning the premature babies were biologically younger at each time point they were compared and so differences in maturity could have explained the differences found. The authors concluded that the premature infants experienced as much interaction as the full-term infants over time but their mothers were not constant in the amount of time they spent in the same room as them. They suggest mothers may have been appropriately responding to their infants' current developmental level.

Greenberg and Crnic followed up 30 mother preterm (<38 weeks gestation and <1,801 g) and 40 mother full-term dyads who had taken part in an earlier study exploring differences between full and preterm infants during their first year of life (Crnic, Ragozin et al. 1983). The full-term infants were matched to the premature infants on infants' race, mother's education and whether they were a single parent family. Greenberg and Crnic found that by two years old there were no significant differences on any child development, mother child interaction or maternal attitudinal measure with the one exception that premature infants had significantly poorer motor skills (Greenberg and Crnic 1988). The authors point out that the premature babies in this study were relatively healthy and suggest differences found in other studies may reflect health status rather than prematurity. The mothers in the sample were also predominantly white and middle-class suggesting a relatively advantaged group.

However, Barnard and colleagues found in a study of 88 preterm (≤34 weeks gestation) and 166 full-term infants at four, eight and 24 months interacting with their mothers different patterns of interaction even at 24 months (Barnard, Bee et al. 1984). Initially the preterm infants were less responsive despite being a healthy sample (babies requiring assisted respiration were excluded), which their mothers responded to by increasing their levels of stimulation. By 24 months the premature infants were more responsive and involved however, their mothers were significantly less positive during the teaching task and described themselves as less involved with their child than the mothers of term infants did.

Further evidence of mothers having problems interacting with their infants comes from the study previously mentioned by Singer and colleagues. The study reported scores on the Parenting Stress Index (PSI) which indicated that mothers of high risk very low birth weight babies found their children at one and three years old to be more distractible, hyperactive and demanding with significantly higher scores on the child domain score of the PSI than mothers of term babies (Singer, Salvator et al. 1999).

Rocissano and Yatchmink explored the relationship between the child's linguistic skills and dyadic joint attention (Rocissano and Yatchmink 1983). Joint attention is the process of sharing one's experience of observing an object or event, by following another person's gaze or pointing gestures and is critical for social development, language acquisition and cognitive development. Twenty healthy premature babies (<36 weeks gestation and <2,500 g) and their working class mothers were observed interacting at 24 months and their language skills evaluated. There were wide variations in the infants' language abilities, and the infants were divided into two groups based on language ability. The high language group used word

combinations productively and talked about relations between objects and events, while the low language group used few word combinations and were limited in the relations they talked about. Differences in interaction were found between the groups. Mothers and infants in the high language group showed more synchronous turns (maintained their partner's previous focus of attention) when interacting and the authors suggest that because the mother follows the child's lead while interacting this reduces the burden on the child so allowing them more processing capacity for language learning. This study suggests ways in which differences in mother-infant interaction may account for the differences in language abilities often seen in prematurely born infants.

Gerner looked at emotional interactions between premature very low birth weight babies (<33 weeks gestation, <1,500g and with from 0-4 neonatal risk factors such as brain haemorrhage) and healthy full-term babies and their mothers, and reports finding no significant differences in face to face interactions at three months (Gerner 1999). However, the authors report that by six months, premature babies and their mothers interacted more poorly during feeding than full-term babies and their mothers; moreover this interaction was significantly correlated with psychomotor development at 10 months old.

A study by Holditch-Davis and colleagues attempted to further explore the relationship between prematurity, mother-infant interaction and later developmental status (Holditch-Davis, Bartlett et al. 2000). Forty-nine infants who had been born prematurely (mean gestational age 28.2 weeks) and their primary caregivers were studied when the infants were three years old using standardised tests including the HOME and the NCATS and naturalistic observations of interaction. Sub-groups of children with, and

without developmental problems including low IQ, language and attention problems were compared. Children in the low IQ group when in a play situation were more likely to be passive and not to play. Children in the normal IQ group scored higher on the NCATS responsiveness to parents sub-scale, while their mothers scored higher on the provision of play materials scale of the HOME and on the NCATS sensitivity to cues, social-emotional growth fostering, and cognitive growth fostering sub-scales. The mothers of children with language concerns were found to interact less, talk less, were more negative and scored lower on all the NCATS sub-scales and the HOME. Children with attention problems were found to be significantly more motor active and their mothers scored lower on the NCATS social and emotional growth fostering sub-scale.

The authors discuss the reciprocal relationship between the child's developmental status and the quality of their social environment; suggesting a positive feedback loop whereby the mother is less involved, so the child has poorer language comprehension and this in turn further discourages maternal involvement. However, the authors did not explore the possible additional impact of the child's prematurity on the mother-child interaction. Lack of responsiveness caused by prematurity may have contributed to the mother's lack of involvement and so been another element of the feedback loop.

More recently a study by Muller-Nix and colleagues concluded that maternal traumatic experience related to a premature birth had a long term influence on mother child interactions (Muller-Nix, Forcada-Guex et al. 2004). Mothers and their 47 preterm (<34 weeks gestation) and 25 full-term infants were observed during a play interaction at six and 18 months old. Maternal stress was evaluated using the Perinatal

Posttraumatic Stress Disorder Questionnaire and mothers were divided into a high or low stress group. The infant's risk factors were assessed with the Perinatal Risk Inventory and they were split into a high and low risk group. Significant differences in interaction were found at six months: mothers of high risk premature infants and mothers who were highly stressed were more controlling and less sensitive while playing with their infants. The authors suggest that the impact of maternal stress was greater than the impact of the infant's risk on maternal interaction.

By 18 months old there were no significant differences in maternal interactive behaviour between preterm and full-term dyads. However, the infants' behaviour was different at 18 months but only in relation to their mothers' stress scores with preterm infants of low stressed mothers scoring higher for passivity and infants of high stressed mothers scoring higher on compliance-compulsivity. These measures are taken from a seven item scale assessing mother and infants interactive behaviour with the infant's behaviour assessed according to four qualifications: cooperative, compulsive compliant, difficult and passive. Unfortunately they give no examples of these behaviours. This study emphasises the complexities of the impact of a premature birth on the mother child interactions.

3.1-iv Why do mothers and premature infants interact differently?

Prematurity Stereotyping

As mentioned earlier one reason why mothers of premature infants interact differently with their infants may be to do with their expectations of the infant. This idea was put forward by Harrison and Magill-Evans as a possible explanation for the differences they found in the interactions between mothers of term and premature infants (Harrison and Magill-

Evans 1996). This idea of parents viewing premature babies differently and having different expectations of them which will then lead to a stereotype of prematurity has been explored by a number of researchers. Leavitt found mothers responded differently to a baby's cries if they were told the baby was premature, normal or difficult (Leavitt 1999).

Stern and colleagues conducted a study to explore whether mothers would interact and rate differently full-term and premature babies randomly described as either full-term or premature (Stern, Karraker et al. 2000). Mothers were found to show more positive responses to babies labelled 'full-term' than to babies labelled 'premature'. Mothers of full-term babies showed more prematurity stereotyping than mothers of premature babies; the authors suggest this should be seen as an encouraging sign that actual contact with a premature baby reduces stereotyping and so will reduce the possibility of negative interactions. The authors introduced a brief cognitive intervention in the form of an information leaflet promoting the positive aspects of prematurity and this was given to some mothers of premature babies. However, the intervention rather than reducing stereotyping increased it with mothers' interactions being described by an observer as more negative if they had received the information leaflet. The authors suggest this may have been because the information made mothers more anxious about their behaviour and so more tentative and careful in their interactions.

The concept of prematurity stereotyping was further explored by Miles and Holditch-Davis as part of their research with a group of premature three year olds (Miles and Holditch-Davis 1995). The researchers carried out semi-structured interviews with the mothers when their infants were three years old and mothers completed the Maternal Attitudes Scale which

assesses mothers' perceptions of "a child born prematurely", "an average child" and "my child", as well as the Vulnerable Child Scale which explores mothers' perceptions of how vulnerable their child is, and the Social Assets Inventory which assesses mothers' perceptions of their infants' social strengths. Mothers were found to rate their child's characteristics as similar to those of an average three year old on the Maternal Attitudes Scale and Social Assets Inventory and more positively than a prematurely born child although they did rate their child as vulnerable with low scores reported for this scale. The authors found that when asked to rate prematurely born children the mothers did rate them much less positively than an average three year old suggesting that the stereotype persists despite parenting a prematurely born child oneself. However, mothers did not apply the stereotype to their own child and this seems to have been tied in with their viewing their own child as both special and normal.

A later study by Stern and colleagues further explored some of these ideas by looking at the effects of prematurity stereotyping, mother-infant interactions and the child's cognitive development (Stern, Karraker et al. 2006). Mothers were found to respond more negatively to babies labelled as premature perceiving them as less cognitively competent, weaker physically and mothers chose less appropriate: younger play programs. This finding was consistent across the age range from 5 to 12 months. However, there were individual differences in the mothers' ratings and some mothers of premature and full-term babies rated the prematurely labelled babies more positively. The authors found some evidence for stereotyping predicting later development. Mothers who rated their babies as more vulnerable, and mothers of premature babies who engaged in more prematurity stereotyping at five months had infants who achieved lower scores on the Mental Scale of the Bayley Scales of Infant

Development at 32 months old. The fact this relationship was not found at nine and 12 months suggests the relationship may be more complex. However, there does appear to be some evidence for a circular relationship. Poor interactions seem to confirm mothers' perceptions, which leads to further poor interactions and lowered expectations which then become self-fulfilling. A very recent study also found that higher perceptions of child vulnerability among mothers of premature babies were associated with lower scores on the Vineland Adaptive Behaviour Scales composite score (Hallenbeck 2002).

Infant problems

Another reason why mothers of premature infants interact differently with their infants may be because of problems with how the infant interacts with them. The study by Crnic and colleagues already mentioned as finding mothers of premature infants less effective and less sensitive in their maternal behaviour as shown by lower scores on subscales of the NCATS also found premature infants were less active, less responsive and both smiled and vocalised less than full-term babies (Crnic, Ragozin et al. 1983). The authors suggest the pattern of interaction is circular and reciprocal with the infant's unresponsiveness eliciting greater maternal activity, which the infant then tries to control by gaze aversion and inattentiveness.

Harrison and Magill-Evans however, although finding as already reported significant differences in mother-infants interactions between mothers of preterm and term infants (Harrison and Magill-Evans 1996) found no significant differences in the infants' scores. Moreover, infants' scores increased over time with both preterm and term infants becoming more responsive to their parents and clearer in their cues. The longitudinal

study by Crawford also found that although the 16 premature infants (<33 weeks gestation and <1,850g) were more fretful and vocalised less at six months than the 17 term infants by 14 months the only significant difference between the premature and full-term babies was that the premature babies vocalised less (Crawford 1982).

Landry and colleagues (1990) explored the additional effect of medical risk on the way premature infants interacted (Landry, Chapieski et al. 1990). This study observed three groups of infants: low birth weight and high medical risk (<36 weeks gestation, <1,600g and Bronchopulmonary dysplasia and severe degree of intraventricular haemorrhage), low birth weight and low medical risk (<36 weeks gestation, <1,600g and respiratory distress syndrome and mild to moderate degree of intraventricular haemorrhage), and healthy full-term controls interacting with their mothers in teaching and social contexts at three years old. Degree of medical risk was associated with the child's self directed behaviour with the high risk group showing less self-directed behaviours in both cognitive and social contexts than the low risk group. The high risk infants also showed more inappropriate responses to maternal directives than the full term infants. However, the authors argue the mother and children influence each others' behaviour in a similar way to that of mothers and their full-term children.

One aspect of mother baby interaction already mentioned as an important precursor to the development of problem solving and language skills is the development of joint attention. Garner and colleagues (1991) predicted that this might be particularly difficult for medically high risk, low birth weight babies (Garner, Landry et al. 1991). Their longitudinal study did find high risk low birth weight (<1,600g and intraventricular hemorrhage

grades III and IV with progressive dilation or bronchopulmonary dysplasia neonataly) infants showed deficits in their exploratory and communicative joint attention responses. The infants displayed more passive looking and a lower proportion of functional play at all times during their first 24 months than full-term and low birth weight, low risk (<1,600g and respiratory distress and or intraventricular haemorrhage grades I and II) matched controls.

3.1-v Will a multiple birth impact on early mother-infant interaction?

The research already reviewed suggests a premature birth does impact on the mother-infant interaction however findings are not always consistent with some suggesting the mother works harder and others that the mother is less sensitive and effective. There does appear to be evidence though, that differences in interaction impact on the infant's subsequent development. Mothers of multiples have to interact with more than one infant and this may be a separate and additional problem to that of interacting with a premature infant. Certainly twin status has often been quoted as a cause of language delay in children, however it can be hard to determine which of the three risk factors outlined by Rutter and Redshaw: biological risk factors, environmental factors or presence of same-age peer are responsible (Rutter and Redshaw 1991).

Rutter and colleagues used data from the Avon Longitudinal study of parents and children to explore these issues (Rutter, Thorpe et al. 2003). In the first part of the study they confirmed that the 96 twin pairs when compared to 98 singleton pairs (each singleton matched to a twin was paired with a sibling born within 30 months) did have slower language development and were about three months behind by three years old. The twins also showed a verbal cognitive score half a standard deviation below

the singletons. The study included only healthy twins free from disability and adjusted for the twins being born prematurely; with these controls the study found there was no association between any of the obstetric or perinatal features explored and language outcome.

In the second part of the study the investigators went on to explore whether patterns of parent child interaction and communication were causing this delay in language (Rutter, Thorpe et al. 2003)[b]. Using both standardised questionnaires and observations in the home they concluded that there were significant differences in the patterns of mother-child interaction. Mothers of twins provided fewer positive language interactions such as encouraging the child to speak or reading to the child and scored lower on the HOME for responsiveness, involvement and range of experiences provided. The authors maintain these differences did not reflect difference in the mother's education or social disadvantage as the groups were well matched; but rather suggest they were caused by mothers of singletons raising their level of interaction to the level of the older paired singleton. These studies offer some support for the theory that the delay in language development found in twins is caused at least in part by the presence of the twin.

Robin and colleagues in a study already mentioned in chapter 2 section 2.1-ii explored the problems of mother-twin interaction in a longitudinal study of 20 families of twins (Robin, Josse et al. 1988). The study outlined the difficulties mothers faced when trying to engage with two infants simultaneously. Mothers were found to respond to the problems of dealing with the situation along a continuum from treating the twins as a single unit to trying at all costs to maintain a dyadic relationship with each baby. More recently Robin and Casati argue that researchers should move away

from focusing on the dyadic relationship between mother and baby and focus instead on the triadic relationship (Robin and Casati 1994).

The study by Holditch-Davis and Roberts already mentioned in Chapter two section 2.1-iii looked at early parental interactions with, and perceptions of, seven sets of twins and one set of triplets compared to 49 singletons (Holditch-Davis, Roberts et al. 1999). Seventy five percent of the couples giving birth to multiples had had treatment for infertility as had 61% of the parents of singletons. The multiple birth babies were all healthy and term or near term. Parents were observed interacting with their babies at between two and three weeks after the baby came home and then a week later. These observations were naturalistic and in the case of multiples each baby was observed at the same time by a different observer. The study found that a multiple birth did impact on the parent child interaction this seemed to be at least in part due to time constraints as parents were observed spending as much time feeding and changing their babies which inevitably meant they had less time to spend with their babies in non care-giving activities. This was reflected in the concerns expressed by the parents during interviews about issues of attachment and spending quality time with more than infant. Multiple birth babies were also found to spend more time alone and interacting with someone other than their parents. In addition they had less visual and verbal contact than singleton babies. The fact multiples were more likely to be premature did not account for all the differences between the groups (Holditch-Davis, Roberts et al. 1999).

An interesting qualitative study by twin professors of family nursing looked at mother-twin attachment (Anderson and Anderson 1990). This study did not use the Strange Situation to assess quality of attachment using instead a grounded theory analysis of mothers' accounts of developing an

attachment to their twins over their first year of life. Individuation was the core category and this was assisted by the strategies polarisation and differentiation. Other major categories were maternal justice and support. Of interest is the fact mothers described how their infants' responsiveness was an important factor in helping them to identify personality characteristics to help polarise and differentiate their infants.

Feldman and colleagues suggested that the cognitive development of triplets may be less optimal because of their multiple birth status (Feldman, Eidelman et al. 2004). The authors argue that the high levels of stress experienced by mothers of triplets will make it harder for her to form a relationship with each child and so provide the sensitive mothering they suggest is essential for the infant's cognitive development. To explore these ideas they conducted a study of 23 consecutive sets of triplets born in Jerusalem matched with a set of twins and a singleton from the same hospital nursery. The babies were matched for birth weight (< 1661g), gestational age (<33 weeks gestation) and medical risk and for parental age and education with all families described as middle-class by Israeli standards. The infants and their families were assessed, and observed interacting postpartum and at three, six and 12 months corrected age. In addition the infants' cognitive development was assessed at 12 months corrected age using the Mental Development Index (MDI) of the Scales of Infant Development.

Parents of triplets were found, as expected, to be significantly more stressed than parents of twins or singletons with a mean overall score on the Parenting Stress Index above the 90th percentile indicating substantial stress. No significant differences were found related to multiple birth status for infants' emotion regulation as rated postpartum by the NBAS (a

measure of newborns' neuro-behavioural maturation developed by Brazelton). However, among triplets and twins the sickest infant showed worse regulation than their siblings.

Symbolic play (time spent in pretend play with self and or others) was assessed at 12 months corrected age by watching the infants play for 10 minutes with their mother and selected toys. Triplets were found to spend less time in symbolic play than twins and singletons. The sickest infant in both the twin and triplet group spent less time than their siblings in this type of play. Significant differences were found on the MDI with triplets scoring significantly lower than twins and singletons. The sickest triplet scored lower than its siblings but this was not the case for twins. Multiple birth status, higher emotion regulation, lower parenting stress and higher maternal sensitivity all predicted the infant's symbolic play. Cognitive development was predicted independently by lower medical risk at birth, multiple birth status, higher emotion regulation and higher maternal sensitivity. Although social support correlated significantly with parenting stress, maternal sensitivity and the infant's symbolic play and cognitive development it did not independently predict variance in symbolic play and cognitive development. The authors argue that their findings confirm the role of mother child reciprocal exchange in the infant's cognitive and symbolic growth. They also emphasise the particular stress of a triplet birth due to the inevitable decrease in exclusive parenting and increased parental stress and the increased risks to the sickest triplet.

Further study of these singleton, twin and triplet infants explored the infant's development over the first two years in relation to parental interaction patterns and the home environment (Feldman and Eidelman 2004). The authors argue being born and raised as part of a triplet set

does expose the infant to a unique risk because of the loss of the parents' exclusive focus and involvement which is impossible when two parents have to divide themselves between three infants. At two years old child behaviour problems were assessed with the Child Behaviour Checklist. Triplets scored higher on internalising problems and total behaviour problems than twins and singletons, and also scored higher on the Anxious/Depressed and Withdrawn subscales than the twins and singletons. Multiple regressions showed that behaviour problems were predicted by infant's medical risk, multiple birth status, maternal postpartum depression, parent-infant synchrony at 3 months and maternal adjustment at 12 months. Triplets with intrauterine growth retardation: a birth weight discordant from its siblings by more than 15%, were most disadvantaged receiving the lowest levels of parent-infant synchrony and showing the poorest behavioural outcomes compared to their siblings.

The authors maintain they found few differences between singletons and twins in parenting or child outcomes and claim that parents are able to access enough resources to deal with twins. However, they do suggest what they describe as a dose-response pattern with singletons showing more optimal outcomes than twins. They also maintain that the fact triplets are more likely to be born prematurely will interact with multiple birth status and enhance its negative effect.

3.1-vi Why do mothers and multiple infants interact differently?

The research reviewed so far suggests that having to interact with two infants at once will inevitably impact on the way the mother interacts with her infant, it may be however, that twin or triplet infants have unique characteristics which will also impact on this interaction. One such

characteristic might be the phenomenon described as secret twin language, which was explored in a study by Thorpe and colleagues (Thorpe, Greenwood et al. 2001). Data were collected from 76 pairs of twins and 80 pairs of singletons no more than 30 months apart, at 20 months, three and 6 years old. The authors found what they term 'shared verbal understanding' to be common among the children although twice as likely in twin as singleton pairs. The authors describe this as a normal developmental feature with young children just starting to speak being more understandable to each other than to their parents or other adults. Private language, described as a form of communication focused on the twin or sibling pair to the exclusion of others, was rare occurring at three years old in only 6% of the twin pairs and one singleton pair. Among four pairs normal language did not develop alongside this private language and at six years old their language and general cognitive functioning were substantially impaired compared to the three pairs where normal language developed at the same time. The authors found no differences in the home environment or patterns of parent child interaction which appeared to have caused the development of this private language however, it did seem to be preceded by poor language attainment. This study suggests that secret twin language per se will be unlikely to have an impact on mother-child interaction as it appears to be rare and usually caused by developmental problems.

A recent study investigating educational and behavioural problems in premature babies also explored the impact of social, antenatal and perinatal risk factors including a multiple pregnancy. The study followed up 176 of 187 babies born at 32-35 weeks gestation during 1990 whose mothers were resident in Oxfordshire (Huddy, Johnson et al. 2001). GPs, parents and teachers were asked to complete postal questionnaires about

the children's health, behaviour and education and teachers completed the Strengths and Difficulties questionnaire when the children were seven years old. The authors found, almost a third of the 117 children for whom data were available were identified as having school problems and 18% were rated as scoring abnormally high for hyperactivity compared to the 10% expected in a normal population. The authors looked at the effects of social risk factors on school performance however they only found maternal smoking was related to outcome, social class and maternal education were not. When looking at antenatal and perinatal risk factors multiparity was significantly related, however a multiple pregnancy was not although this may have been because of the small sample size with only 38 twins and 3 triplets. The authors went on to look at the interaction of risk factors by entering variables into a logistic regression, only two remained significant: discharge from the special baby care unit >36 weeks and male sex.

Although the study confirmed the longer term developmental disadvantages of preterm delivery it did not find significant interactions with multiple birth status or socio economic status. However, this was a small study with only 34 children identified as having poor school performance and the authors report a higher percentage of multiple births in the non-responders and a higher proportion of parents from social class I and II from the responders which may have masked these findings. Of interest is the finding that multiparity was associated with poor school performance suggesting there is a disadvantage when the mother has to share her attention in any interactions with the premature infant.

3.1-vii Can attachment theory help explain the links between birth-status, social risk factors, mother-infant interaction and infant development?

Attachment theory as introduced in the introduction section 1.9 would suggest that any problems with mother-infant interaction could affect the quality of attachment. Bee and Boyd describe how the newborn baby will use a repertoire of behaviours such as crying, making eye contact and responding to the caregiver's attempts to soothe; to interact and maintain proximity with the caregiver (Bee and Boyd 2002). However, the research discussed earlier in this chapter suggests that premature infants may be less active and responsive to their mothers than full-term infants (Crnic, Ragozin et al. 1983; Bee, Barnard et al. 1982) although other studies have found differences only in the mother's interactions not the infants (Jarvis, Myers et al. 1989, Harrison and Magill-Evans 1996).

Evidence for the importance of synchronous interaction comes from the finding reported earlier in 3.1-iii that premature infants with greater language abilities displayed more synchronous turns at 24 months than those described as having poorer language (Rocissano and Yatchmink 1983). More recently a study by Saxon and colleagues has explored mother-infant interaction profiles and later cognitive development (Saxon, Colombo et al. 2000). The authors found that for the majority of mother infant dyads (n=17) in their study interaction patterns between 6 and 8 months of age developed such that periods of joint attention increased while the mother's role in maintaining and initiating these periods decreased. However, for a small group of dyads (n=6) there was little joint attention despite high levels of maternal initiation. Infants in the larger group who showed improved quality of interaction had significantly higher scores on a measure of language ability at 24 months and cognitive ability at 40 months.

As mentioned in the background to this chapter, studies exploring the impact of maternal post-partum depression on mother-infant interaction have shown differences in the quality of the mother-infant interaction (Field 1995; Cooper and Murray 1998). Cooper and Murray argue that it is this impaired interaction which causes the association found between postnatal depression and poorer cognitive and emotional child development. An argument supported by the findings reported in section 3.1-v that one of the factors predicting behaviour problems at two years old was maternal post-partum depression (Feldman and Eidelman 2004).

Factors such as postnatal depression, birth status and social risk may interact, which could create an additional impact on mother-infant interaction and subsequent attachment. A study by Poehlmann and Fiese explored the possible interaction of maternal and infant vulnerabilities on developing attachment relationships (Poehlmann and Fiese 2001)[a]. Security of infant attachment was assessed using Ainsworth's Strange Situation and compared for preterm (>37 weeks gestation and >2500 g) and full-term infants, controlling for neonatal health complications such as Apgar score and days hospitalised and mother's sub clinical depressive symptoms. The authors excluded mothers scoring in the clinical range of the Depression scale of the Symptom Checklist-90-Revised in order to assess whether even sub clinical depressive symptoms would interfere with the mother's ability to sensitively respond to her infant. The primary finding of this research was that the combination of sub clinical depressive symptoms and preterm birth predicted infant-mother attachment with fewer infants securely attached after controlling for neonatal complications. The authors argue that contributions from both the infant and mother over time influence the quality of the dyadic relationship.

Such interactions may also explain some of the differences found in premature infants' cognitive and social development. The Bavarian longitudinal study mentioned in chapter one, section 1.6 followed up a large sample of 264 very premature children (<32 weeks gestation) and 264 full-term controls matched for socioeconomic status, mother's age and marital status until they were six years old (Wolke 1998). Compared to their matched peers the premature children scored significantly lower on all measures of cognitive and language abilities. The study also found that for all children socioeconomic status was related to cognitive and language outcomes, although for the premature children the effect of their preterm birth was greater than the effect of socioeconomic status, the effects of prematurity and socioeconomic status were independent from each other, thus becoming an additive or double jeopardy for some children.

A study by Miceli and colleagues suggests that although prematurity and low birth weight, were predictive of developmental outcomes by 36 months these outcomes were more closely related to aspects of the infants' early social environment (Miceli, Goeke-Morey et al. 2000). This study included 30 mother, and premature, low birth weight (<1,515g and $\leq$32 weeks gestation) infant dyads. They examined the effect of birth status (using a composite score derived from the infant's birth weight and gestational age such that a lower score indicates a younger, smaller infant), medical complications, maternal support and maternal distress on infant development at four, 13 and 36 months.

Birth status was associated with developmental outcome, with younger smaller infants showing less optimal development on the Bayley Scale of Infant Development mental and psychomotor scales at four and 13 months corrected age. However, if medical condition was entered into the model,

birth status no longer had a significant effect and medical condition accounted for between 22% and 37% of the variance. This is in agreement with other studies which have suggested that health status is more important then prematurity per se. The effect of these factors was shown to diminish over time as by 36 months they no longer had a significant effect.

This study made the very interesting observation that the early social environment became more important over time so that post-natal ratings of stress, depression and social support were related to infant outcome at 36 months. Infants whose mothers had reported greater distress were found to show more internalising and externalising behaviours as measured by the Achenbach Child Behaviour Check list at 36 months. Infants of mothers who reported greater social support were also found to show better receptive language functioning (as measured by the Peabody Picture Vocabulary Test) and fewer internalising behaviour problems at 36 months. These findings would fit with attachment theory with these infants being seen as less able to form a secure attachment.

An early study by Escalona followed up 114 low birth weight (<2,250g) premature (> 4 weeks) babies until four years old (Escalona 1982). The families were predominantly poor and from ethnic minority groups. After excluding babies with extensive brain damage at birth or severe mental retardation at seven months (IQ < 75) the 97 infants left in the study were found to decline on standardised measures of cognitive ability after the first year with the biggest decline at two years old. The authors report a significant difference in mean IQ scores as a function of social class from this age on. A high proportion (over 30%) of the sample, were also found to have serious behavioural maladjustment and this was related to lower

cognitive scores. A finding one would expect if attachment had been disrupted. The authors argue premature babies' development may be particularly vulnerable to environmental disadvantages.

Van IJzendoorn and colleagues carried out a meta-analysis of studies exploring the relative effects of maternal and child factors on the quality of attachment (van IJzendoorn, Goldberg et al. 1992). This was an attempt to evaluate the relative contributions of infant and mother behaviour to subsequent attachment. Only studies using the Strange Situation were included in the analysis and all were North American to avoid confounding cultural factors. The clinical samples (n=34, representing 1,624 Strange Situation classifications) consisted of those reflecting problems with the infant such as premature birth or deafness, problems with the mother such as psychiatric diagnosis or maltreatment and others such as studies of adopted infants. These were compared to normative samples (n=21, representing 1,584 Strange Situation classifications). Analyses showed that while maternal problems increased insecure attachment as classified using the Strange Situation there were few effects of child problems. The authors argue that when considering clinical samples the mother plays the most important role in quality of attachment and she can generally compensate for any potential handicap to the dyadic relationship posed by mental or physical problems with the child. This does however raise the question of how many problems the mother can compensate for? Perhaps a premature and multiple birth, would be too much?

The quality of mother-infant interactions and infant attachment might be expected to affect infant social and cognitive development. Many studies have explored these issues. Two early studies reported by Lewis and Coates in 1980 found that measures of maternal responsiveness and

mother-infant interaction were significantly positively correlated with measures of their infants' cognitive ability as measured by the Bayley Mental Development Index of the Bayley Scales of Infant Development (MDI) at 12 weeks old (Lewis and Coates 1980). However, the amount of maternal stimulation was not related to MDI scores. The authors also point out that, although strong, the correlations only account for 5% of the variance and that the study does not determine causality it may be that mothers are more responsive to infants who are more competent.

An important study by Laucht and colleagues in 2002 explored the role of mother-child interaction in the development of children at risk (Laucht, Esser et al. 2002). This prospective longitudinal study followed up a group of infants disadvantaged in terms of biological risk (obstetric complications) and psychosocial risk (family disadvantage), from birth to eight years old. Family risk factors were found to mainly affect cognitive and social emotional functioning, while perinatal complications affected motor and cognitive outcome. However, they found outcome was heterogeneous and the quality of both mother and baby interaction moderated the effects on outcome at school age, but this was much more important in the at risk infants. For example, very low birth weight infants were found to do better at eight years old, in terms of verbal intelligence the more varied maternal stimulation they received, and had fewer internalising problem behaviours the more sensitive and responsive their mothers had been during interactions at three months.

The baby's behaviour during interaction at three months was also important however, very low birth weight babies who smiled more at their mothers at three months old were found to do better in terms of behavioural and cognitive development at age eight. The authors suggest

that being smiled at was very rewarding for the mothers of low birth weight babies who responded by engaging more with their infants thus promoting their development. Another factor to consider here is that within the very low birth weight group of babies, babies able to smile more may have been less biologically vulnerable.

Further evidence of the complex interaction between risk factors and early mother-infant interaction was provided by a further study by these authors exploring early mother-infant interaction as a precursor to social withdrawal at four, five and eight years old (Gerhold, Laucht et al. 2002). Regression analysis showed that child behaviours such as smiling and gazing, and maternal behaviours including facial and motor responsiveness predicted social withdrawal; biological risks were also found to contribute to outcome. The authors suggest an interplay between biological risk and the pattern of early mother-child interaction whereby perinatal risks mean some babies smile and gaze less at their mothers, their mothers then respond by interacting on a more physical level in an attempt to evoke a response or to continue an interaction; this pattern of over stimulation may lead the infants to withdraw socially from their mothers.

Bakeman and Brown explored differences in early interaction between black, low socio-economic status mothers and pre-term (mean 32.4 weeks gestation, and $\leq$1,950 g) and full-term dyads (Bakeman and Brown 1980). Although, they found differences in early interactions between the dyads these differences did not predict cognitive ability or social development at age three. The only variable associated with outcome at three years was infant responsiveness. However, the authors argue that this may not be a true measure of interaction but rather a measure of the baby's temperament. Birth status did predict cognitive development with pre-

term babies, as predicted, doing worse. However birth status had no significant impact on social development at age three. This study provided further evidence for the cumulative effects of disadvantage with those babies born prematurely in this disadvantaged sample faring the worst developmentally at three years old.

Bee and colleagues carried out a comprehensive study looking at the prediction of IQ and language skill from perinatal status, child performance, family characteristics and mother-infant interaction (Bee, Barnard et al. 1982). They concluded that assessment of mother-infant interaction and measures of environmental quality were good predictors of later IQ and language development even in a healthy above average socio-economic group. The authors were surprised to find that among mothers with only high school or less education, greater social support was predictive of IQ and language development in their infants and expectations that their infant would benefit from being talked to earlier predicted greater receptive language skills in the infants.

A more recent study by Mantymaa and colleagues has looked at the impact of early mother-infant interaction on symptoms of emotional and behavioural problems in toddlers (Mantymaa, Puura et al. 2004). Fifty mother and healthy full-term infant dyads were observed interacting when the infants were between eight and 11 weeks old. Behavioural and emotional problems were investigated using the Child Behaviour Checklist (CBCL). Mother's whose interactions were scored as showing aspects of hostility and or intrusiveness had children with significantly higher externalising and total problem scores. The authors suggest that the child will try to avoid the mother's intrusiveness and hostility in interactions but

eventually if this is unsuccessful may become angry and frustrated and so display more externalising and problem behaviours.

3.1-viii Can maternal interaction compensate for disadvantage?

Researchers across disciplines have debated whether superior mother child interaction could enhance subsequent development or protect and compensate for early disadvantage such as from a premature or multiple birth. Attachment theory would suggest that increasing positive and reciprocal mother-infant interactions would increase the likelihood of secure attachment which in turn should lead to improved social and cognitive developmental outcomes for the infant. Although the previously mentioned study by Greenberg and Crnic found significant differences between premature and full-term infants at age two, only for motor development, they did find that the premature infants were more strongly influenced by the degree of direct stimulation provided in the home environment (Greenberg and Crnic 1988). The authors point out that the premature babies in this study were relatively healthy and suggest differences in development found in other studies may reflect health status rather than prematurity.

However, the authors suggest premature infants have a different developmental path than full-term infants. They maintain that caring for these vulnerable infants generated more positive attitudes towards their child and the parenting role which lead mothers to produce a more positive caretaking and home environment. They suggest evidence for this is shown by the significant positive correlations between the mothers' attitudes (a composite score of marital satisfaction, life satisfaction and satisfaction with parenting) and scores on the HOME (this included the

HOME subscales: provision of play materials and variety of stimulation). This positive environment in turn leads to superior developmental and behavioural interaction outcomes as shown by the significant positive correlations between the HOME score and the Bayley Mental Development Index (MDI) of the Bayley Scales of Infant Development, mean length of utterance, and increased mother child observed interaction scores at two years.

Regression analyses showed that for the preterm infants for most outcome measures at two years, 40-60% of the variance could be accounted for where as for full-term infants it was much lower at only 15-30%. This study suggests that for premature infants more positive caretaking and home environments can benefit their developmental functioning. The mothers in the sample were predominantly white and middle-class suggesting a relatively advantaged group which may explain how they were able to provide such a compensatory environment, mothers from a more disadvantaged background may be less able to do so.

More recently a study by Poehlmann and Fiese explored the quality of maternal infant interaction as a possible mediator between neonatal risk status and cognitive development at 122 months old (Poehlmann and Fiese 2001)[b]. Mothers and their full term (n=44), preterm low birth weight (>37 weeks gestation and >2500 g) (n=20) and preterm very low birth weight (>37 weeks gestation and >1500 g) (n=20) infants were observed interacting at 6 months and scored for degree of reciprocity and engagement. Infant cognitive skills were assessed at 12 months old using the Mental Scale of the Bayley Scales of Infant Development (MDI). Multiple regression analyses showed that, controlling for infant age, maternal demographic risk, neonatal risk (coded based on birth weight,

Apgar scores, length of hospitalisation and intubation and presence of respiratory complications) and the interaction between risk factors, quality of interaction predicted cognitive scores. More reciprocal, affectively positive and engaging interactions resulted in increased MDI scores at 12 months old.

An earlier study by Wille looked at the relationship between infant risk factors, mother-infant interaction and subsequent attachment (Wille 1991). The study found a greater proportion of preterm infants were insecurely attached at one year than full-term infants in a sample of 54 predominantly low socioeconomic status mother infant dyads. This study looked at the impact of a preterm birth (< 2500g at birth and < 36 weeks gestation) and perinatal medical status (baby required > 48 hours of oxygen or had intraventricular hemorrhage) on mother-infant interaction at 6 months and quality of attachment at one year. Preterm birth did predict quality of attachment as measured by the Ainsworth Strange Situation in this less advantaged group, with significantly more of the preterm infants classified as insecurely attached. Perinatal medical status did not have an impact on the quality of attachment at one year. Maternal interaction at six months did not mediate the impact of a preterm birth on attachment and the author suggests a combination of preterm birth and low socioeconomic status may have an effect on quality of attachment.

Gerner also found some evidence of vulnerable preterm infants being sensitive to environmental factors (Gerner 1999). This study of 20 premature infants (<1500g and <33 weeks gestation) and 20 full-term infants matched for mother's age, education, parity and infant's gender, observed the emotional interaction between mother and infant at three and six months corrected age. In addition the infant's development was

assessed at 10 months using the Griffiths mental development scale. There were no significant differences in the mother infant face to face interaction at 3 months between the preterm and full-term infants. However, mother's education did have a significant impact on interaction at 3 months: mothers with a higher level of education were evaluated as interacting better with their babies. By six months old the preterm infants had lower interaction scores. Although these scores did not correlate significantly with maternal or infant variables higher interaction scores did correlate with level of psychomotor development at 10 months. The author suggests that by six months the mother can no longer compensate for the disadvantages of a premature birth.

An American study by Spiker and colleagues also provides some limited support for the idea that premature infants may be more vulnerable to environmental disadvantage and so may benefit more than full-term infants from positive intervention (Spiker, Ferguson et al. 1993). The authors looked at the effects of an intensive and comprehensive long-term intervention, on the interaction of 683 low birth weight ($\leq$ 2,500g) premature ($\leq$37 weeks gestation) infants, with their mothers at age 30 months. Some small but significant positive effects were found. The intervention mothers were rated higher on quality of assistance and the intervention infants were rated higher for persistence, enthusiasm and overall ratings of child competence and involvement. The intervention infants also spent a lower percentage of time off-task and the intervention dyads were rated as more synchronous. Regardless of treatment mothers with higher levels of education and who were not black, (both these variables being indicators of greater social advantage), were rated as being more supportive and giving more assistance. For the infants higher ratings on all the significant variables were associated with being not black. For

persistence, enthusiasm and overall ratings higher ratings were associated with higher birth weights. However interaction effects were found for only two variables: for black infants (a marker of social disadvantage in this group) there was a positive treatment effect for enthusiasm and percentage of time-off task.

The authors maintain that finding ethnicity and maternal education were significant predictors of mother-infant interaction is consistent with other studies. The effects may be due to cultural differences in child-rearing and socialisation practices and their association with poverty, suggesting they are markers for social disadvantage. The intervention was therefore able to offer only a limited advantage to these more vulnerable infants.

A later American study by Smith and colleagues provides evidence of an interaction between the infant's risk status, the mother child interaction and the infant's development over the first year (Smith, Landry et al. 1996). This study followed up 212 very low birth weight ($\leq$1600g) premature ($\leq$36 weeks gestation) babies of whom 89 were considered to be high risk medically (diagnosed with one or more severe medical complications) and 123 medically low risk (diagnosed with one or less severe medical complications); and 128 healthy full-term babies. All the babies in the sample were from low socioeconomic homes. The mother infant dyads were observed interacting at home during a toy play situation and a one hour naturalistic period of daily activity at six and 12 months corrected age. The infant's cognitive development was assessed using the Bayley Scales of Infant Development. Receptive and expressive language skills were assessed using the Sequenced Inventory of Communication Development and the Daily Living Skills subscale of the Vineland Adaptive Behaviour Scale was used to assess daily living skills. Three maternal

behaviours were observed: warm sensitivity a composite score consisting of global ratings for positive affect, warm concern/acceptance and responsiveness/flexibility; as well as a quantitative measure of maintaining infant's attention and directing infant's attention.

As expected the medically high risk premature babies had lower cognitive receptive language and daily living scores at six months and showed less change from six to 12 months than the medically low risk premature or full-term babies. The mothers' interactive behaviours were similar across the groups for the first year and all mothers showed an increase in the proportion of interactions in which they maintained the infant's interest and a decrease in warm sensitivity. The most interesting finding was that although for both groups higher levels of maternal attention were positively related to infant development it was more strongly related to cognitive and language skills for both groups of premature infants. The authors suggest that for these more vulnerable infants having their mothers help them focus on an object of interest so achieving joint attention, rather than asking them to shift attention places fewer demands on them so they are able to learn more, thus benefiting their cognitive development. This study provides evidence that even in less advantaged families infant development can be influenced by the quality of the mother child interaction and this may interact with the risk status or vulnerability of the infant during the first year.

A more recent study by Holditch-Davis and colleagues provides evidence of the influence of maternal interactive behaviours on their medically fragile infants' development (Holditch-Davis, Docherty et al. 2001). In this study the authors compared the developmental outcomes and mother–infant interactions of 23 infants with bronchopulmonary dysplasia (BPD) and 39

medically fragile infants without BPD and their mothers. There were no significant differences between the two groups for developmental outcomes or interactive behaviour suggesting that any differences found in other studies were the result of health problems rather than problems uniquely caused by the condition BPD. However positive correlations were found between the Mental Development Index of the Bayley Scales of Infant Development, scores on the HOME and the amount of positive attention. Positive attention was a composite score of interaction with the infant, talking to the infant and positive affect for example touching or smiling. The infants' adaptive behaviour was measured by the Vineland Adaptive Behaviour Scale and this correlated with mother's negative affect. Multiple regression analyses found adaptive behaviour in the infant was significantly predicted by scores on the HOME and the mother's negative affect. The authors suggest that improving maternal interactive behaviours may positively affect the mother infant relationship and so positively benefit the development of these vulnerable infants. In particular they suggest mothers might be encouraged to talk to their infants more as both groups of mothers were found to talk less to their infants than well infant mother dyads despite superior HOME scores suggesting a positive home environment.

Only one study has been found so far which also investigates the impact of twin status. This very large scale study exploring the interaction of prematurity with genetic and environmental influences on the cognitive development of twins targeted all twins born in England and Wales during 1994 (Koeppen-Schomerus, Eley et al. 2000). Despite a high attrition rate the final sample of 2223 twin pairs included 1134 monozygotic and 1089 dizygotic twin pairs. The authors divided the sample into high risk (<32 weeks gestation), medium risk (32-33 weeks gestation) and low risk (>34

weeks gestation) and looked at verbal (measured using the McArthur Communicative Development Inventory (MCDI)) and non-verbal cognitive development (measured using Parent Report of Children's Cognitive Abilities (PARCA)) at two years old. The authors report a clear linear relationship between degree of prematurity and both verbal and non-verbal cognitive outcome. They point out however that these differences only account for a small amount of variance and that there is a large range of individual differences within all the risk groups.

To explore the impact of genetic risk the authors looked at the twin intra class correlations for verbal and non-verbal development for the monozygotic and dizygotic same sex twins as a function of gestational risk. Within the high-risk group the correlations for both monozygotic and dizygotic same sex twins were very similar indicating the importance of shared environmental influence rather than genetic influence, whereas for the two lower risk groups differences in the correlations between monozygotic and dizygotic same sex twins were much greater indicating a greater contribution from genetic factors. These patterns of twin correlations were tested by applying a structured equation model. For both verbal and non-verbal cognitive development the best fitting model was one which assumed distinct genetic and environmental parameter estimates across the three risk groups. Using this model for the high-risk group, 84% of the variance for verbal cognitive development could be accounted for by shared environmental factors compared to 73% for the low risk group. This study suggests the particular importance of environmental factors such as mother-infant interactions for babies at high risk.

3.1-ix Will a twin premature birth be an additional disadvantage for mother-infant interaction and attachment?

The findings discussed so far would all suggest that a twin premature birth would be a significant additional disadvantage for the mother child relationship and interaction. However there are very few studies which have explored these issues as studies of premature babies usually select only singletons to avoid the additional complication of multiple birth status. One of the few studies which did not exclude multiples was the study already described, by Muller-Nix and colleagues (Muller-Nix, Forcada-Guex et al. 2004). This study purposefully included 10 (21%) of infants born after a multiple pregnancy in the preterm group. The authors found no significant differences in the interactions of the mothers or infants at either six or 18 months between the singleton and twin preterm dyads. However, the authors report no details about the maternal characteristics of these two groups so we cannot tell how closely matched they were.

An early study by Goldberg and colleagues attempted to look at maternal behaviour and attachment in low birth weight twins and singletons (Goldberg, Perrotta et al. 1986). The infants all weighed less than 1,501g at birth and were free of major physical malformations; 31 were twins (from 17 pairs of twins, 3 excluded due to physical handicap) and 25 were singletons, including 5 survivors from a twin pair). Home observations were made when the infants were 6 weeks, 3, 6 and 9 months past term and in the laboratory at 1 year past term. Home observations included global ratings of the mother's sensitivity, acceptance, accessibility and cooperation and the infant's social responsiveness, mood and attention to mother. Attachment was assessed using the Strange Situation. The authors found attachment classification was comparable to that predicted on the basis of normative data and that the classification of twins and

singletons as secure and insecure did not differ significantly. Ratings of maternal behaviour were related to subsequent attachment while ratings of infant behaviour were not. Mothers whose infants were classified as securely attached were rated as more attentive and responsive to their infants at all stages. Although twins were not significantly more likely to be rated as insecurely attached, the authors suggest the fact more infants were rated as having elements of an angry or avoidant relationship than expected, suggests mothers may find forming satisfying relationships with their low birth weight babies more difficult. The authors also make the interesting suggestion that the reason more twins were classified as marginally secure could have been because although the mother struggled to meet both their infants' demands the presence of their sibling may have compensated.

The only study identified so far which has attempted to explore again the impact of a twin premature birth on the mother child interaction is a study by Ostfeld and colleagues which compared the interactions of 22 mothers with their premature singleton babies to four mothers with their premature twins matched for demographic and medical status, at one and eight months corrected age (Ostfeld, Smith et al. 2000). The children were followed up at 18 months old and the Bayley Scales of Infant Development Mental Development Index (MDI) and Physical Development Index (PDI) scales and the HOME inventory were administered. The authors found that both frequency and quality of maternal interaction differed significantly and that these measures were significantly correlated with lower cognitive development in the premature twins (Ostfeld, Smith et al. 2000).

The study found that mothers of twins were significantly less likely to pick up, touch, pat or talk to their baby when unprompted by their baby than

were mothers of singletons. Twin babies were also more likely not to prompt their mothers to this behaviour; this may create an even greater compound effect. The authors did not include an assessment of attachment as Goldberg and colleagues had done in the study mentioned previously. We cannot know whether these differences in interaction would result in differences in quality of attachment as might be expected given the correlations found with later development. There are, however some limitations to this study the most important being the small number of twins with only four sets or eight babies included. Another factor to be taken into consideration is that mothers were observed interacting in a naturalistic setting with their twins so both babies were present during the interaction, mothers may interact with twin babies in a similar way to that with singletons if offered the opportunity for one to one interaction.

3.1-x The need for a further study

The research reviewed so far suggests that a premature twin may well be doubly disadvantaged. Studies exploring the impact of a premature birth on mother-infant interaction reveal mothers often work harder for example (Beckwith and Cohen 1978; Greene Fox et al. 1983) although this may sometimes be more intrusive (Wijnroks 1999). However, the infants themselves may be less responsive (e.g. Crnic, Rgozin et al. 1983). One problem with many of the studies in this area has been one of definition. This has been so particularly with regard to premature birth, with many studies treating all babies born before 37 weeks as premature, while others only looked at extremely premature babies: those born before 32 weeks. Different definitions and descriptions have also been used regarding birth weight. Medical complications and health status has been shown to be very important with some researchers suggesting these are more

important than how premature or how low birth weight the baby is (Greenberg and Crnic 1988; Miceli, Goeke-Morey et al. 2000). Studies also provide evidence of how infant risk factors, such as premature birth or neonatal health complications, mother risk factors such as depressive symptoms or low socio economic status, interact in contributing to the quality of the mother-infant interaction (Bee, Barnard et al. 1982; Saxon, Colombo et al. 2000; Poelman and Fiese 2001; Laucht, Esser et al. 2002; Gerhold, Laucht et al. 2002). Future studies need to explore the additional disadvantage of a premature and low birth weight birth while controlling for health status.

The possible additional impact of twin status on the mother-infant interaction has been little researched with, as already discussed, many studies excluding twins and multiples because of the additional complications including them creates. The only two studies so far identified report interesting results. The study by Goldberg and colleagues found no significant effect of twin status on classification as securely or insecurely attached (Goldberg, Perrotta et al. 1986). Although the study found infants classified as securely attached had mothers who were rated as more responsive and attentive, these ratings were not reported for twins and singletons separately. The study by Ostfeld and colleagues found significant differences in mother-infant interactions for mothers of twins and singletons and that these predicted later cognitive development. However the very small sample size makes it imperative to replicate the study with a larger sample.

The increase in the number of twin births and their increased risk of prematurity make it important to explore further what impact a twin premature birth will have on mother-infant interaction. One important

issue to consider is how this interaction is observed. Some studies have favoured naturalistic observations of the mother interacting with both babies as in the previously mentioned study by Ostfeld and colleagues (Ostfeld, Smith et al. 2000). Mothers of multiples or mothers with more than one infant may be obliged to interact with more than one of their children in all naturalistic settings. Exploring the mother child interaction within a more structured and formal assessment using a standardised method of assessment should provide a more direct measure of maternal sensitivity a limitation identified by Poehlmann and Fiese in their study (Poehlmann and Fiese 2001)[b].

Attachment theory provides an important rationale for looking at mother-infant interaction with mothers and premature twins. Studies reviewed in this chapter suggest quality of interaction will be a factor in predicting secure attachment (Poehlmann and Fiese 2001)[a]. Given that quality of attachment can only be evaluated when the infant is twelve months or older, quality of interaction may be used as an indicator of how this will develop. The authors of the Nursing Child Assessment Teaching Scale (NCATS) a widely used standardised measure of caregiver-infant interaction report on its predictive validity with regard to attachment (Sumner and Spietz 1994). This study followed a sample of pregnant women enrolled in treatment programs through pregnancy and the child's first year. Scores on the NCATS at three months were correlated with attachment security in the Strange Situation at 13 months. Infant Clarity of cues and Responsiveness to caregiver sub-scale scores as well as Child total scores were all positively correlated with later attachment security; and these correlations were significant. Only the Parent total score was significantly positively correlated with attachment security. Measures of this interaction which explore maternal sensitivity and responsiveness to

infant signals should be particularly revealing, as was found in the study by Golberg and colleagues (Goldberg, Perrotta et al. 1986). Research discussed in this chapter suggests that both quality of mother-infant interaction and attachment impact on the infant's cognitive and social development for example (Rocissano and Yatchmink 1983; Gerner 1999; Holditch-Davis, Bartlett et al. 2000; Saxon, Colombo et al. 2000; Poehlmann and Fiese 2001[b]; Feldman Eidelman et al. 2004, Mantymaa, Puura et al. 2004). Evidence of any negative impact caused by a twin premature birth would be an important factor to consider when debating the number of embryos to transfer and the desirability of a multiple birth.

A randomised trial of a parenting intervention during neonatal intensive care had by chance included a sample of babies born after a multiple gestation (Glazebrook, Marlow et al. 2007). The study to be reported in this chapter will take advantage of this unique opportunity to explore the impact of a twin birth on mother-infant interaction while controlling for prematurity.

AIMS

- To compare the interactions of mothers and their very premature twins with the interactions of mothers and their very premature singletons
- To explore levels of parenting stress in mothers of very premature twins and singletons

HYPOTHESES

1. Mothers of very premature twins will experience higher levels of stress than mothers of very premature singletons.

2. Mothers of very premature twins will be less responsive to their infants than mothers of very premature singletons.

3.2 METHOD

3.2-i Design

This study was part of a cluster randomised crossover trial of a parenting intervention study with parents of very premature (< 32 weeks gestation) infants born at six neonatal centres in the UK (Glazebrook, Marlow et al. 2007).

3.2-ii Ethics

The study received full ethical approval from the relevant ethics committees.

3.2-iii Participants

Mothers were recruited from six neonatal centres, three from the south-west and three from Trent. Inclusion criteria stipulated that all infants should be born at less than 32 weeks of gestation and admitted to one of the six participating centres. Infants were excluded if they lived outside the study's catchment areas and, or if they had an illness incompatible with life. During the recruitment period 496 infants were born below 32 weeks gestation and were admitted to the study centres. However, 156 lived outside the study's catchment area and 33 infants died. The parents of the remaining 307 eligible infants were all invited to participate in the study 233 (76%) consented to do so. The authors of the original study report finding no significant differences between those who consented to take part in the study and those who did not in terms of birth weight, gestational

age, gender or whether they had been a multiple pregnancy (Glazebrook, Marlow et al. 2007).

3.2-iv Measures and Procedure:

Index of multiple deprivation (IMD)

The index of multiple deprivation (Noble, Wright et al. 2004) provides a score calculated for each infant based on their postcode. The score is derived from data on deprivation at the small area level in seven domains: income, employment, health and disability, education skills and training, barriers to housing and services, living environment and crime. Scores in England can range from 0.59 (the least deprived) to 86.36 (most deprived) with a median of 17.02.

Nursing Child Assessment Teaching Scale (NCATS)

The Nursing Child Assessment Teaching Scale (NCATS) (Sumner and Spietz 1994) is a widely used standardised assessment of the quality of caregiver-child interaction, based on the concept that positive, quality interactions will lead to superior intellectual and language abilities in the child and more secure attachment. The scale consists of 73 binary items related to child and caregiver behaviour, some items also reflect contingency between the child and caregiver. Items are scored while the caregiver attempts to teach the child a skill. Caregivers are shown a list of sensory motor skills in ascending order of difficulty and asked to select the first skill on the list the child has not yet acquired.

The scale is organised into 6 sub-scales two describe the child's behaviour: 1) child's clarity of cues and 2) responsiveness to caregiver. These two sub-scales are added together to give a total child score. Scores can range

form 0 to 23 with higher scores indicating greater clarity of cues and responsiveness to the parent. Four of the subscales describe the caregiver's behaviour: 3) sensitivity to cues, 4) response to child's distress, 5) social emotional growth fostering and 6) cognitive growth fostering. The 4 caregiver sub-scales can be added together to provide a caregiver total score this can range from 0 to 50 with higher scores indicating more sensitive and responsive interactions. The authors report high internal consistency for the caregiver total score (Cronbach's alpha 0.87) and for the child total scores (Cronbach's alpha 0.81). The NCATS has been validated for the assessment of caregiver child interactions for children up to three years old (Sumner and Spietz 1994). Moreover, the scale has been effectively used with newborn infants (Leitch 1999) and 3 month old premature infants (Harrison and Magill-Evans 1996). Scores below the 10th percentile are considered to be below the lower limit of the normal range and to give cause for concern. A large data base exists for the scale which allows for comparison with 10th percentile cut-offs for groups from different ethnic and educational backgrounds.

The NCATS assessments were carried out in the week prior to discharge (videotaped by a research nurse) and at a home visit when the infant reached 3 months corrected age (videotaped by the psychologist). The same rater: the author of this thesis rated all the videotaped interactions. The rater was blind to intervention group but not to twin status. The rater had been trained to >90% reliability and any uncertainties over ratings were resolved by discussion with a second blind rater who had also been trained to > 90% reliability. Forty NCATS assessments (10%) balanced for time and phase of study were re-rated at least 6 months later. Test re-test reliability was excellent with an ICC of 0.93 for the caregiver total score and 0.915 for the child total score.

Home Observation for Measurement of the Environment (HOME) – Responsivity subscale

The HOME is a widely used standardised instrument consisting of 45 binary items (Caldwell and Bradley 2001). Assessment is carried out during a visit to the child's home where the mother or main caregiver, and child are observed interacting. Observational methods and some interview questions are used to measure the quality of the child's family environment. The scale is based on the assumption that certain experiences and objects if present or absent from the child's life will make a difference to their social and cognitive development. The Responsivity subscale consists of 11 items, 10 of which are completed by observation. The scale items explore the extent, to which the parent responds to the child's behaviour, offers verbal, tactile and emotional reinforcement for desired behaviour and communicates through words and actions. Scores range from 0 to 11 with higher scores reflecting greater emotional and verbal responsiveness.

The Responsivity subscale has been found to have moderate to high internal consistency Cronbach's alpha 0.61 and was found to significantly correlate with naturalistic observations of mother child interactions (Tesh and Holditch-Davis 1997). The HOME has been successfully used in a study of premature twins and their mothers at one and eight months corrected age (Ostfeld, Smith et al. 2000).

Assessments were carried out by one of three psychologists during a home visit at 3 months corrected age. The raters were all blind to intervention group but not to twin status. Inter-rater reliability was good with 92.9% item agreement for 8 assessments.

Parenting Stress Index short form (PSI-SF)

The Parenting Stress Index was designed to provide a measure of the stress in the parent-child system so as to identify families most at need of help or intervention (Abdin 1995). The original instrument was very lengthy and time consuming so the short-form was developed based on a factor analysis of the original indicating a three factor solution. The short-form consists of three subscales: Parental Distress, Parent-Child Dysfunctional Interaction and Difficult Child. Each subscale consists of 12 items rated from 1 'strongly disagree' to 5 'strongly agree'. The Parental Distress scale measures the distress a parent experiences in their role as a parent and explores issues such as feelings of competence, conflict with the other parent and restrictions on their life. The Parent-Child Dysfunctional Interaction focuses on the perception by the parent that the child does not meet their expectations and interactions with the child are not reinforcing for them. The Difficult Child subscale focuses on characteristics of the child which makes them easy or difficult to manage. Higher scores on these subscales and the total score (a composite score of the three subscales added together) reflect higher levels of stress. In addition seven items are summed to form a Defensive Responding subscale which assesses the extent to which respondents try to present a favourable impression and minimise any problems or stress. The author recommends raw scores should be converted to percentile scores with those falling between the 15^{th} and 80^{th} percentile considered within the normal range while scores above the 85^{th} percentile should be seen as high. Parents who obtain a Total Stress score at, or above the 90^{th} percentile should the author claims, be regarded as experiencing clinically significant levels of stress.

The author reports excellent correlations: R=0.94 with the original version and good internal consistency with Cronbach's alpha's ranging from 0.68 for the Parent Child Dysfunctional Interaction subscale to 0.85 for the Parental Distress subscale. Further support for the internal consistency of the subscales and support for use in a more diverse population is given by Reitman and colleagues' evaluation of the scale in a Head Start population of predominantly single, lower socioeconomic, African American mothers (Reitman, Currier et al. 2002). More recently further support for the validity of the PSI-SF has been provided by Haskett and colleagues whose factor analysis revealed two scales measuring parental distress and dysfunctional parent child interactions which correlated with measures of parent psychopathology, parental perceptions of child adjustment and observations of parent child behaviour (Haskett, Ahern et al. 2006). Not only has the PSI-SF been widely used but it has also been successfully used with mothers of three month old twins and triplets (Feldman, Eidelman et al. 2004). Parents were sent the PSI-SF to complete at home when their infant was three months (by corrected age). The questionnaire was collected by one of the researchers during the home visit which took place approximately one week later.

3.2-v Analysis

Quantitative data were analysed using SPSS version 15.0. Continuous data with a non-Gaussian distribution were analysed using non-parametric tests: Wilcoxon Signed Ranks or Mann-Whitney U tests, while those with a normal distribution were analysed using Paired and Unpaired T tests and repeated measures analysis of variance. Categorical data were analysed using Chi-square tests.

3.3 RESULTS

Of the 233 infants who participated and fulfilled the inclusion criteria for the original study there were 23 pairs of twins. Subsequently 2 pairs of twins were withdrawn from the study and in 4 pairs one or both sadly died. This resulted in 17 pairs of twins participating in the present study. One twin from each pair was selected at random. Each mother of a twin was matched to a singleton mother for parity, mother's age at birth of baby and highest educational attainment achieved (see table 15). The mothers were all white Europeans, with 40% educated to degree level or beyond and most were married or cohabiting.

Table 15: **maternal demographic characteristics**

	Twins (n=17)	Singletons (n=17)
Mean age (SD)	32.5 (5.48)	31.8 (5.01)
White European	17 (100%)	17 (100%)
Married / cohabiting	16 (94%)	16 (94%)
First baby	10 (59%)	10 (59%)
Highest level of education NVQ, GCSE	5 (29%)	5 (29%)
Degree / postgraduate	7 (41%)	7 (41%)

3.3-i Infant characteristics

Although the infants had not been matched, there were no significant differences between the singletons and twins for gestational age, weight at birth, number of days ventilated prior to discharge, gender, or index of multiple deprivation (see table 16). More of the twins 10 (58.8%) had

received the intervention package compared to 4 (23.5%) of the singleton babies. However, this was not statistically significant and the intervention had not been found, to have a significant measurable effect on short-term infant neuro-behavioural function, mother-child interaction or parenting stress (Glazebrook, Marlow et al. 2007). Data were also collected on whether the mother had conceived following fertility treatment, although this was missing for 8 mothers, four of singletons and four of twins. Six of the singletons were conceived after treatment for infertility: 3 mothers had received medication and 3 IVF or ICSI. Only one twin was conceived after treatment for infertility: IVF or ICSI. Although more of the singletons were conceived after treatment for infertility 6 (46.2%) than the twins 1 (7.7%) this was not significantly different.

Table 16: infant characteristics

	Twins (n=17)	Singletons (n=17)
Median gestational age in weeks (Interquartile range)	30 (28-31)	29 (27-31)
Range	25-31	26-31
Median weight in grams (Interquartile range)	1260 (920-1625)	1195 (929-1500)
Range	768-1700	635-1850
Median IMD (Interquartile range)	12.55 (7.76-19.28)	14.05 (7.59-17.97)
Range	5.11-43.29	5.51-24.54
Median number of days ventilated prior to discharge (Interquartile range)	1.0 (0-5)	1.0 (0-10)
Range	0-15	0-36
Male infant (%)	6 (35%)	6 (35%)

3.3-ii Results at 3 months corrected age

HOME Responsivity subscale Score

Mothers of twins scored significantly lower on the HOME Responsivity subscale, median score 9.0 score compared to a median score of 10.0 for mothers of singletons (Z= -2.332 p=0.020). Although scores on this subscale were not normally distributed in this study and so non-parametric statistics were used other studies have reported means and standard deviations. These reported scores provide a useful comparison (see table 17).

Table 17: HOME Responsivity subscale scores

	Infant group	Mean	Standard Deviation
The present study	**Singletons** (n=17) at 3 months	9.71	0.85
	Twins (n=17) at 3 months	8.77	1.44
Armstrong et al study (mothers recruited on basis of self-reported vulnerability factors)	**Intervention group** (n=90) at 6 weeks	9.54	1.16
	Comparison group (n=91) at 6 weeks	8.80	1.61
Bakeman and Brown study	**Preterm** (n=21) at 9 months	8.5	1.7
	Term (n=22) at 9 months	9.7	1.1

HOME Responsivity subscale scores correlated significantly with IMD scores Spearman's rho (r=-0.370 n=34 p=0.031). The higher the IMD score indicating greater levels of deprivation, the lower the mother's HOME Responsivity subscale score.

PSI-SF

One mother of a singleton did not complete all the questions on the PSI and so paired analyses were carried out for 16 of the mother infant dyads. Scores for the mothers of twins and singletons were compared using paired tests as the mothers were matched. The difficult child score is calculated based on the mothers' responses and so although the infants themselves were not matched scores on this scale were also compared using matched tests. The total PSI-SF and all the subscale scores were normally distributed except the parental distress subscale and so paired t-tests were used to compare the data except for this last subscale which was compared using a Wilcoxon Signed Ranks test.

The Defensive responding scale is used to explore whether parents are trying to portray a favourable impression and the authors of the PSI-SF suggest scores at or below 10 should be viewed with caution and may suggest that the parent is trying to portray themselves as a very competent individual, or that they are not invested in their role as a parent, or that they are indeed a very competent individual with excellent relationships (Abdin 1995). Low scores: below 10 were found for 5 mothers, of whom 4 were the mothers of twins however, this was not statistically significant.

Total stress scores were higher for the mothers of twins however, the difference was not statistically significant (see table 18). Four (25%) of the mothers of twins scored above the 90th percentile which the author maintains should be seen as reflecting clinically significant levels of stress. None of the mothers of singletons scored above the 90th percentile and this was significant (Fisher's Exact Test (one sided) P=0.05. Scores for the twin mothers were higher for all the subscales however, this was only statistically significant for the parent child dysfunctional interaction scale (t=-2.155, df 15, p=0.048) (see table 18). Higher scores on this scale indicate that the mothers of very premature twins found interacting with their three month old infants less reinforcing than mothers of singletons and that their infants were less likely to meet their expectations.

Table 18: PSI-SF scores at 3 months corrected age

	Twins (n=16)	**Singletons (n=16)**
Mean PSI Defensive responding subscale	15.0	15.44
(SD)	(5.34)	(4.66)
Mean PSI Parent child dysfunctional Interaction subscale *	21.5	17.38
(SD)	(6.70)	(3.86)
Mean PSI Difficult child subscale	23.0	20.81
(SD)	(7.67)	(5.27)
Median PSI Parental distress subscale	28.5	23.5
(Interquartile range)	(17.5-33.75)	(21.25-27.75)
Mean Total PSI	70.94	63.75
(SD)	(21.58)	(11.57)

*p<0.05

NCATS: mothers' scores

Paired t-tests were used to compare the mothers as they had been closely matched and the scores were normally distributed. The subscale scores were not normally distributed and so were compared using Wilcoxon Signed Ranks tests. There were no significant differences between the scores of mothers of twins and singletons for any of the subscale scores or the total score (see table 19).

Table 19: NCATS Caregiver scores at 3 months corrected age

	Twins (n=17)	**Singletons (n=17)**
Median NCATS Response to distress subscale (Interquartile range)	11.0 (10-11)	11.0 (9-11)
Median NCATS Sensitivity to cues subscale (Interquartile range)	10.0 (9-11)	9.0 (9-10)
Median NCATS Social emotional growth fostering subscale (Interquartile range)	8.0 (6.5-9)	8.0 (7-8)
Median NCATS Cognitive growth fostering subscale (Interquartile range)	12.0 (9-13)	12.0 (8.5-14)
Mean NCATS Total score (SD)	39.12 (4.44)	38.59 (4.90)

Total scores were low with 3 (17.6%) of the twin mothers and 4 (23.5%) of the singleton mothers scoring at or below the 10th percentile.

NCATS: Child scores

The NCATS task was successfully completed by all 17 mothers and infants at 3 months corrected age. The infants were not matched and so independent tests were carried out. Total scores and Clarity of cues subscale scores were normally distributed and were compared using independent t-tests. Scores on the Responsiveness to caregiver subscale were not normally distributed and were compared using a Mann-Whitney U test. Twin infants had significantly lower total scores (t=2.2, df 32, p=0.036). Twins also scored lower on both subscales although only clarity of cues was significantly different (see table 20). The observer rated twin infants as less responsive to their mothers, and less clear in the cues they gave, than singleton infants.

Table 20: NCATS Child scores at 3 months corrected age

	Twins (n=17)	**Singletons (n=17)**
Median NCATS Responsiveness to caregiver subscale	7.0	9.0
(Interquartile range)	(6-9)	(7-10.5)
Mean NCATS Clarity of cues subscale*	5.76	7.12
(SD)	(1.44)	(1.54)
Mean NCATS Total score*	13.18	15.71
(SD)	(3.38)	(3.35)

***** $p<0.05$

Total scores were low with 17.6% of the infants scoring at or below the 10th percentile. However, although more twins 5 (29.4%) scored below the 10th percentile this was not significantly different to the number of singletons 1 (5.9%).

3.3-iii Change in NCATS scores over time

NCATS tasks were completed at discharge as well as at 3 months, as described in the study procedure. This meant the interaction of twin or singleton status with NCATS scores could be explored over time. One singleton and one twin baby were too sleepy for the mother to complete the NCATS task at discharge from hospital and so these babies and the baby they were paired with were not used in the following analyses giving a total of 15 matched twin singleton pairs. Both the child total and caregiver total scores were normally distributed and were analysed using repeated measures analysis of variance.

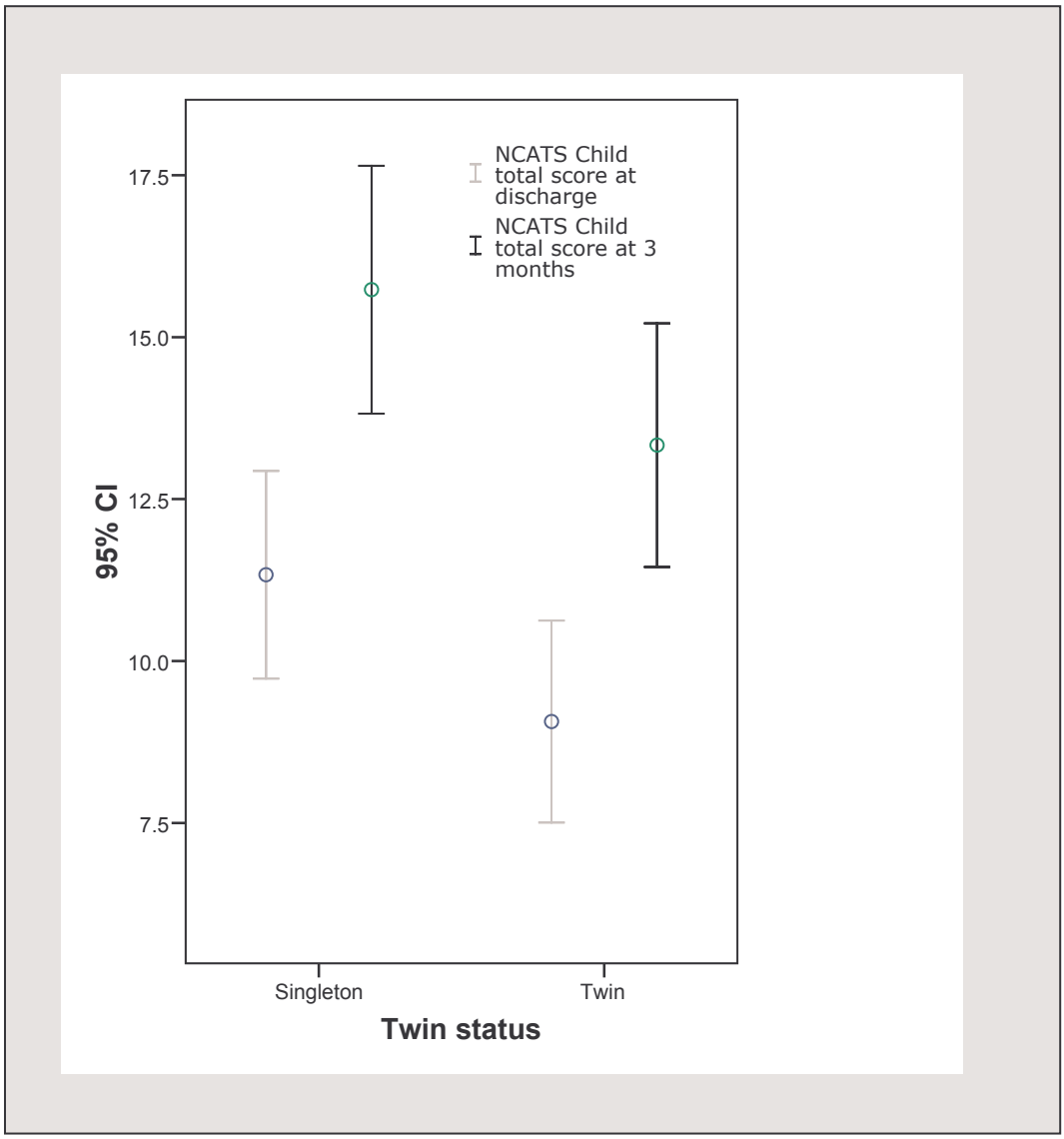
A repeated measures analysis of variance with twin/singleton status as the between–subjects factor was computed for the caregiver total score at discharge and 3 months corrected age. There were no significant main or interaction effects. Mothers of twins and singletons interacted with their infants in a very similar way as illustrated by their very similar scores. Although they became slightly more responsive and stimulating over time this was not significant, nor were there any significant interactions. The pattern of results for the subscale scores was broadly similar (see table 21).

Table 21: NCATS Caregiver scores at discharge and 3 months corrected age

		Twins (n=15)	Singletons (n=15)
Mean NCATS Response to distress subscale (SD)	At discharge	9.60 (2.13)	9.87 (1.41)
	At 3 months	10.40 (1.30)	10.27 (1.16)
Mean NCATS Sensitivity to cues subscale (SD)	At discharge	9.40 (1.40)	9.40 (1.30)
	At 3 months	9.87 (0.92)	9.53 (0.83)
Mean NCATS Social emotional growth fostering subscale (SD)	At discharge	8.07 (1.62)	8.33 (1.50)
	At 3 months	7.93 (1.67)	7.67 (1.05)
Mean NCATS Cognitive growth fostering subscale (SD)	At discharge	9.67 (2.92)	10.07 (2.55)
	At 3 months	11.33 (2.09)	11.47 (3.18)
Mean NCATS Total score (SD)	At discharge	36.73 (5.47)	37.67 (4.30)
	At 3 months	39.53 (4.17)	38.93 (4.15)

A repeated measures analysis of variance with twin/singleton status as the between – subjects factor was computed for the child total score at discharge and 3 months corrected age. A significant overall main effect was found for time (Wilks' Lambda F (1, 28) = 27.36, p <0.001), and a significant between-subjects effect of twin /singleton status (F=8.52, df 1, p=0.007) with no significant interaction effects (see figure 5 and table 22).

Figure 5: graph showing twin and singleton NCATS child total scores at discharge and at 3 months



Similar patterns were found in the two subscale scores (see table 22).

Table 22: NCATS Child scores at discharge and 3 months corrected age

		Twins (n=15)	Singletons (n=15)
Mean NCATS Responsiveness to caregiver subscale (SD)	At discharge	5.6 (1.68)	7.0 (1.85)
	At 3 months	7.53 (2.47)	8.73 (2.25)
Mean NCATS Clarity of cues subscale (SD)	At discharge	3.47 (1.41)	4.33 (1.29)
	At 3 months	5.80 (1.21)	7.00 (1.56)
Mean NCATS Total score * (SD)	At discharge	9.07 (2.81)	11.33 (2.89)
	At 3 months	13.33 (3.39)	15.73 (3.45)

*$p<0.01$

3.3-iv Exploration of correlations between outcome variables

Mothers' scores on the HOME Responsivity subscale were not significantly correlated with their total stress score on the PSI-SF. HOME Responsivity subscale scores were also not significantly correlated with either, total caregiver, total child, or any of the subscale scores on the NCATS at discharge or three months corrected age.

Although total caregiver and total child NCATS scores at discharge did not significantly correlate with mothers' total PSI-SF scores, two of the NCATS subscale scores at discharge did significantly correlate with total maternal PSI-SF stress scores at three months corrected age. Scores on the NCATS subscales were not normally distributed and so non-parametric Spearman rho correlations were carried out. Mothers' social and emotional growth fostering subscale score at discharge was significantly negatively correlated

with their total PSI-SF score (Spearman's rho -0.414, n= 31, p=0.021). The more sensitive the mother was to her baby's social and emotional growth fostering needs at discharge from hospital the lower her stress on the PSI-SF when the infant was three months old. Child responsiveness to caregiver subscale score at discharge also significantly negatively correlated with mother's total PSI-SF score (Spearman's rho -0.371, n= 31, p=0.040). The more responsive the baby was to its mother at discharge from hospital the lower the mother's stress on the PSI-SF when the infant was three months old. There were no significant correlations between total caregiver, total child or any of the NCATS subscale scores at three months corrected age and total maternal PSI-SF stress scores.

The number of days the infant was ventilated prior to discharge gives an indication of how sick the infant was. This variable did not significantly correlate with mothers' total PSI-SF stress scores, the HOME Responsivity subscale score or NCATS total child or caregiver scores at discharge from hospital or three months corrected age. However, number of days ventilated was significantly positively correlated with caregiver response to distress subscale score at discharge (Spearman's rho 0.379, n= 32, p=0.033). The more days the infant had been ventilated for prior to discharge the higher the mother scored on the response to distress subscale.

3.4 DISCUSSION

One aim of the present study was to compare the interactions of mothers and their very premature twins with the interactions of mothers and their very premature singletons. It was hypothesised that mothers of very premature twins would be less responsive to their infants than mothers of

very premature singletons. Some evidence was found in support of this hypothesis. Mothers of twins scored significantly lower on the HOME Responsivity subscale than mothers of singletons. Moreover, the mean score for mothers of twins appears quite low when compared to the mean scores found by Armstrong and colleagues as shown in table 17 (Armstrong, Fraser et al. 1999). The 181 mothers were recruited on the basis of self-reported vulnerability factors to a randomised double-blind control study of a support/intervention program. In comparison mothers in the present study were not disadvantaged. It is also interesting to note that the intervention in that study did significantly increase the scores for the intervention group (Armstrong, Fraser et al. 1999).

A study by Barnard and colleagues which compared maternal interactions with term and preterm infants at 24 months did not find a significant difference on scores for the HOME Responsivity subscale although they did find significantly higher total HOME scores and two other subscale scores for the term group (Barnard, Bee et al. 1984). One point to consider is that the HOME Responsivity subscale is designed, as described in the method section to be completed by observation and interview in the participant's home however, in their study it was adapted to questionnaire and observation during a clinic visit which may have affected the results. The authors did find significant differences between the term and preterm groups for three other HOME subscale scores with mothers of preterm infants having lower scores for organisation of the home environment, maternal involvement and variety in stimulation. Another point is that the two groups differed on mother's educational level and parity and, as already mentioned the Responsivity subscale correlates with mother's educational level. Although the authors claim analyses of the data co-

varying out mother's education made no fundamental differences it may have introduced enough variability to remove any significant effects.

Thorpe and colleagues study also found, as in the present study, lower scores for mothers of twins on the HOME for both the total score and four of the six subscale scores including Responsivity (Thorpe, Rutter et al. 2003). Mothers in the study were well matched for education and social disadvantage. The authors report that differences in interaction were associated with language outcomes at 36 months and this they suggest may be part of the explanation for twin/singleton language differences at 36 months. An argument which suggests the twins observed in this study may continue to be disadvantaged. Of particular interest is the authors' conclusion that "environmentally mediated family influences may play a slightly greater role with respect to individual differences in language (within the normal range) in twins than singletons" (page 353) (Thorpe, Rutter et al. 2003). The study provides further support for the idea that being a twin is an additional vulnerability factor over and above any other disadvantages such as prematurity, economic or educational disadvantage. It also highlights the particular salience of the quality of maternal interactions for development in twins.

However, Feldman and Eidelman's study exploring parent interactions with singletons, twins and triplets matched for gestational age, birth weight, medical risk, and parental age and education found no significant differences between the multiple birth groups on the Responsivity subscale although they found significant differences for some of the other subscales (Feldman, Eidelman et al. 2004). Their study did use an earlier 55 item version of the HOME which may account for the difference in findings or this might be accounted for by the fact matching twins and singletons to a triplet for gestational age and birth weight may be creating more

differences than it controls for. For example a singleton matched for gestational age and weight to a triplet is likely to be much sicker at birth.

One of the few studies to look at maternal behaviour and interaction with premature twins and which also used the HOME was carried out by Ostfeld and colleagues (Ostfeld, Smith et al. 2000). They found no significant differences between premature twins and singletons for the HOME Responsivity subscale in their study although they did find significant differences on two other subscales. As already mentioned in section 3.1-ix of the present study one major limitation to their study was the very small sample size with only four sets of twins, although the authors included all 8 infants in the twin sample. The twin and singleton mothers were not closely matched as in the present study although the authors do claim that the two groups were very similar with no significant differences. However for a scale like the HOME Responsivity subscale scored in a naturalistic setting when the mother was interacting with both infants at once their scores are likely to be similar making it very hard with such a small sample size to find a significant difference. Unfortunately the authors did not publish their mean or median scores so it is not possible to compare the scores with those found in the present study.

The present study found mothers' scores on the HOME Responsivity subscale were correlated with their IMD scores. This was not an unexpected finding as the HOME has been found to be sensitive to mother's social background (Burston, Puckering et al. 2005), education (Bee, Barnard et al. 1982; Tesh and Holditch-Davis 1997), and even intervention programs (Armstrong, Fraser et al. 1999). However, the mothers in this study were from a fairly homogenous group with few apparent disadvantages, they were in their thirties, nearly all were married

or living with a partner and all were educated to at least GCSE level or above. Mothers of twins and singletons also did not differ significantly on the IMD and with median scores of 12.55 for twins and 14.05 for singletons both were well below (higher scores indicate greater levels of deprivation) the 17.02 median for England as a whole (Noble, Wright et al. 2004). This close matching of the two groups makes the finding of a significant difference in HOME Responsivity subscale scores more interesting as they cannot be explained simply by differences in the mothers' social circumstances or education. Mothers of twins when observed interacting in normal day to day situations are found to be less responsive to their premature infants than mothers of singleton premature infants.

However, other findings from this study did not support the hypothesis that mothers of very premature twins would be less responsive to their infants than mothers of very premature singletons. Mothers' scores on the Nursing Child Assessment Teaching Scale (NCATS) at 3 months did not differ significantly between the twins and singletons. This suggests that in a one to one situation as in the NCATS task the mother interacts with her twin infant in a very similar way to a mother interacting with a singleton. Close matching of the mothers, using only very premature infants, meant the infants were also very similar in gestational age and birth weight so these factors could not affect the NCATS results. Mothers' scores were low however, suggesting they had problems interacting with their infants. Harrison and Magill-Evans had compared mothers of term and preterm infants in their study and it is interesting to see that the low scores they report for the mothers of preterm infants (mean = 39.9) were very similar to those found for both the mothers of twins (mean = 39.12) and singletons (mean = 38.59) found in this study (Harrison and Magill-Evans 1996).

This study had not expected to find a significant difference between infants' scores on the NCATS. Twin infants' NCATS scores at three months corrected age were lower on both the subscales and the total infant score. Differences were statistically significant for the clarity of cues subscale and the total score. Although a much larger sample than the one reported by Ostfeld and colleagues in their study (Ostfeld, Smith et al. 2000), the sample size may have lacked the power to detect a significant difference for the responsiveness to caregiver subscale. Scores for all the infants were low suggesting they would be difficult partners for their mothers to interact with and the twin scores were particularly low with 29% scoring at or below the 10^{th} percentile. Comparison with the scores reported by Harrison and Magill-Evans illustrates how low the twin scores were in this study. Preterm infants at three months were reported in their study as having a score of (mean = 15.8) very similar to the score found for singletons in this study (mean = 15.71). However with a score of (mean = 13.18) it is possible to see how much less interactive the twins are, and suggests that this cannot be accounted for just by their prematurity.

Although finding that the twins scored significantly lower than the singletons was unexpected, Ostfeld and colleagues in their study of premature twins and singletons had found twins exchanged fewer smiles and mutual gazes with their mothers at 8 months corrected age although not at one month (Ostfeld, Smith et al. 2000). Studies of singleton premature infants have found premature infants to be less responsive to their mothers than infants born at term. For example studies have found premature babies to score lower than the population mean on the Nursing Child Assessment Feeding Scale responsiveness to caregiver subscale (Davis, Edwards et al. 2003), and to score lower on this subscale than a

control group of full-term infants (Alfasi, Schwartz et al. 1985). Other studies have looked at particular aspects of early communication for example Barratt and colleagues looked at vocalisations, smiles and visual attention in a sample of 24 preterm ($\leq$ 36 weeks gestational age) and 24 term infants (Barratt, Roach et al. 1992). During structured observational sessions when the infants were four months corrected age they found the term infants made more vocalisations and spent more time looking at their mothers. Reissland and Stephenson found term infants were more likely to follow their mothers' vocalisations with one of their own than premature infants (Reissland and Stephenson 1998). A very recent review of research on premature infant –mother interaction over the last 15 years concluded that preterm infants were generally found to be less facially expressive and responsive than term infants while their mothers were more sensitive and responsive (Bozzette 2007). Research does suggest therefore that infant ability to respond and interact with their mothers is a marker of disadvantage.

It is important to consider whether early ability to respond and interact will continue to impact on the infant's development as they get older. Greenberg and Crnic explored this issue in their longitudinal assessment of premature infants (Greenberg and Crnic 1988). The two child subscale scores of the NCATS: clarity of cues and responsiveness to parents at eight months old were used as a component of a child behaviour summary measure. Scores on this composite measure were related to mental, physical and receptive language development as well as to the length and affective quality of observed mother-child interactions at 24 months. Moreover, in an earlier study with these infants premature infants were found to have significantly lower scores on both the subscales than term

infants (Crnic, Ragozin et al. 1983). Their studies illustrate the importance for premature infants of early interactive behaviour

Holditch–Davis and colleagues in their study of premature infant-mother interactions had followed up the infants for even longer until they were three years old (Holditch-Davis, Bartlett et al. 2000). The 49 infants in this study were categorised according to whether they had normal or low IQ, showed normal language development or cause for concern, and normal attention spans or cause for concern. Their results illustrate the potential impact of the mother's interaction as infants with normal IQs and normal language development all had mothers who scored significantly higher on the NCATS subscales sensitivity to cues, social-emotional growth fostering and cognitive growth fostering. Mothers' scores for the infants who showed cause for concern with regard to attention had lower scores on only the social emotional growth fostering subscale. Infants' scores only differed significantly for one group: infants with low IQ had lower responsiveness to parent scores. A study by Sumner and Spitz (1994) found infant NCATS scores at three months were significantly correlated with later attachment security as was the total parent score, although not the sub-scale scores (Sumner and Spitz 1994). This is of particular relevance to this study as the infants were also assessed on the NCATS at three months old. Also, given their mothers had low social support and were enrolled in treatment programs, the infants may have been more vulnerable. Results from all these researchers suggest that the differences and indeed low scores found for the twins in this study should be seen as a cause of concern as they may impact on their future development.

Mothers' scores on the NCATS showed no significant changes over time although total scores and all subscale scores except social emotional

growth fostering, increased. There were no significant interactions with twin singleton status. Harrison and Magill-Evans had also looked at change over time in their study of term and preterm infants and their mothers although observations were made at 3 and 12 months old (Harrison and Magill-Evans 1996). Unlike the present study they did find a significant change over time however, they found mothers' total scores were lower at 12 than at three months with significantly lower scores on the response to distress and social emotional growth fostering subscales. The finding of lower scores on the social emotional growth fostering subscale is of interest as it mirrors the finding in the present study as this was the only subscale which decreased rather than increased over time. They also reported no significant interactions.

Analysis of the NCATS total child scores indicated the observer rated both twins and singletons as more responsive to their mothers and clearer in their cues at three months than at discharge. This finding might have been expected as the authors of the scale report a positive r=0.11 correlation of child total score with child's age (Sumner and Spietz 1994) and Harrison and Magill-Evans also report significant increases in the infants' scores over time in their study (Harrison and Magill-Evans 1996). The finding that twins had significantly lower scores than singletons was not expected, nor was there any significant interaction effect which might have explained it. Harrison and Magill-Evans found no significant differences between their premature and term infants at 3 months although the premature infants did have lower scores (Harrison and Magill-Evans 1996). One argument might be that the mothers of twins interacted and stimulated them less but if this was the case one would have expected their scores to decrease over time as the effect was compounded. Moreover, analysis of the mothers'

scores showed no significant differences in the way they interacted with their twins or singletons when interacting one to one as in the NCAST task.

The second aim of this study was to explore parenting stress in mothers of very premature twins and singletons. We hypothesised that mothers of twins would have higher levels of stress than mothers of singletons. Mothers of twins did score highly on the PSI indicating they were experiencing considerable levels of stress and indeed 25% scored above the 90th percentile which the author of the scale suggests should be seen as a parent experiencing clinically significant levels of stress (Abdin 1995). However, there were no significant differences between the total scores of mothers' of twins and singletons. This may have been significant if a larger sample had been used which had the power to detect a smaller difference. Harrison and Magill-Evans also looked at parenting stress in their study although they used the earlier long form of the PSI (Harrison and Magill-Evans 1996). They found no significant differences between the scores of preterm and term infants' parents on the parent or child domain score. Feldman and colleagues in their longitudinal study of singletons, twins and triplets also found high levels of stress for PSI-SF total stress scores and report that their mean score for triplets was above the 90th percentile (Feldman, Eidelman et al. 2004). Although the scores they report for the parents of singletons (mean score = 67.5) and twins (mean score = 79.22) were higher than those in this study (mean score = 63.75) for singletons and (mean score = 70.94) for twins, they found significant differences between the singleton and twin parents' total stress scores.

Mothers of twins had significantly higher scores on the PSI-SF parent child dysfunctional interaction scale. This finding shows some support for our hypothesis that they would experience higher levels of stress than mothers

of singletons. Although Feldman and colleagues do not report the means for the subscales they do report finding that scores on this subscale were significantly higher for parents of triplets, which suggests these scores may reflect the additional stress of parenting infants who are harder to interact with. A suggestion supported by the findings in the present study that although twin mothers in a one to one teaching task with their infants scored no lower than mothers of singletons their infants did, offering less clear cues.

Some mothers in the present study (n=5) did have very low scores on the defensive responding scale. The authors of the scale suggest this may mean that the parent is trying to portray themselves as a very competent individual, or that they are not invested in their role as a parent, or that they are indeed a very competent individual with excellent relationships (Abdin 1995). An examination of these five mother's scores on the other scales of the PSI-SF show they scored below the 10th percentile on all except Parent Child Dysfunctional Interaction. This could be seen as support for the idea that these mothers were less engaged with their child.

Correlations between the HOME Responsivity subscale, the NCATS and PSI-SF scores were explored to see if they explained any of the significant findings. Magill-Evans and Harrison found no significant correlations between PSI and NCATS scores however in this study we found mother's social emotional growth fostering subscale score at discharge was correlated with total PSI-SF scores at three months, the more sensitive the mother was to her baby's needs at discharge from hospital the lower her stress scores when the baby was three months. The potential impact of the infant's responsiveness on the mother's level of stress can be seen in the significant correlation found between the child's responsiveness to

caregiver subscale score on the NCATS at discharge from hospital and the mother's total PSI-SF stress score at three months. The less responsive the infant was at discharge from hospital the greater the mother's stress. A study by Veddovi and colleagues already mentioned in chapter two section 2.1-viii, also found an association between being a firstborn infant who was more sleepy and drowsy and greater maternal parenting stress (using the full form of the Parenting Stress Index) at 12 months (Veddovi, Gibson et al. 2004). Although the correlations found in this study were not large they were statistically significant and did account for at least 13% of the variance. Moreover, correlations of 0.3 and above have been defined by one Behavioural Scientist as having a medium effect size (Cohen 1977).

The infant's gestational age was not significantly correlated with any of the outcome measures suggesting that any differences found could not simply be accounted for by their degree of prematurity. Number of days ventilated prior to discharge was used as a marker of how sick the infant was. The only significant correlation between this variable and the outcome measures was a significant positive correlation with mothers' response to distress at discharge. The more responsive the mother was to her infant's distress at discharge the greater the number of days her infant had been ventilated while in hospital. This finding fits with the accounts of mothers in Miles and Holditch-Davis' study (Miles and Holditch-Davis 1995). Qualitative analysis of the mother's accounts of parenting their premature infants revealed how distressing they found watching their infant in special care and this lead to a compensatory style of parenting. However, there was no significant correlation by three months corrected age.

Feldman and colleagues found that when considering the scores of all mothers and their infant (they randomly chose one case from each twin and triplet set) higher PSI stress scores at 3 months were correlated with less sensitive mothering, lower infant symbolic play and cognitive development at 12 months (Feldman, Eidelman et al. 2004). These findings suggest the possible future impact of parenting stress on the child's development. This is supported by Miceli and colleagues who found a composite score of parenting stress and depression at 4 months was related to child behavioural outcome at 36 months (Miceli, Goeke-Morey et al. 2000). Mothers reporting greater stress and depression at 4 months had children rated as showing more internalising and externalising problem behaviours at 36 months.

The finding of significant differences between twin and singleton very premature infants suggests that there is an additional disadvantage to a twin infant over and beyond that of a premature birth. Moreover, twin status does not appear to be simply a proxy measure for how sick the infant was and that this impacted on the mother-infant interaction because there was no significant difference in number of days ventilated prior to discharge. This variable was used as a measure of how sick the infant was prior to discharge. The finding fits with Koeppen-Schomerus and colleagues work which found that, for the highest risk group of twins, genetics mattered less than environment (Koeppen-Schomerus, Eley et al. 2000) and also fits with Laucht and colleagues' findings about the greater impact of quality of environment for the most disadvantaged infants in their study (Laucht, Esser et al. 2002).

This disadvantage may relate to their mothers being less responsive as illustrated by their lower scores on the HOME Responsivity subscale score.

Although able to interact with their infants individually in a way very similar to mothers of singletons, in real life settings, when forced to cope with two infants at once, there was a difference in the quality of environment offered to these very vulnerable infants. Certainly Reissland and colleagues found mothers' verbal interactions differed depending on the situation (Reissland, Shepherd et al. 1999).

Another possibility is that mothers of twin premature infants may be less able to employ some of the compensatory techniques which Barratt and colleagues found mothers of preterm infants using (Barratt, Roach et al. 1992), or the compensatory parenting style described by parents of premature infants in interviews with Miles and Holditch-Davis (Miles and Holditch-Davis 1995), because they always have to interact with two babies at the same time.

Studies reviewed in the introduction to this chapter suggest infants whose mothers are less sensitive and responsive during mother-infant interactions may have poorer cognitive and social development (Rocissano and Yatchmink 1983; Smith, Landry et al. 1996; Holditch-Davis, Bartlett et al. 2000; Poehlmann and Fiese 2001[b]; Laucht, Esser et al. 2002;) and are less likely to be securely attached (Wille 1991; Goldberg, Perrotta et al.). Furthermore, the findings from this study suggest we should be aware that maternal and infant vulnerabilities may not only interact but also be cumulative. The combination of interacting with a very premature infant and interacting in a real life situation with the additional demands of another premature infant present may explain why mothers of twins scored significantly lower on the HOME Responsivity subscale but not when assessed during a one to one situation such as the NCATS. Significant correlations found between child NCATS scores at discharge and mothers'

total PSI-SF scores also suggest an additional impact of an infant who is harder to care for. Continued study of the infants from this study would enable us to explore these issues in a particularly vulnerable sample. Findings from the study by Olivennes and colleagues that, compared to parents of singletons, parents of twin infants at 2-5 years old had higher stress scores and infants with significantly poorer cognitive functioning make this even more pertinent (Olivennes, Golombok et al. 2005).

3.4-i Implications of the study for future interventions

The recognition of a possible interaction between disadvantage, mother-child interaction and the infant's cognitive and social development and quality of attachment has encouraged the development of intervention studies. The study discussed earlier in section 3.1-viii by Poehlmann and Fiese found a mediating effect of quality of interactions on cognitive outcomes with reciprocal and engaging interactions predicting higher cognitive scores after controlling for maternal and neonatal risks (Poehlmann and Fiese[b]). This study suggests the possible benefits of improving mother-infant interactions. Attachment theory stresses the importance of sensitive maternal responsiveness to infants developing a secure attachment any intervention promoting such interaction will be beneficial. A further study by Poehlmann and Fiese previously discussed in section 3.1-vii found that the combination of sub clinical depressive symptoms and preterm birth predicted insecure attachment (Poehlmann and Fiese 2001[a]). A combination of vulnerabilities such as a multiple and preterm birth should be viewed with concern especially as the study reported in the previous chapter suggested mothers of multiples may be more likely to experience depressive symptoms.

A recent meta-analysis of studies of early preventative interventions on parental sensitivity and infant attachment security looked at 70 published studies (Bakermans-Kranenburg, Van IJzendoorn et al. 2003). The authors concluded they could be significantly and moderately effective in increasing maternal sensitivity. Interventions which just focused on sensitivity were the most effective, while interventions with fewer than five sessions were as effective as those with more. Surprisingly interventions which started later were more effective than ones starting pre-natally. Characteristics of the sample such as socio-economic status, prematurity, adolescent mothers and multiple risk factors were not associated with significantly different effect sizes between the studies. Similar results were found for the 29 studies focusing on attachment security although it appeared harder to change showing smaller differences in effect size. Interventions successful in enhancing maternal sensitivity tended also to enhance infant attachment security.

These findings from existing studies on intervention taken with the findings from this present study suggest there may be a place for intervention with parents and their infants after a multiple birth. The high levels of parenting stress found for the mothers in this study suggest they could benefit from interventions to help reduce this stress and to promote effective interaction with their infants particularly given the finding of a significant correlation between total stress scores and two of the NCATS subscale scores: the social and emotional growth fostering and child responsiveness to caregiver subscale at discharge. A study exploring psychological treatments for postpartum depression found that although early interventions showed only some short term benefits, counselling did produce more sensitive early mother-infant interactions (Murray, Cooper et al. 2003). Although these authors did not find any effect of treatment on

infant attachment and certainly the meta analysis of intervention studies (Bakermans-Kranenburg, van IJzendoorn et al. 2003) reported above concluded attachment was difficult to change, issues of attachment security should not be ignored. Further research is needed to explore whether parenting stress affects security of attachment and the possible impact of mother-infant interactions on such attachment. Ideas for interventions designed for parents of premature and multiple infants will be explored further in the final discussion of this thesis.

3.4-ii Strengths and weaknesses of the study

This was a multi-centred study which ensured the recruitment of a large sample of high risk very premature infants, thus controlling for the experience of neonatal intensive care. This made it possible to identify a sample of twins and closely match them to a sample of singletons based on their mothers' characteristics. The sample size of 17 twins was considerably larger than the four pairs of twins in the study by Ostfeld and colleagues whose findings had provided an impetus for this study (Ostfeld, Smith et al. 2000). However, as mentioned earlier, the size of the sample may still have been too small to have the power to detect smaller differences between mothers' PSI scores, and infants' NCATS scores. Mothers' scores for the NCATS appear so similar this is not likely to have been an issue for those results. As part of a longitudinal study we were able to relate quality of interaction at discharge with quality of interaction at three months. In the future it will be possible to relate these measures to cognitive development at 2 years old. The study employed standardised, reliable and well validated measures to assess outcomes. Excellent reliability was demonstrated for both the HOME and the NCATS. Moreover, interactions were assessed both in a structured one to one

setting with each twin, using the NCATS, and a real life home setting with the mother and both twins, using the HOME. This study was not able to explore attachment using the Strange Situation because assessments were carried out at discharge and three months. However, the use of validated and reliable measures of mother-infant interaction provided an insight into how attachment might develop. Moreover, higher scores on this measure have been found to correlate positively with attachment security in the Strange Situation at 13 months (Sumner and Spietz 1994).

Raters were not blind to twin status, the way in which the HOME is scored and administered would have precluded blind rating for that measure, and practically it would have been difficult to remove all indications from the video recordings used for the NCATS. However, the study was not originally designed to explore twin status this became a possibility only after a number of twins were recruited. Although a small sample the twins were closely matched for mothers' characteristics to a sample of singletons and there were no significant differences between the twin and singleton infants for gestational age, birth weight, number of days ventilated prior to discharge or IMD. The only variable the two groups were not matched for was intervention however, as already mentioned in the method section no relationship between outcomes and intervention had been found in an earlier study (Glazebrook, Marlow et al. 2007). All the researchers were blind to intervention allocation and in practice more twin than singleton infants received the intervention, though this difference was not significant. No adjustments to significance levels were made to account for multiple comparisons. In view of the small sample size it was felt using Bonferroni corrections, for example, would increase the chance of a type two error. The use of planned comparisons, carefully matched groups and appropriate statistical tests aimed to reduce the risk of a type one error.

3.5 CONCLUSIONS

In support of our hypothesis, mothers of twins were found to show higher levels of parenting stress than mothers of singletons and this was statistically significant for the scale evaluating their interactions with their infants. Given research showing associations between quality of mother-infant interactions and parenting stress with infant cognitive and behavioural development these results should be viewed with concern.

Premature twins were found to be more vulnerable than premature singletons, they provided less clear cues and were less responsive to their mothers when interacting in a one to one teaching task. Mothers of very premature twins were not less responsive or stimulating when interacting with their infants during this task than mothers of singletons; however, they were less responsive during day to day interactions with their infants. These findings together with previous research findings of the importance of environmental factors for high-risk twins and the increased effect of quality of interaction for at risk infants suggest twin status can represent an additional risk independent of prematurity.

The study's results also have implications for IVF patients and clinicians regarding decisions about embryo transfer. After reviewing international data Blondel and Kaminski suggest that the contribution of assisted reproductive techniques to multiple deliveries ranges from two to 24% for twin pregnancies (Blondel and Kaminski 2002). However, these twin pregnancies have in effect been chosen as the transfer of more than one embryo immediately creates the potential for a twin birth. Findings such as these need to be presented to both prospective parents and clinicians involved in such decisions. The next chapter of this thesis will explore

further the choices and decision making process which is a part of all ART pregnancies. The need to investigate how and why couples decide on the number of embryos to be transferred is increasingly important as only 9.1% of UK embryo transfers between 2002 and 2003 were single embryo transfers (HFEA 2005).

CHAPTER FOUR - Study III: Factors affecting couples' decisions about how many embryos to transfer during IVF treatment

4.1 BACKGROUND

The research and studies described in the previous two chapters have shown that mothers of multiples are at increased risk of poorer emotional well-being and that premature twins were more vulnerable than premature singletons in that they provided less clear cues and were less responsive overall to their mothers when interacting. Although, mothers of twins were not less responsive or stimulating when interacting with their infants during a one to one teaching task, they were less responsive during day to day interactions with their infants. These findings are of concern given that the most recent figures available as already reported in chapter two section 2.1, show 23.6 % of all IVF births in the UK are twin or triplet (HFEA 2006) and The National Office of Statistics has suggested that the greater use of fertility treatments is an important factor in the increased rate of multiple births in the UK (National Statistics 2001).

Figures such as these prompted the Human Fertilisation and Embryology Authority (HFEA) to issue guidelines restricting the number of embryos transferred to only two in 2001 (Deech 2001). However, some researchers argued even these guidelines would not be enough to significantly reduce the incidence of twins based on experience from previous attempts to restrict the number of embryos transferred. For example, Engmann and colleagues reviewed the incidence of multiple births after IVF treatment at one assisted

conception centre in the UK between 1984 and 1997. They found that during this period despite the introduction of restrictions during that time which limited the maximum number of embryos transferred to three, there was no change in the probability of a multiple birth (Engmann, Maconochie et al. 2001). Recently the expert group on multiple births after IVF have reported that although the HFEA'S sixth edition of the Code of Practice tightened the policy still further so that a maximum of two embryos could be transferred to women under 40 with no exceptions and a maximum of three to women aged 40 and over (HFEA 2003), while triplet births did decrease twin births continued to rise (Braude 2006). Given that all multiple births, including twins, are seen by the medical community as a complication of IVF because of the increased risk of maternal and neonatal medical complications (Elster 2000; ESHRE 2001), and psychological costs to the families (Colpin, Munter et al. 1999; Glazebrook, Sheard et al. 2004; Olivennes, Golombok et al. 2005) all of which have been discussed in detail earlier in this thesis these figures are worrying.

The health belief model (HBM) briefly described in the introduction section 1.9, can provide a useful framework to explore how and why couples decide to transfer more than one embryo, a decision with the potential consequence of a multiple birth. Abraham and Sheeran describe six factors believed to be important in health care decisions underpinned by this model (Abraham and Sheeran 2005). One factor in the HBM relates to beliefs about susceptibility to the illness, disease or consequences of taking action. For prospective IVF couples this will reflect how susceptible to a multiple pregnancy they believe they are. This will be influenced by information presented to them by the

clinics and so the first section of this chapter will focus on how clinics report success, which will arguably affect this perception.

Two very important aspects of the model are perceived barriers or costs and benefits. Costs or barriers will include both the physical and emotional costs to the couples. The costs to society of embryo transfer will not affect couples' decisions directly however; they will influence legislation, the provision of financial help and possibly information provision and so will also be reviewed. In the case of multiple embryo transfer the most extreme solution is multifetal pregnancy reduction and the literature regarding the costs of this issue will be debated. Different countries have responded to these issues and the costs of multiple embryo transfer in very different ways and the chapter will next review these responses in relation to reducing the number of embryos transferred and current legislation and guidelines. One of the most important aspects of the model to be covered in this chapter relates to the perceived benefits or value of the treatment. With regard to the decision about how many embryos to transfer this will reflect how greatly couples' value the outcome of a singleton or multiple birth. This will involve exploring whether couples are actively seeking a multiple birth.

A further factor in the health belief model relates to the individual's perception of the severity of the illness, or consequences of their action. This will be explored by reviewing couples' knowledge of the risks of a multiple birth and what impact provision of additional risk information can have on their decision. Clinicians' own beliefs and knowledge about the possible risks of a multiple birth will also be important to consider here as these are likely to impact on how information is presented to couples.

This introduction will explore whether the HBM can provide a useful framework to review and guide research about embryo transfer. The chapter will then report a study looking at the factors involved in the decision about how many embryos to transfer. This study should help us to better understand how couples' perceive the benefits and costs of a multiple birth, as well as their own risk of such a birth. Cues to action will be returned to in the discussion section of this chapter. The discussion will debate how both the literature reviewed and the results from the study reported can be used to improve these cues.

4.1-i Perceived susceptibility: how clinics report success

As mentioned, one factor of the health belief model concerns perceived susceptibility: the way in which clinics present their successful pregnancy rates may affect how likely couples see the chance of a multiple pregnancy. Jones and Schnorr while calling for action on multiple pregnancies, talk of the competition among treatment programs to achieve and report high pregnancy rates (Jones and Schnorr 2001). Hazekamp and colleagues in their debate on how to avoid multiple pregnancies advocated clinics publishing success rates in terms of birth per embryo transferred which although at first sight might appear to lower success rates actually reflects the chance of a healthy baby (Hazekamp, Bergh et al. 2000). Indeed the ESHRE Capri Workshop Group went so far as to suggest clinics should publish twin and triplet rates separately as complications of ART procedures (ESHRE 2000). Pennings suggests that multiple pregnancies would never be tolerated if the standard 'the best interest of the child' was adhered to (Pennings 2000). In 2002 the chairman of ESHRE described multiple pregnancies as, both the most serious

and most frequent complication of Assisted Reproductive Techniques (ART). He concluded his seminar on female sub-fertility with the injunction that the most appropriate outcome measure of ART was singleton live birth rate per cycle rather than pregnancy rate (Evers 2002).

This plea for changing the way success is represented has been echoed increasingly by others in the field. In 2004 Min and colleagues argued that the most relevant standard of success for couples considering IVF was, delivery of a single term gestation live baby per cycle initiated which they termed BESST (Birth Emphasizing a Successful Singleton at Term) (Gardner, Surrey et al. 2004). The authors claimed that despite this being so obviously the statistic needed by couples, and one might argue by couples trying to compare clinics; they could find no references in the literature to such an outcome measure. In an attempt to encourage others to do the same they went on to report such a statistic for Monash IVF programme in Australia for 2001 as 11.1%. Another member of the Monash team argued that only by adopting BESST could there be a philosophical shift from the emphasis on achieving a pregnancy to delivery of a single healthy baby (Healy 2004). However, Alper argues patients inevitably focus on delivery rates and will not appreciate that a lower pregnancy rate with a lower multiple pregnancy rate is actually better (Alper 2004). This argument was born out by one study which actually asked how patients had chosen the private UK IVF clinic they attended (Lass and Brinsden 2001). This questionnaire survey of 175 patients found the most important factor in their choice was the clinic's success or delivery rate.

These arguments have spawned a whole series of debate articles in one of the most important journals publishing in the area of ART: Human Reproduction.

Buckett and Tan for example argue that in other areas, medical interventions do not exclude from successes cases in which complications have arisen, and so they argue that the safe delivery of healthy twins should not be excluded, rather couples need to be counselled concerning the risks so they can make informed decisions (Buckett and Tan 2004). Dickey and colleagues also argue against only singleton births being viewed as successes. They maintain that before 1998 when transfer of three or more embryos was common the increased incidence of premature birth in twins was often as a result of the pregnancy starting out as a triplet or higher order birth (Dickey, Sartor et al. 2004). Wennerholm and Bergh take issue with another assumption of BESST arguing that singleton live births should include preterm births because of the multifactorial aetiology of preterm births which means the rate can be little influenced by individual clinics and is associated with the population studied (Wennerholm and Bergh 2004). Davies and colleagues suggested a further problem with the use of BESST: that when applied over time because it placed weight on the implantation rate which also increased over time it was possible for the BESST score to improve over time although the multiple pregnancy rate also increased (Davies, Wang et al. 2004).

Pinborg and colleagues go further and maintain that no one measure of success can adequately reflect the complexities of ART and propose instead three parameters of success: 1) the number of oocytes per aspiration, 2) the number of ongoing implanatations per embryo transferred and 3) the number of deliveries per embryo transferred. This will enable all aspects of ART to be evaluated: the stimulation, the laboratory embryo transfer stage and the outcome. They also call for separate recording of the proportion of elective and non elective single embryo transfer (Pinborg, Loft et al. 2004)[e]. Land and

Evers also maintain that the elective single embryo transfer rate is the ultimate measure of a clinic's safety and efficacy and as such is the most relevant qualifier of performance, although they acknowledge (eSET) cannot be mandatory for all patients (Land and Evers 2004).

Heijen and colleagues argue that not only should the success rate be defined in terms of the number of term singleton babies but that the denominator should be changed also and the number of term singleton babies should be expressed as the rate per IVF treatment or within a given treatment period. They suggest that by presenting outcomes in terms of each IVF treatment it will be easier to demonstrate to couples the advantages of transferring only one embryo (Heijnen, Macklon et al. 2004). Further argument in support of such reporting is provided by the finding by Olivius and colleagues that 54% of patients at one centre discontinued their IVF program before achieving a live birth and completing the three free IVF cycles they were entitled to; and that the most common reason for this, applying to 26% of the couples, was psychological burden.

These findings suggest how difficult it will be to try and get patients to sign up for treatments which might take longer to yield results and how beneficial protocols which are less psychologically burdensome would be (Olivius, Friden et al. 2004). We must acknowledge however, that this could pose problems for clinics as if they try to publish success rates at for example, regular yearly intervals, they would have problems knowing when to include some patients. Griesinger and colleagues also argue against one universal standard of success for ART being employed suggesting the most useful outcome measure for patients will be live birth per ovarian stimulation started, while for clinical

studies the outcome measures should depend on the hypotheses tested questioning for example what we mean by 'healthy' (Griesinger, Dafopoulos et al. 2004). Goldfarb in a recent letter to the editor has suggested that rather than pregnancy rates implantation rates should be reported (Goldfarb 2006) and so the debate continues.

4.1-ii Costs

Economics also play a determining role in decisions about embryo transfer and are inevitably a consideration for all involved from health care providers, insurance companies to the individual couples themselves. Schmittlein and Morrison's study of the marketing of IVF brings together the issues of success rates and economics (Schmittlein and Morrison 2003). They reported on the growing number of clinics in the USA which offer couples a one off fee which covers up to three cycles of IVF and their money back if they are unsuccessful. However the authors argue such marketing will induce couples to start on IVF before trying other less invasive techniques and so although likely to be successful they are also more likely to conceive multiples.

The economic consequences of preterm birth and low birth weight have been documented by Petrou both of which outcomes are more likely after a multiple birth (Petrou 2003). In his survey of the scientific literature reporting on the economic costs of such births he found that hospital costs during the neonatal period were more than four times higher for babies born weighing less than 1000g compared to those weighing at least 1500g. Costs after the neonatal period were also higher and these included not only the increased likelihood of use of hospital and community services, and special schooling but also

economic consequences for the mothers who may not be able to return to employment as they had intended.

Recent studies of the cost analysis of singleton versus twin pregnancies in Europe have shown, hardly surprisingly, that the medical costs for a twin pregnancy are higher. A twin pregnancy costs five times more than a singleton in the Netherlands, primarily due to the increased maternal and neonatal hospital admissions (Lukassen, Schonbeck et al. 2004). A cohort study in Finland compared the costs of twin and singleton IVF neonates to matched controls. IVF singletons were more expensive than control singletons and while IVF twins were no more expensive than control twins, twins were three times as expensive as singletons. The authors also advise that these calculated costs were likely to be an under estimate as they did not take into account travelling costs and days lost due to sickness which are likely to have been an issue for mothers of twins (Koivurova, Hartikainen et al. 2002). Garceau and colleagues carried out a systematic review of the economic implications of assisted reproductive techniques in 2002 and they also made the point that most studies do not take into consideration the indirect costs to society such as the loss to the workforce of couples who may have previously been highly productive (Garceau, Henderson et al. 2002).

In America there has been fierce debate over whether there should be mandated insurance coverage for ART, at present some states have insurance coverage for ART while others do not. Part of this debate has centred on the argument that insurance coverage will lower the number of multiple births, due to pressure from the companies to transfer fewer embryos to reduce the increased costs of such a birth. Addor and colleagues suggest that infertility

treatments "increase the absolute number of fragile infants that use specialized care" (page 214) (Addor, Santos-Eggimann et al. 1998). While evidence from a study of Swedish IVF children found that an IVF twin born in 1991-1993 used an average of 13 days hospital care compared to only 5.6 days for a singleton IVF child (Ericson, Nygren et al. 2002). Researchers have calculated that a twin delivery doubles the maternal and neonatal charges in America (Callahan, Hall et al. 1994).

Reynolds and colleagues carried out a study to explore whether insurance coverage really did have a significant affect on embryo transfer (Reynolds, Schieve et al. 2003). The number of embryos transferred and the multiple birth rates of three American states with mandated insurance coverage were compared to three without coverage. They concluded that mandated coverage for ART did affect embryo transfer practices with fewer embryos being transferred. However, they were unable to make any conclusive statements about the effect of mandated insurance coverage on the risks of a multiple birth. This was because although the proportion of triplet or higher order multiple births was lower in all three states with insurance coverage it was only significant for one where it was linked to differences in implantation rates and foetal losses and the authors suggest this may have been due to differences in patient selection. Further research is needed before the full impact of mandated insurance on multiple birth rates can be ascertained.

There are of course enormous financial implications associated with the decision about the number of embryos to transfer for the couples themselves. A multiple birth will inevitably bring increased costs from the obvious ones such as increased initial outlay for equipment (Bryan 2002) to the finding that

mothers of multiples were significantly less likely to be in paid employment one year postpartum (Glazebrook, Sheard et al. 2004) and when the infants were even older (Olivennes, Golombok et al. 2005). In the UK where provision of IVF on the NHS has been patchy with many couples funding their own ART they have had to balance the potential expected costs of a multiple birth with the known costs of further treatment cycles. We might expect to see changes here in the UK as a result of the new NICE guidelines described in chapter two section 2.5 (NICE 2004). However, in the first instance the government is only committing to funding one cycle so couples may still feel financial pressure to transfer more than one embryo. How different countries are dealing with issues of costs and funding relates also to legislation and policy decisions within countries which will be explored further in a later section of this chapter.

Recent analysis of the costs to the National Health Service (NHS) in the UK have clearly shown the increased maternal and infant costs of a twin or triplet IVF birth compared to a singleton birth (Ledger, Anumba et al. 2006). The ratio of costs per singleton versus twin family was 1:2.75. Moreover, based on figures for the year studied 2000-2001 although IVF singletons represented 73% of the total number of live IVF births they incurred only 46% of the total costs of IVF. While separate bodies continue to bear the burden of different aspects of fertility treatment, with couples funding the ART and the NHS the maternal and neonatal health care costs, it is unlikely that we will see a cost-effectiveness analysis of the options available here in the UK. In Sweden just such an analysis was carried out, comparing the hypothetical costs to society of the transfer of two actual or one hypothetical embryo. The researchers concluded that even though more treatment cycles might be needed to

achieve the same take home baby rate when only one embryo was transferred it was still more cost effective because of the associated lower risk of a twin pregnancy (Wolner-Hansen 1998).

In a later study De Sutter and colleagues were able to utilise published data from pregnancy registers and hospital records to calculate the cost per child born in terms of IVF procedure, pregnancy and neonatal related costs for double and single embryo transfer. They were able to demonstrate that although more ART cycles would be required to obtain the same number of children born after single embryo transfer because of the avoidance of twins the cost per child would still be no more and long term costs would be reduced because of the increased morbidity of twins (De Sutter, Gerris et al. 2002).

In a more recent study Gerris and colleagues analysed the differences in maternal and neonatal costs in a prospective study of women less than 38 years old and in their first IVF/ICSI cycle choosing single (eSET) or double (DET) embryo transfer. They found no significant differences in the live delivery rate for these good prognosis patients however the total costs for DET were significantly higher due to the increased neonatal costs caused by some very expensive twins. Moreover, as the authors point out the costs of raising twins will be greater every year compared to those for raising a singleton (Gerris, De Sutter et al. 2004).

A randomised controlled trial in the Netherlands compared two cycles with single embryo transfer to one cycle with double embryo transfer for women aged less than 35 on their first IVF cycle with at least one good quality embryo available (Lukassen, D.Braat et al. 2005). Results showed two cycles with SET

were as effective as one with DET and the medical costs per live birth up to 6 weeks were similar. However, if lifetime increased costs of handicap in the DET group were included the authors argue the costs would be higher. Researchers in Sweden calculated and compared the outcomes and total costs to society of two embryo transfer strategies, cumulative eSET (one fresh single embryo transfer followed by one additional frozen-thawed SET if no live birth) and DET until six months after delivery. This study included women who were under 36 years old and undergoing their first or second IVF cycle and had at least two good quality embryos (Kjellberg, Carlsson et al. 2006). Results showed that the DET strategy although achieving more deliveries of at least one live-born child had higher costs in terms of more premature and low birth weight babies and increased maternal and neonatal complications resulting in significantly increased costs for maternal and paediatric health care and loss of productivity.

Arguing that the above study did not go far enough because it only used a sub-sample of good prognosis patients Fiddelers and colleagues went on to carry out a similar study which randomised all consenting women on their first cycle of IVF to one fresh cycle of (eSET) or to one fresh cycle double embryo transfer (DET) (Fiddelers, van Montfoort et al. 2006). They found that one cycle eSET was less expensive, with significantly lower total societal costs per couple, calculated at €7334 compared to €10 924 for the DET couples. However, it was also less effective resulting in 20.8% successful pregnancies compared to 39.6% for the DET group although there were no twin pregnancies compared to 19.5% in the DET group.

Belgium has produced an innovative scheme to simultaneously reduce the number of multiple births and reimburse couples for the cost of IVF treatment (Ombelet, De Sutter et al. 2005). Based on the estimated cost reductions of reducing twin pregnancies by 50% the government now fund all laboratory costs of up to 6 cycles in a lifetime. Based on their findings that 70% of twins and triplets are admitted to the Neonatal Intensive Care Unit (NICU) they calculated that in the short term alone 87.6% of the costs of reimbursing couples would be met while long term costs of for example special schooling would also be reduced. The results from the first year 2003 to 2004 of this policy have since been evaluated and show that the multiple pregnancy rates went down from 24.4% the year before to 8.5% while the ongoing pregnancy rate was 29.7% (De Neubourg, Gerris et al. 2006).

There are however other ways to evaluate costs and outcomes. For example Ryan, a health economist, argues that health outcomes are not all that should be considered when measuring the benefits from health care interventions (Ryan 1999). She argues that using the technique of conjoint analysis it is possible when evaluating IVF to take account of patient preferences and consider attributes beyond just health outcomes. Using conjoint analysis she found that couples were interested in factors other than just the chance of having a child and were for instance prepared to trade a slight decrease in the chance of taking home a child for continuity of care from staff during treatment. Greater knowledge of the way individuals make these trade-offs could perhaps be used to promote single embryo transfer.

4.1-iii-Mutifetal pregnancy reduction

Perhaps the most extreme solution to the side effect of a multiple preganacy is multifetal pregnancy reduction (MPR). Berkowitz and colleagues advised the use of this term "whenever the reduction of an apparently normal fetus is performed in an attempt to reduce the risk of premature delivery of other fetuses in the same uterus" (page 1266) (Berkowitz, Lynch et al. 1996). In 1996 they reported on their experience of the technique for 400 cases in their unit at the Mount Sinai Medical Centre (Berkowitz, Lynch et al. 1996). They found that there were medical advantages for the technique in the case of women with four or more foetuses but it was less clear for triplets. By 2002 the Mount Sinai group was able to report on data covering 1000 cases of multifetal pregnancy reduction. By this time they found that unintended loss rates were stable at 5.4% and that gestational age at delivery for finishing numbers of one, two or three fetuses were similar to those of non reduced pregnancies, however they did find that birth weights decreased with higher starting numbers (Berkowitz, Lynch et al. 1996).

The potential benefits of reducing triplets to twins have been extensively debated; as the issue seems to be more controversial. One study looking at the reduction of triplets to twins and comparing them with non reduced twins and triplets found that reduction to twins resulted in fewer pregnancy losses and premature deliveries and that these twins were comparable to expectantly managed twins (Yaron, Bryant-Greenwood et al. 1999). The authors give no details about why some pregnancies were reduced and although they maintain there were no significant differences between the groups for maternal age and parity they were not matched on these variables. A single centre prospective study in France also found reducing triplets to twins significantly reduced the incidence of prematurity and low birth weight (Boulot, Vignal et al. 2000).

Although a prospective study, again we are given no details of why 44% of couples chose to reduce their triplets to twins.

Leondires and colleagues argued that the evidence was not conclusive about the benefits of reducing a triplet to twin pregnancy and so carried out a further study reporting on the outcome of all triplet pregnancies conceived following ART from 1995 to 1997 at one centre in Maryland USA. Of the 127 triplet pregnancies 36% were reduced with 95% being reduced to twins. They found that multifetal pregnancy reduction did not have a significant impact on the probability of a live birth or on gestational age at delivery although the birth weights of the reduced group were significantly higher (Leondires, Ernst et al. 2000). A meta-analysis of all studies published on the MEDLINE data base with more than 20 patients undergoing MPR to reduce triplets to twins looked at outcomes. The authors compared the outcomes of the reduced twins to studies of unreduced triplets during the same time period: 1984 to 2001 (Wimalasundera, Trew et al. 2003). Results showed that the reduced twins were less likely to be delivered before 28 weeks gestation and perinatal mortality was lower and the take home baby rate grater compared to the non-reduced triplets. However, all these studies are hampered by the fact we have no information about the factors involved in the couples' decision and ethical considerations rule out the possibility of a randomised design.

Dodd and Crowther carried out a systematic review of all trials comparing mothers and infants after multifetal pregnancy reduction of triplet and higher order multiples to twins, with outcomes for mothers and infants in twin or triplet pregnancies managed expectantly. Not surprisingly they found no randomised controlled trials, however they identified six prospective studies

with prospective control groups. They concluded that multifetal pregnancy reduction to twins compared to expectant management was effective and outcomes for mother and babies were not significantly different from those for twin pregnancies spontaneously or ART conceived. However, as the authors point out selection bias may well have influenced the results (Dodd and Crowther 2004). All researchers involved in this area acknowledge what a difficult decision couples have to make when deciding whether to proceed with multifetal pregnancy reduction particularly for triplet pregnancies where the potential benefits are less clear.

Although the medical benefits of multifetal pregnancy reduction are continually being evaluated, not only has there been considerably less research on the psychological consequences of such reductions but there are also fewer criteria against which to measure such consequences. Researchers carried out retrospective telephone interviews with 91 of the first 100 women who underwent multifetal pregnancy reduction at the Mount Sinai Medical Centre (Schreiner-Engel, Walther et al. 1995). They found that the women remembered the procedure as very stressful, very painful emotionally and very frightening, despite this 93% said they would choose reduction again. The fact the women did not regret their decision should not belittle the emotional cost of making such a decision and 20% were still experiencing what the authors describe as "moderately strong and persistent dysphoric feelings" (page 546) (Schreiner-Engel, Walther et al. 1995).

An American study looking at the psychological effects of MPR included a control group of women who had conceived twins or singletons after IVF but did not consider MPR (McKinney, Downey et al. 1995). The 34 women in each

group were interviewed by telephone between two months and one year after the procedure. Women who had MPR and were pregnant or postpartum at the time of the interview were no more likely than the control women to report episodes of depression or high levels of symptoms on the Brief Symptom Inventory. Of interest though is the fact that if women were depressed after a selective reduction they were likely to attribute the cause of their depression to the reduction. Women in both groups who spontaneously aborted were more likely to experience periods of depression. The most frequently reported emotion related to the reduction was anxiety. The majority also had feelings of sadness, depression and guilt on the day of the reduction.

To overcome the shortcomings of the above studies being retrospective, French researchers carried out a prospective longitudinal study of women following a multifetal pregnancy reduction and compared them to mothers who did not undergo a reduction and went on to deliver triplets (Garel, Stark et al. 1997). They also concluded that women found the reduction stressful and distressing but that after two years most of the women still in the study had overcome any difficulties experienced. However as the authors point out there were a number of limitations with the study which may have reduced its potential power, these included the small sample size, the fact nearly one third of the eligible sample were not followed up and the relatively short timescale, only 2 years after the delivery. Probably the most important limitation is the fact they were unable to follow up so many women, particularly as the evidence suggests they were likely to have been the most distressed as this group included women who had aborted the entire pregnancy, and those who refused an interview on the grounds they were too upset. The comparison of mothers who had a reduction with mothers who delivered triplets clearly

showed that the triplet mothers had more acute psychosocial problems than the mothers who had a reduction. Moreover as the mothers of triplets were a select sample being of high or intermediate socio-economic status, and none of the children presented any health problems, mothers' problems were likely to have been under rather than over estimated.

Despite the seemingly positive outcomes of multifetal pregnancy reduction these did seem to be linked with the women feeling they were following the advice of their doctor and that it was a part of the process of assisted reproduction. Evidence to suggest that multifetal pregnancy reduction has become an accepted part of fertility treatment comes from what Stone and colleagues describe as the increasing number of multifetal pregnancy reductions performed at their centre: the Mt Sinai Medical Centre with 162 performed in the last year of their study 1999 (Berkowitz, Lynch et al. 1996). Leondires and colleagues review of all their triplet pregnancies found 46 of 127 (36%) patients chose multifetal reduction (Stone, Eddleman et al. 2002).

There is an increasing trend, noted by Stone and colleagues in their above mentioned study, for elective reduction to a singleton since it was first offered in 1993 at their institution. This has culminated in a recent study by Evans and colleagues of their experience of foetal reduction from twins to a singleton at the St. Luke's Roosevelt Hospital Centre USA (Evans, Kaufman et al. 2004). The authors argue that for the small proportion of couples requesting such a reduction, (twin to singleton reductions represented less than 3% of the reductions performed at their hospital) it should be considered a viable request in view of the known risks of a twin birth. Moreover, after carrying out 52 twins to singleton reductions they concluded that couples were more

likely to take home a baby after such a reduction and that the outcomes more closely reflected those for singletons than twins. Despite the undoubted force of these arguments in favour of considering multifetal reduction even in the case of twins to singletons; we need to question whether we can continue to view such reductions as an integral part of assisted reproduction while we continue to transfer more than one fertilised embryo with its concomitant risk of a multiple birth.

4.1-iv Responses to the increase in multiple births - Reducing the number of embryos transferred

In a bid to increase the pressure on clinics to reduce the number of embryos transferred and hence the possible risk of a multiple birth, researchers have looked at both the theoretical and actual impact of transferring fewer embryos. They have also and explored the possibility of screening for patients most at risk of a multiple birth. In 1994 the Danish National IVF Registry was established in Denmark and this provides invaluable information on the treatment, pregnancy outcomes and complications of IVF. Westergaard and colleagues reported that evidence from Denmark during 1994 to 1995 showed that transferring two rather than three embryos did not result in significantly lower pregnancy rates but did reduce the risk of a multiple pregnancy (Westergaard, Johansen et al. 2000).

Researchers in Sweden, after studying the outcome of 1441 women undergoing IVF in Sweden in 1995 to 1997 at a time when two embryos were routinely transferred, concluded that the two most important predictors of birth and multiple birth were maternal age and number of good quality embryos transferred (Standell, Bergh et al. 2000). Using a theoretical model

they concluded that single embryo transfer for selected women: those under 33 could reduce the multiple birth rates, by half from 25% to 13% and that the total birth rate could be maintained by providing an additional transfer of one frozen embryo in those who did not achieve a term pregnancy. Engmann and colleagues as mentioned at the start of this chapter in section 4.1 explored the impact of the HFEA restricting the maximum number of embryos transferred in the UK to 3 on the probability of birth and multiple birth at one UK centre between 1984 and 1997 (Engmann, Maconochie et al. 2001). They found that the likelihood of birth significantly increased over time, while the likelihood of multiple birth remained high at ~30% of all births, this they argued was mainly due to the increase in the number of embryos which reflected improvements in the clinic protocol and laboratory techniques. Retrospective research from the US also concluded that the risk of a multiple birth varies by maternal age and number of embryos transferred (Schieve, Peterson et al. 1999).

Findings such as these have prompted research exploring the possible outcomes of one versus two embryo transfer. Gerris and colleagues demonstrated in a prospective randomised study of single or double embryo transfer in women under 34 with two top quality embryos available, that it was possible to achieve an ongoing pregnancy rate of 38.5%, one similar to that in normal fertile couples (Gerris, De Neubourg et al. 1999). The authors concluded their study by arguing that patients who achieve at least one top quality embryo should be offered single embryo transfer for at least one treatment cycle.

Another study in 1999 by Vilska and colleagues looked at pregnancy rates in two clinics in Helsinki in all cases were only one embryo was transferred during 1997 (Vilska, Tiitinen et al. 1999). One embryo was transferred if only one embryo was available or if elected for by the patient this could be due to the patients' own wishes, medical reasons or risk of ovarian hyperstimulation syndrome. Pregnancy rates if only one embryo was available were 20.2% and 29.7%, this was comparable to the 29.4% rate for two embryo transfers, however 23.9% of these resulted in multiple pregnancies. Although a retrospective study the authors were able to recommend elective transfer of one embryo. Moreover the study can be considered quite conservative as it included women with only one embryo available for transfer, and hence less likely to conceive. Researchers in a later prospective randomized multi-centre trial were able to show that for women with at least four good quality embryos available, by transferring only one embryo dizygotic twins could be prevented with no significant decrease in the pregnancy rate (Veleva, Vilska et al. 2006). These were also possibly less demanding criteria than the two top quality embryos insisted on by Geris and colleagues in their 1990's study.

After the promising results they achieved in 1999 (Gerris, De Neubourg et al. 1999), Gerris and colleagues went on to introduce single embryo transfer into their clinical practice (Gerris, De Neubourg et al. 2002). Patients who were less than 38 years old in their first IVF/ICSI cycle or after a previous delivery were told of the chances of pregnancy after transfer of one top quality embryo and that this would not decrease their chance of pregnancy compared to the rate for the whole IVF/ICSI patient group, couples then chose whether to have one or two embryos transferred. For patients choosing and receiving one top quality embryo transfer there was an ongoing pregnancy rate of 43% while for

patients choosing and receiving two embryos the rate was 44% with a 29% chance of a twin pregnancy. Patients who did not have one top quality embryo were advised to have two embryos replaced, when these patients are added to those with single embryo transfer the pregnancy rate was still 43% with only a 2% rate for twin pregnancies. The authors conclude that single embryo transfer can easily be included in clinical practice for women with a high risk of a multiple birth.

Bhattacharya and Templeton reviewed the literature on SET and concluded that while success in IVF continued to be defined in terms of live birth rates per fresh IVF cycle results from eSET will never convince patients or clinicians as they will always be lower than after DET (Bhattacharya and Templeton 2004). The authors also point out that differences in the funding of IVF will inevitably influence the adoption of SET. In European countries where IVF is subsidised as in Belgium where as already mentioned women under 42 are eligible for 6 fully funded cycles of IVF with a policy of eSET for women under 35 for the first two cycles, eSET can work well as discussed earlier in this chapter in section 4.1-ii in relation to the costs of IVF. In contrast here in the UK they argue, where couples even under the new NICE guidelines will have to fund all but the first cycle we can expect fewer couples to opt for eSET (Bhattacharya and Templeton 2004).

A recent study by Van Montfoort and colleagues studied eSET policy retrospectively (van Montfoort, Dumoulin et al. 2005). They showed that in women less than 38 years old with at least one top quality embryo eSET could be the policy of choice in at least the first three treatment cycles. This was because there were no significant differences in pregnancy rates between

eSET and DET for the first three cycles. The authors described at the end of this study their intention to start a prospective randomised control trial of transfer of one or two embryos irrespective of whether there was a top quality embryo available as they believed their embryo selection criteria had been too strict. Results from this trial are now available and show that to avoid twin pregnancies eSET should be applied to all patients although this halves the ongoing pregnancy rate compared to DET (van Montfoort, Fiddelers et al. 2006). Applying eSET to only good prognosis patients still resulted in a twin pregnancy rate of 12.95% which they argue is unacceptable high.

Even more recent results are now available from these trials which looked at outcomes after a maximum of three IVF cycles (van Montfoort, Fiddelers et al. 2007). The conclusions from this study were that eSET for the first cycle for all patients was not an effective policy. This was because the live birth rate for the first cycle was lower in the case of eSET. The authors suggest this may be because of the high likelihood of the embryo being chromosomally abnormal and so not resulting in a pregnancy in the case of eSET whereas they found with DET there is more likely to be one normal embryo as illustrated by the fact similar live birth rates were found for one good or one moderate quality embryo. Subsequent cycles with DET after the failed eSET cycle meant the twin rate was no longer significantly lower at 10.1% versus 13.4%.

Thurin and colleagues report on a randomised multi-centre control trial of women less than 36 years old with at least two good quality embryos available who were randomly assigned to transfer of a single fresh embryo and if not successful later transfer of a single frozen and thawed embryo or a single

transfer of two fresh embryos. Although they were not able to demonstrate equivalence in terms of rates of live births from the two approaches they were able to show that transferring one fresh embryo and then a subsequent frozen thawed embryo reduced the rates of multiple births and the rate of live births was not substantially lower than that from a double embryo transfer (Thurin, Hausken et al. 2004).

In a further analysis of results from this study Thurin and colleagues looked at only those cycles where all or none of the transferred embryos implanted, in order to explore what maternal and embryo variables predicted implantation (Thurin, Hardarson et al. 2005). They found four variables correlated independently with implantation: first treatment cycle of IVF/ICSI, IVF rather than ICSI treatment, transfer of four cell embryos on day two and ovarian sensitivity. The authors suggest these findings should be used to help women decide on the number of embryos to be transferred.

Most recently Bergh (2005) has carried out a literature review of studies of eSET these included 4 randomised controlled trials and 7 observational studies. She concluded that the results from the randomised control trials showed that for good prognosis patients a satisfactory delivery rate could be achieved although it was significantly lower compared to DET, however subsequent transfers with frozen-thawed embryos could help increase the delivery rate. Inevitably the rates of multiple births were significantly lower after eSET (Bergh 2005). A review by Gerris in the same year concluded that for women under 36 and on their first or second IVF cycle eSET should be advised however it needed to be accompanied by other measures such as reimbursement of costs of IVF/ICSI cryopreservation and changes in the way

results are reported because results from eSET can never equal those from DET (Gerris 2005). An argument supported by research already discussed in the costs section 4.1-ii of this chapter which showed that two SET cycles were needed to match the success rates of DET (Lukassen, D.Braat et al. 2005) and Cochrane review findings that while single embryo transfer reduced the number of twin and multiple births the live birth rate was lower (Pandian, Templeton et al. 2005).

Spurred on by success rates of eSET with younger women regardless of prognosis researchers have explored the possibility of extending eSET to older women. A recent study analysing the results from different treatment approaches for women aged 36 to 39 years old concluded that eSET was effective showing lower cumulative rates of multiple births than for DET and similar live birth rates to younger women after eSET (Veleva, Vilska et al. 2006). The authors suggest that the quality of the embryo rather than the woman's age was important and that embryo morphology should be used to decide on the suitability for eSET among these women.

De Neubourg and Gerris have questioned whether the rate of twins can be even further reduced although by 2004 the number of SETs had increased to 63% of transfers in their centre (De Neubourg and Gerris 2006). In order to do this they analysed the 14 twin pregnancies which had occurred during that year after DET and compared these cycles to those resulting in a singleton pregnancy after DET. They found no significant differences in patient's age, number of cycles in which a top quality embryo was transferred or cycles with embryos for cyropreservation. They conclude by suggesting that to further cut the twin rate eSET needs to be extended to women up to the age of 38.

One interesting and significant finding from the introduction of the Belgian policy of reimbursing IVF in 2003 is that singletons born after eSET are at an advantage compared to singletons born after DET (De Sutter, Delbaere et al. 2006). Singletons born after DET were found to have a significantly lower birth weight and were more likely to be born before 37 weeks gestation than singletons born after eSET even after adjusting for maternal age, parity, treatment characteristics, gender, and embryo characteristics. The authors suggest that the reason for this is because with DET there can be the problem of vanishing twins as discussed in the introduction section 1.4. These studies show that although the chance of a live birth per embryo transfer are lower with eSET, the rates of multiple births are significantly lower, there is an advantage for the baby and the pregnancy rates are promising. However, compromises may have to be made with regard to the need for increased cycles of IVF/ICSI.

4.1-v Responses to the increase in multiple births: single blastocyst transfer

Another development in the transfer of embryos is to delay the transfer until the blastocyst stage. Recent advances have made it possible to culture human blastocysts in the laboratory this process is designed to increase the implantation rate so making the transfer of only one embryo a more attractive and viable option. Gardner and colleagues report on a prospective randomised trial of single versus double blastocyst transfer in 48 good prognosis women under 36 years old (Gardner, Surrey et al. 2004). High pregnancy rates of 60.9% were achieved with single blastocyst transfer and these were not

significantly lower than the 76% achieved when two blastocysts were transferred. However there was no incidence of twins in contrast to the 47% of pregnancies resulting in twins when two blastocysts were transferred. Although these results seem very promising this was a small study of only 48 patients and they were self-selecting, in addition the authors commented that only a small percentage elected to volunteer for the study (Gardner, Surrey et al. 2004).

A larger prospective cohort study in Australia also reports encouraging results. Women with three or more suitable blastocysts elected to have either one embryo transferred (121 women) or two (285 women) during 2000 to 2001 (Henman, Catt et al. 2005). The implantation rate for the embryos was similar for both groups however the multiple pregnancy rate was reduced by over 75%, and there was a slight increase in the chance of taking home a live baby.

An American study looked retrospectively at the outcomes of 41 women who had elective transfer of a single blastocyst and 66 who had two blastocysts transferred (Criniti, Thyer et al. 2005). Results showed that for those women meeting the clinic's strict criteria for single embryo transfer at the blastocyst stage transfer of two blastocysts did not result in improved pregnancy rates however there were significantly more twin pregnancies.

Recently Papanikolaou and colleagues have reported the results of a prospective randomised controlled trial comparing single cleavage stage embryo transfer with single blastocyst stage transfer (Papanikolaou, Camus et al. 2006). The study was stopped early as significantly higher pregnancy rates

were found for the 175 women under 36 years old, assigned to single blastocyst transfer. The rate of delivery was also significantly higher at 32% compared to 21.6% for this group. There were only two cases of twins both monozygotic and these were in the cleavage stage group. These results were very promising although the authors acknowledge that the study did not have sufficient power to assess the potential risks associated with the extension of embryo culture to day five such as birth defects and long term health outcomes.

4.1-vi Responses to the increase in multiple births – legislation and recommendations

Concern over the increase in multiple births after ART has produced a myriad of different responses in terms of laws, regulations and recommendations from around the world. Jain and colleagues in their analysis of trends in embryo-transfer practice in the USA from 1995 to 2001 reported that since 1997 there has been a decline in the number of embryos transferred, and in the percentage of pregnancies with three or more foetuses but an increase in the percentage of live births per cycle (Jain 2004). There is however no federal regulation and decisions about the number of embryos to be transferred are left to the couples and their physicians. However, there are published guidelines recommending a transfer of no more than two embryos for women with what is termed a most favourable prognosis. This includes women less than 35 years old, with good quality embryos and sufficient quantity for cryopreservation.

Given these recommendations it is perhaps not surprising that although the figures show birth rates from triplets or higher order multiple gestations have

declined there was a consistent increase in the rate of twin births from 1980 to 2001, and the percentage of singleton pregnancies has not increased since 1997 (Jain 2004). Reynolds and Schieve reviewed embryo transfer procedures and multiple gestation rates in the USA from 1996 to 2002 (Reynolds and Schieve 2006). They found that increasing numbers of couples were using ART, and although the proportion of IVF procedures in which three or more embryos were transferred had declined this was still the norm. There was no increase in the rate of single embryo transfer, and among patients known to have more than one embryo available rates did not reach even 1.5%. Moreover the rate of transferring two embryos had doubled and multiple gestation rates increased from 21.7% in 1996 to 39.25 in 2002.

Gleicher and colleagues compared ART practices between Europe and the USA and maintain that pregnancy and delivery rates in the USA are higher and that this is not simply accounted for by the transfer of more embryos and so argue that differences in regulations benefit the USA (Gleicher, Weghofer et al. 2006). However they do acknowledge the significantly higher multiple birth rates. Hogue makes the comment in her evaluation of ART that there are issues peculiar to the American system which will make the introduction of a strategy to transfer only one embryo there hard (Hogue 2002). These include a sense of urgency among couples which encourages them to seek out more aggressive treatments, poor or nonexistent health care coverage and competitive pressures on clinicians to achieve higher pregnancy rates.

Australia has not passed any restrictive legislation regarding ART relying instead on the accreditation system it operates for clinics which requests them generally to transfer no more than two embryos. Wang and colleagues

suggest that although the benefits of eSET are discussed many clinics and patients still choose DET (Wang, Lane et al. 2006). However, they do describe how providing detailed information about the risks of twins made it difficult to recruit patients to a randomised eSET trial and that eSET has increased in their clinic as a result of such information from 17% in 2001 to nearly 50% in 2004.

In France there seems to be a growing recognition of the dangers of a twin birth with Olivennes arguing that a twin pregnancy is what he describes as "an adverse outcome" (page 1663) and that twin as well as triplet pregnancies should become the target of new transfer policies (Olivennes 2000). Furthermore as Jones points out in his debate on the reporting of IVF treatments France is the only country to record the number of multifetal and selective fetal reductions, an essential requirement as delivery rates are inevitably influenced by these (Jones 2004).

In the UK too there is increasing debate about the desirability of a twin birth with Templeton decrying the fact that what he describes as the greatest risk to the health of a child the fact that they are born premature is still seen by many as a side issue (Templeton 2000). He urges the UK to follow the lead of the Scandinavian countries, Belgium and the Netherlands and to explore one embryo replacement. He argues that if the uterus is receptive all viable embryos are likely to implant, so limiting the number of embryos replaced and increasing the number of occasions embryos are replaced will give the uterus more opportunities to be receptive.

The NICE guidelines of 2004 on IVF treatment (NICE 2004) as described in chapter two section 2.5 were greeted with great enthusiasm. However, it has quickly become apparent that there are huge geographical variations in how they are being applied meaning that a free market economy is still driving the provision of IVF. The impact of this legislation and the HFEA's current policies on embryo transfer will be more fully discussed in the final discussion of this thesis.

To date Northern European and Scandinavian countries have been the most proactive in reducing the number of embryos transferred. In 2000 the Infertility clinic of Helsinki University Central Hospital introduced a policy of single embryo transfer, with over half of all transfers being elective single embryo transfer (eSET) when at least two embryos are available. Results showed that single embryo transfer can lower the incidence of multiple birth without decreasing the overall pregnancy rate in women under 38 years old (Tiitinen, Unkila-Kallio et al. 2003). Tiitinen and Gissler looked at the change in number of embryos transferred and the multiple delivery rates for the years 1994 to 2002 in Finland. They found a significant increase in the proportion of single embryo transfers from 16.9% to 38.8% in 2002 while the proportion of multiple deliveries significantly decreased from 25.6% in 1995 to 13.9% in 2002 (Tiitinen and Gissler 2004). In January 2003 the Swedish National Board of Health and Welfare released a decree that all IVF treatments should be eSET unless the risk for twinning was considered to be low.

Saldeen and Sundstrom looked at the effect of these recent changes in Swedish legislation and found no decrease in the clinical pregnancy rate but a significant decrease in the rate of twinning after the introduction of the eSET

policy (Saldeen and Sundstrom 2005). These findings were confirmed by Bergh's review already mentioned in section 4.1-iv of this chapter, who reported that preliminary data for 2004 suggested a further increase in the SET rate , an unchanged delivery rate and a multiple birth rate below 10% (Bergh 2005). Research already discussed in section 4.1-ii of this chapter looking at cost effectiveness and number of deliveries with at least one live born child in Sweden also supported SET rather than DET (Kjellberg, Carlsson et al. 2006).

Witsenburg and colleagues presented retrospective data from patients treated at clinics in the Netherlands during 1996-2000 (Witsenburg, Dieben et al. 2005). They report a high dropout rate of couples from treatment after the third cycle of treatment which they link to the reimbursement policy of Dutch insurance companies which usually pay for a maximum of three cycles of IVF. The authors found that despite a policy to transfer only a limited number of embryos and an average of two embryos being transferred there was a twin rate of 24.8%. Consequently in 2002 they started a protocol for single embryo transfer resulting in 29% of transfers being single embryo in 2003 which has reduced the rate of multiple pregnancies to 10%.

To date Belgium has been the only country to actually impose eSET by means of its funding policies for IVF treatment. Since July 2003 a reimbursement system for up to six IVF/ICSI cycles in a lifetime has been introduced (Gerris 2004). Patients who are covered under Belgian health insurance provisions are covered for their medical costs of treatment but can now claim for laboratory costs as well however the number of embryos transferred is regulated by law. All women under 36 years old in their first cycle of IVF can

receive only one embryo regardless of its quality. As discussed in section 4.1-iv of this chapter, early results have been promising with multiple pregnancy rates down to 8.5% (De Neubourg, Gerris et al. 2006). The policy has been described by researchers as "a good example of cost efficient health care through responsible, well considered clinical practice" (page 3) (Ombelet, De Sutter et al. 2005).

The situation in Switzerland and Germany is different however as the law restricts the number of embryos which can be kept beyond the two-pronuclear zygote stage to three. As Germond and colleagues point out this makes eSET impossible in practice as it necessitates the selection of the most suitable embryo (Germond, Urner et al. 2004). These policies have however ensured the development of high standard cyropreservation programmes and so they call for success to be judged in terms of the cumulated delivery rate per oocyte pick-up, further broken down to what they call the cumulated singleton delivery rate (CUSIDERA) and the cumulated twin delivery rate (CUTWIDERA) (Germond, Urner et al. 2004).

Italy has introduced one of the most restrictive laws in Europe on fertility treatment and this fuelled debate here in the UK see for example the BBC world news report (BBC News 2004). The new law states that no fertilisation procedure can produce more than three embryos and that all fertilised pre-embryos must be implanted simultaneously (Boggio 2005). However, infertile couples do have access to free treatment as providing their infertility is properly certified and documented, Italian law requires infertility to be treated. These restrictions could lead to an increase in reproductive tourism by Italian couples.

4.1-vii Perceived benefits: do infertile couples want a multiple birth?

The major justification for the continued practice of transferring multiple embryos has been the argument that infertile couples favour a multiple birth. However, a review of the literature on attitudes towards a multiple birth shows the issue is more complex than just a desire for a multiple birth and many other factors are involved (see table 23 for a summary of the findings). Research looking at attitudes towards multiple births began in the 1990's when Leiblum and colleagues confirmed their hypothesis that after years of failure to conceive infertile women would be more receptive to the idea of a multiple birth than fertile women (Leiblum, Kemmann et al. 1990). The study used a purpose designed questionnaire to assess the attitudes of 3 groups of women undergoing fertility treatment: an IVF group, a group participating in an ovarian stimulation program and therefore at risk of a multiple birth and a group enrolled in a program of artificial insemination with donor semen. A control group of female medical and graduate psychology students was also recruited. All the infertile groups were found as predicted, to be significantly more positive about a multiple birth: they answered yes to the question "would you like to have more than one child in a single pregnancy?" than the control group by more than two to one.

This was followed by the widely reported study by Gleicher and colleagues: one of the first investigations of the attitudes of infertility patients themselves (Gleicher, Campbell et al. 1995). This survey of 3800 couples currently receiving treatment for infertility or who had been seen at the Centre for Human Reproduction in Chicago during the preceding three years found of the

582 couples who responded (only a 15% response rate) 67% expressed a desire for the conception of twins. The desire for twins was significantly positively correlated with the couples' age. In addition the authors argue that although couples indicated an awareness of the increased risk of a twin birth they did not view it as a major concern. On the basis of these findings and the fact that only a multiple birth beyond triplets was rejected by the majority of couples the authors concluded that patients' attitudes were not in agreement with current practices. Another study in the 1990's attempted to explore differences in couples' attitudes by asking each partner to complete a self-report questionnaire independently (Goldfarb, Kinzer et al. 1996). They found all the women expressed favourable or very favourable attitudes towards twins and that they rated twins significantly more favourably than did their male partners. Only 1% of both partners were prepared to consider multifetal pregnancy reduction of twins, and though significantly more men would consider it for triplets this was still only 18% compared to 7% of the women.

Table 23: preference for a multiple pregnancy in infertile women

Author	Year	No	Country	Question/scenario	Timing of question	Preference for multiple pregnancy
Leiblum et al.	*1990*	*51*	*USA*	*% of women responding "would like to have more than one child in a single pregnancy?"*	*During participation in University hospital IVF program*	*89.8%*
Gleicher et al.	*1995*	*582*	*USA*	*% of couples responding "we would have loved to conceive twins"*	*During treatment or <1 year after treatment*	*67%*
Goldfarb et al.	*1996*	*27*	*USA*	*Women's favourability rating for twin outcome*	*On entry to l IVF treatment program*	*4.5*[+]
Murdoch	*1997*	*150*	*UK*	*% of couples responding "one baby" the ideal outcome of IVF treatment*	*Survey of CHILD support group, 30% of respondents had conceived.*	*31%*
Grobman et al.	*2001*	*200*	*USA*	*% of women rating twins desirable or very desirable*	*Attending infertility clinic, at different stages of treatment*	*66.5%*
Hartshorne & Lilford	*2002*	*20*	*UK*	*% of women preferring outcome of blastocyst transfer as higher chance of pregnancy even if same/increased risk of multiple pregnancy*	*Attending patient support group meeting, majority at least one failed IVF/ICSI attempt*	*78%*
Pinborg et al.	*2003*	*870*	*Denmark*	*% of mothers wishing for twins as the first child*	*IVF/ICSI mothers of twins and singletons gave birth in 1997*	*62.3% (singletons) 84.7% (twins)*
Kalra et al.	*2003*	*90*	*USA*	*% of women rating twin pregnancy most desirable outcome*	*Attending university based infertility clinic*	*38%*
Ryan et al.	*2004*	*449*	*USA*	*% of women rating twin/ multiple pregnancy as preferred outcome*	*New patients at 3 clinical sites presenting with infertility*	*20.3%*
Child et al.	*2004*	*460*	*Canada*	*% of women saying twins ideal number with next fertility treatment*	*Attending university hospital fertility clinic*	*38.9%*
Murray et al.	*2004*	*200*	*UK*	*% of couples responding no to "would you prefer a single baby?"*	*Attending at Assisted Reproduction Unit for first IVF cycle*	*38.5%*
Steures et al.	*2005*	*40*	*The Netherlands*	*% of couples wishing to continue even if 100% chance of multiple pregnancy*	*First visit to gynaecologist for sub-fertility*	*77%*
Blennborn et al.	*2005*	*137*	*Sweden*	*%of women having 2 embryos transferred*	*After embryo transfer*	*58.8%*
Porter & Bhattacharya	*2005*	*12*	*UK*	*Number accepting the possibility of twins as outcome of DET*	*On waiting list for IVF treatment*	*12*
Coetzee et al.	*2007*	*298*	*New Zealand*	*% of SET IVF/ICSI cycles*	*Year following policy change to SET and emphasis on healthy singleton birth*	*49%*
Newton et al.	*2007*	*79*	*Canada*	*% of women rating a twin pregnancy as very or extremely desirable*	*Immediately after fresh embryo transfer*	*45%*

[+] Mean rating (1 very unfavourable - 5 very favourable)

The majority of this early research was carried out in the USA however, one study appeared to find favourable attitudes in the UK too, during a survey of all members of CHILD (a support group providing support and information to people undergoing infertility investigations or treatment in Great Britain) in 1997 (Murdoch 1997). The authors received 150 replies to the question "what is the ideal outcome of IVF treatment", of these only 31% of couples answered "one child". The majority of couples (64%) were also prepared to consider selective reduction of high multiple pregnancies so that more embryos could be replaced to increase the chance of pregnancy. However, it is important to remember that 30% of these respondents had already conceived after IVF pregnancy and of these 30% had had a twin birth, and so to some extent their replies may just be justifying decisions already taken. Some support for this theory can be seen in the findings of the study by Pinborg and colleagues which as described in chapter two secton 2.1-viii looked at the attitudes of IVF twin mothers towards twins and single embryo transfer and compared them to a control group of IVF singleton mothers and mothers of naturally conceived twins (Pinborg, Loft et al. 2003)[b]. Perhaps not surprisingly they found that two thirds of the IVF mothers disagreed with single embryo transfer and significantly more preferred twins as their first delivery compared to the IVF singleton mothers or the mothers of naturally conceived twins.

A prospective study by Grobman and colleagues found that although 67% of the 200 non pregnant women attending an American Memorial Hospital infertility clinic expressed a desire to conceive a twin pregnancy they were not able to accurately estimate the risks of such a pregnancy (Grobman, Milad et al. 2001). They also found that the majority of women rated a triplet pregnancy as undesirable, whereas other studies had found only a

multiple pregnancy beyond triplets was rejected (Leiblum, Kemmann et al. 1990; Gleicher, Campbell et al. 1995; Goldfarb, Kinzer et al. 1996).

In an extension of this study researchers reported on differences and similarities found in the responses of 90 couples individually interviewed. Although the women provided significantly higher estimates of the risks they were asked to rate, the majority of women (68%) and their partners (64%) rated a twin pregnancy as desirable (Kalra, Milad et al. 2003). However there was some disagreement between the couples as for 21% only one partner believed a twin gestation to be the most favourable outcome. The researchers were unable to find any identifiable factors for this difference, but suggest it could place an additional strain on those couples who go on to have a multiple birth.

Despite increased media coverage and interest in the debate about multiple births for example the BBC News website coverage of the story headlined "IVF multiples 'strain marriages'" (BBC News 2003), newspaper articles such as "Pointing the finger reducing multiple births could save many babies' lives" in the Times (Parry 2007), and more information available such as the "Have you considered a multiple birth?" website by PregnancyMD.org (PregnancyMD.org) more recent studies also report couples preferring a multiple birth. One study found 41% of patients (at all stages of treatment) attending a fertility clinic in Canada during 2000 desired a multiple birth as the outcome of their fertility treatment (Child, Henderson et al. 2004). Factors increasing the desire for a multiple birth were increasing length of infertility or previous cycles of assisted reproductive treatment which the authors suggests indicates the desire for an 'instant family'. Patients with children already and those recognising

the increased foetal risks of a multiple pregnancy were significantly less likely to want a multiple birth.

Another more recent study found that 20% of new infertility patients surveyed at three clinics in Iowa during 2001 to 2002 ranked a multiple pregnancy as their preferred treatment outcome compared to a singleton pregnancy (Ryan, Zhang et al. 2004). The desire for a multiple birth was found to be associated with a number of patient characteristics: nulliparity, lower family income, younger patient age, previous evaluation for infertility, limited knowledge of the outcomes of a twin gestation and a longer duration of infertility.

Couples' attitudes towards multiple births have also been explored in relation to their attitudes towards multiple embryo transfer. Hartshorne and Lilford explored patients' and health care professionals' different perspectives on multiple embryo transfer in a UK based study (Hartshorne 2002). Past, current and prospective patients attending an open meeting of the Centre for Reproductive Medicine Patient Support Group and delegates attending relevant conferences were presented with baseline information about blastocyst transfer and the risk of a multiple birth and then asked to complete questionnaires about the trade-off between multiple pregnancy, and any pregnancy with blastocyst transfer. The authors were keen to gather this information in preparation for a multi-centre clinical trial comparing blastocyst culture with current embryo transfer (on day two or three). Twenty two patients and 51 delegates (33 embryologists and 18 clinicians) completed questionnaires. Some interesting differences were seen in the responses to the quantitative questions about balancing potential risks of a multiple pregnancy with the potential of a higher pregnancy rate after blastocyst transfer. Almost 80%

of patients preferred options which increased the chance of pregnancy, and nearly half of those accepted an increased risk of a multiple pregnancy. However, fewer than 5% of the health care professionals would prefer the option increasing the chance of a multiple pregnancy. The majority of the patients completing the questionnaires were already on at least their second attempt at IVF/ICSI and their responses seem to reflect a desire for a pregnancy with any associated risks being accepted in order to achieve this outcome.

One UK study asked couples about the acceptability of a hypothetical policy of eSET, their knowledge of the risks associated with a twin IVF pregnancy, how many embryos they would like transferred and how they felt about a twin pregnancy; as part of a study looking at ways of better informing couples about the risks of a multiple birth (Murray, Shetty et al. 2004)**.** They found only 38.5% of couples responded "no" to the question "would you prefer a single baby?", however, over 90% of each group also said they would not mind having twins, and over 70% of all the couples said they would like two embryos transferred. Providing couples with extra information did not influence acceptance of a hypothetical policy of eSET with couples only prepared to accept it if pregnancy rates were unchanged. The study suggests couples' main aim is to achieve a pregnancy and rather than desiring a twin birth they are prepared to accept one in order to achieve a pregnancy.

A study by researchers in the Netherlands looked at acceptance of the risk of a multiple pregnancy in couples attending for their first visit to a gynaecologist for sub-fertility (Steures, Berkhout et al. 2005). They found that even when presented with a 100% risk of a multiple pregnancy 77% of couples chose intrauterine insemination in preference to expectant

management. A Swedish survey of couples following embryo transfer found that, despite good information about the risks of a multiple pregnancy and the physician's positive attitude towards eSET, only a third of the couples with at least two available embryos opted for eSET (Blennborn, Nilsson et al. 2005). However, of those who did nearly 70% reported that their decision had been influenced by the possibility of having twins. Interestingly the most commonly reported factor to have strongly influenced the couples' decisions in both the eSET and DET groups was physician's advice. A recent qualitative study exploring patients attitudes towards eSET found all the 20 couples taking part in the semi-structured interviews had discussed the possibility of twins and although not expressing a preference for twins were happy to accept the possibility, believing DET increased the chance of pregnancy (Porter and Bhattacharya 2005).

A recently published study explored retrospectively the proportion of single and double embryo transfers before and after a private clinic in New Zealand adopted a policy to follow eSET (Coetzee, Stewart et al. 2007). With the new policy emphasis in all patient information was presented in terms of the importance of the birth of a healthy singleton. The change in policy and emphasis of information had a large effect. The uptake for eSET had risen by the last quarter of 2004 (after the introduction of this policy) to 90% for women younger than 36 years old and 45% for those older than 35. The overall pregnancy rate did not significantly decline only changing from 44% to 43%. Ministry of Health funded patients at the clinic were advised that the Ministry was considering funding a second cycle for those women failing to get pregnant provided their first cycle had been SET. The authors acknowledge the importance of funding was shown in the fact that the proportion of eSET cycles went up from 19.4% to 63%

for publicly funded patients while only from 4.8% to 29.6% for privately funded patients.

One Canadian study asked participants to complete a questionnaire immediately after fresh embryo transfer (Newton and McBride 2005). (This study will be discussed here although it was actually only published after the study to be reported in this chapter was carried out and so could not influence it.) Of the 140 couples invited to participate 79 women and 53 men representing 80 couples did so; with both partners interviewed in 52 cases. Participants were asked to rate their satisfaction with the number of embryos they had had transferred and to consider the desirability of eSET, DET, a twin pregnancy, and their personal likelihood of a twin pregnancy. When asked about how many embryos they had wanted transferred 75% of the women rated DET as very or extremely desirable, although only 45% rated a twin pregnancy as very or extremely desirable. The authors looked at factors affecting initial attitudes towards eSET and DET, multiple regression analyses showed that two predictors made unique contributions these were estimate of the personal likelihood of twins and perceived increase in the chance of pregnancy with DET rather than eSET. Findings suggesting women are motivated by a desire to increase their chance of pregnancy.

4.1-viii Perceptions of risk or severity of a twin or multiple birth

As outlined at the start of this chapter the health belief model regards beliefs about the risks or severity of an action as an important factor in determining whether that action will take place. With regard to deciding about the number of embryos to transfer both the couples' and the clinicians' ideas about the risks of a multiple birth need to be explored. Despite considerable debate about ways to reduce the number of multiple

pregnancies, there still appears some reluctance for clinicians to condemn twin births as a complication of ART. Support for this idea that a twin birth is not necessarily seen as a poor outcome by clinicians comes from Hock's survey of board-certified reproductive endocrinologists in the USA (Hock 2002). Although over 90% of practitioners believed it worthwhile to decrease the risk of higher order pregnancies even if this would decrease their overall pregnancy rates only 74% believed it was worthwhile at the risk of decreasing their twin gestation rate. Further evidence can be found in a study by Peterson and colleagues in which they looked at risk data for higher multiple order pregnancies of interest here is the fact a good outcome rate was defined as "singleton or twin deliveries per cycle" (page 1535) (Peterson, Reading et al. 2004).

D'Alton has suggested that one barrier to reducing multiple births is the need to convince and educate the clinicians and physicians themselves of the dangers (D'Alton 2004). For example he suggests one explanation for a recent study's finding that although new infertility patients in Iowa knew of the increased risk of preterm delivery and increased pregnancy and delivery risks for the mother with a multiple pregnancy, they were less well informed about the risks of cerebral palsy and infant mortality (less than half knew of these) (Ryan, Zhang et al. 2004); may be that their physicians too had limited knowledge (D'Alton 2004). An argument supported by Hankins and colleagues who found when surveying practicing obstetricians about their knowledge of neonatal encephalopathy and cerebral palsy that not only did over half rate their knowledge as poor but the majority answered less than half of the knowledge questions correctly (Hankins, Erickson et al. 2003).

Furthermore a study by Paterson-Brown and colleagues found the use of meta-analytical overviews of care (published overviews of randomised controlled trials in English obstetric units) to be low and the authors suggested this reflected a reluctance by obstetricians to adapt their practices as a result of evidence from randomised controlled trials (Paterson-Brown, Fisk et al. 1995). The study thus provides further evidence that clinicians are mostly influenced by their own experience and contacts. Alper made an emotional appeal for doctors to take responsibility for the increase in multiple births in his paper aptly entitled "In vitro fertilization outcomes: why doesn't anyone get it?" (page 514) (Alper 2004). Moreover he recounts an incident were physicians themselves where unable to educate other physicians about the true meaning of their IVF statistics. The potential impact of a clinician's knowledge and conviction can be seen in the studies reporting difficulty recruiting patients to randomised trials of SET such as that described by Wang and colleagues already mentioned in section 4.1-vi of this chapter (Wang, Lane et al. 2006).

Clinicians do not seem to be universally convinced about the benefits of eSET. Gleicher and colleagues argue that in view of lower success rates with eSET and the preference as they describe it of some infertility patients to conceive twins, eSET should not be universally applied and will be the right transfer option for only a minority of patients (Gleicher, Weghofer et al. 2006). Some clinicians go even further and debate whether twins should be seen as an adverse outcome, arguing that typically twin pregnancies result in the birth of two healthy babies (van Wely, Twisk et al. 2006). Support for this view has been recorded in letters to the editor of the journal publishing that opinion (Belaisch-Allart 2007).

With regard to prospective IVF parents' attitudes towards the possible risks of a multiple birth some of the studies already mentioned in section 4.1-vii looked at risk. The prospective study by Grobman and colleagues attempted to explore women's actual knowledge of the risks of a multifetal pregnancy and whether this would affect their desire to achieve a multiple pregnancy (Grobman, Milad et al. 2001). As reported earlier they found that although 67% of the 200 non pregnant women expressed a desire to conceive a twin pregnancy they were not able to accurately estimate the risks of such a pregnancy. Moreover, when women were given the actual probabilities of certain perinatal complications associated with a twin pregnancy, for example delivery of an infant weighing less than 1500g; they expressed significantly less favourable attitudes than those they had originally expressed. This is in contrast with the study by Gleicher and colleagues as they had claimed women were educated about the risks of a multiple pregnancy, however this was only assessed by responding to the question "A twin delivery carries a significantly increased (or very little additional) risk to mother and babies" (Gleicher, Campbell et al. 1995), which as Grobman and colleagues point out allows for an individual interpretation of the risks involved (Grobman, Milad et al. 2001). Confirmation of this theory can be seen by the fact answers were not clearly affirmative or dismissive of these statements. Another interesting finding in the Grobman and colleagues study was that although 89% of the women who had IVF reported being counselled regarding the risks of a multiple gestation, counselling did not significantly affect a woman's risk estimate of the complications associated with a multiple gestation.

In an extension to this study researchers reported on differences and similarities found in the responses of 90 couples individually interviewed. As mentioned earlier despite women providing significantly higher

estimates of the risks they were asked to rate, the majority of women (68%) and their partners (64%) rated a twin pregnancy as desirable (Kalra, Milad et al. 2003). The study by Child and colleagues already mentioned as finding 41% of patients (at all stages of treatment) attending a fertility clinic in Canada desired a multiple birth, did find patients with children already and those recognising the increased foetal risks of a multiple pregnancy were significantly less likely to want a multiple birth (Child, Henderson et al. 2004). The authors argue that as the only significant variable associated with recognition of increased foetal risks of a multiple birth was previous assisted reproductive treatment and that during clinic appointments and counselling sessions patients are informed of the risks of a multiple pregnancy this is an indication of the role patient education could play in reducing the desire for a multiple birth.

The study reporting that 20% of new infertility patients surveyed at three clinics in Iowa ranked a multiple pregnancy as their preferred treatment outcome also looked at risk (Ryan, Zhang et al. 2004). Although most women knew of the increased risk of preterm delivery and increased pregnancy and delivery risks for the mother with a multiple pregnancy, they were less well informed about the risks of cerebral palsy and infant mortality with less than half indicating they knew of these. The desire for a multiple birth was found to be associated with a number of patient characteristics: nulliparity, lower family income, younger patient age, previous evaluation for infertility, limited knowledge of the outcomes of a twin gestation and a longer duration of infertility. The authors argue that patient knowledge is one area which clinicians should be able to influence, particularly as these patients were generally of a high socio-economic and educational status. However, the UK study described previously as looking at the acceptability of a hypothetical policy of eSET found providing

couples with extra information about risk did not influence acceptance of a hypothetical policy of eSET with couples only prepared to accept it if pregnancy rates were unchanged (Murray, Shetty et al. 2004).

The Canadian study looking at attitudes to embryo transfer immediately after fresh embryo transfer had also looked at risk (Newton and McBride 2005). Participants were asked to rate the desirability of a twin pregnancy after being presented with information detailing the risks of pre-eclampsia, low birth weight and postpartum depression with a twin pregnancy as low moderate or high. The provision of risk information did have an impact on transfer preferences: after the provision of low moderate or high risk information about the risks of twins there was a significant increase in the perceived desirability of eSET. Women reported a decrease in their desire for twins once accurate or high risk information was presented while men showed a decrease when even mild risk information was presented.

The studies reviewed in this section suggest perceived severity of the consequences of a multiple birth does play a role in decision making about the number of embryos to transfer. Both IVF patients and their clinicians' knowledge of these risks can be limited and increasing such knowledge could be beneficial.

4.1-ix Use of the health belief model

So far no studies of infertility or its treatment have been found which used the health belief model. However, as shown by the review of the literature above, it does provide a useful focus to explore perceived costs, benefits, and risks associated with decisions about embryo transfer. The concept of health motivation was introduced recently to the HBM. Health motivation incorporates how concerned an individual is with their own health and the

extent to which they are both able and want to influence it. This factor has been relatively neglected in the health belief model literature (Abraham and Sheeran 2005) probably in part because of its recent introduction. Studies exploring couples' decisions about the number of embryos to transfer have not directly tried to evaluate this concept either. However, it is a useful additional concept to consider as it will have a bearing on how information is presented. Couples' presence at an infertility clinic provides evidence of their huge motivation to achieve a pregnancy as especially in the UK they will have had to make a considerable emotional and financial investment in the process. However, high motivation to achieve a pregnancy does not mean they rate their own health highly. Indeed the research reviewed in section 4.1-viii suggests couples are willing to accept the risk of a multiple pregnancy if it will increase their chance of conception.

Health motivation as well as perceived risks, costs and benefits will all play a role in cues to action about embryo transfer. As discussed in the introduction section 1.9 cues to action can vary from internal symptoms to health promotion campaigns. With regard to deciding about embryo transfer they could encompass information from clinics about success rates and risks. Indirect evidence about these cues to action can be found in the literature reviewed showing couples prefer options increasing the chance of pregnancy even if this means an increased risk of a multiple pregnancy (Hartshorne 2002). The debate about how clinics should present their success rates is also relevant, as arguably providing information in terms of healthy singleton births would provide a cue to action. Other cues to action may come from the media for example recent coverage of Jennifer Lopez giving birth to a healthy baby boy and girl (BBC 2008) may encourage couples to view twins positively. The discussion at the end of

this thesis will look at possible future cues to action in the form of developing decision aids for couples.

4.1-x The need for a further study

In summary, a review of the literature suggests that exploring the factors involved in the health belief model is a useful way to try and understand the apparent contradiction of increasing rates of twin births despite growing recognition of the risks for both the mother and baby of such a birth. Although many infertile women do rate a multiple birth favourably, there are problems with assessing preferences hypothetically or retrospectively; the way in which most studies have explored this. Some of the pressure to replace more than one embryo undoubtedly comes from the couples involved. However, the literature reviewed suggests this pressure is in part influenced by beliefs about the increased chance of conceiving after DET, as well as a lack of knowledge, or unwillingness to accept the risks of twins. Moreover, couples may see twins as the only way of achieving the two child family desired by 53% of all respondents in a recent German study (Stobel-Richter, Beutel et al. 2005).

Couples undergoing fertility treatment are involved to a greater or lesser extent in the decision about how many embryos to transfer. We need to know more about how involved couples actually feel in this decision and what factors they consider at the time of the decision. These are essential areas to study if we want to understand better whether couples are making a truly informed decision to have a multiple birth and what information they would need to do so. This study was therefore designed to explore what factors women and their partners say influences their decisions about embryo transfer. At the time of this study no studies had looked at factors affecting couples' decisions regarding the number of embryos to be

transferred close to the actual decision and so, although this would restrict some of the questions which could be asked, it was decided to ask couples about the decision immediately after embryo transfer had taken place. The information needs of couples would also be considered at this time. The study was to take place at a clinic which reported at the time of the study 27.2% of its 298 live births were multiples (CARE 2004). Results from the study would provide useful information for the development of decision aids and an assessment of whether such an aid would be a useful resource for couples.

AIMS

- To explore the factors influencing women and their partner's decisions about embryo transfer
- To investigate the information needs of couples undergoing embryo transfer

4.2 METHOD

4.2-i Design

A cross-sectional survey of women and their partners who had recently undergone embryo transfer.

4.2-ii Ethics

The study conformed to the Human Fertilisation and Embryology Authority guidelines and approval for the study was granted by CARE Fertility Centre Ethics Committee.

4.2-iii Participants

All English speaking women and their partners (if present) undergoing IVF, ICSI (intra-cytoplasmic sperm injection) or frozen embryo transfer between October 2003 and January 2004, at a centre for assisted reproduction in the UK.

4.2-iv Measures

Decision about Embryo Transfer Questionnaire

This was a structured anonymous questionnaire designed for the study (see appendix four for copy of questionnaire). The first part asks respondents to rate a list of 18 factors according to whether each factor had been a major factor, a strong factor, a minor factor or not a factor in their decision regarding the number of embryos to transfer. Review of the literature informed the selection of most factors. For example Grobman and colleagues had asked patients to rate how much they desired pregnancies of different pluralities (Grobman, Milad et al 2001). This resulted in the questions about desire for a single, twin and triplet birth. We were also interested in whether couples were motivated by a desire to avoid a multiple birth and if so at what plurality. This was because Grobman found the majority of women in their study rated a triplet birth as unfavourable (Grobman, Milad et al 2001) whereas other studies such as that by Gleicher and colleagues found only plurality beyond triplets was rejected (Gleicher, Campbell et al. 1995). This resulted in the questions desire to avoid a twin and triplet birth. Other questions were developed to explore what sources of information couples utilised and valued and so questions such as advice from family or friends and medical advice from CARE were included. The questionnaire was reviewed by the CARE Fertility

Centre Ethics Committee who advised that all couples saw a counsellor and they wanted to know whether couples rated this as an important factor. This resulted in the question advice from CARE counsellor.

The second part of the questionnaire asks for basic demographic details and information about the present cycle of IVF and relevant fertility history. Responses to these questions would enable us to see if other researchers' findings such as length of infertility increasing the desire for a multiple birth (Child, Henderson et al. 2004) could be replicated. Respondents were also asked to indicate their agreement to a statement that probed their perception of eSET on treatment outcome. We were interested to explore couples' perceptions about the probability of pregnancy after eSET given the finding by Porter and Bhattacharya that couples believed DET increased the chance of pregnancy (Porter and Bhattacharya 2005).

Open questions – In addition couples were invited to respond to two open questions. The first asked if they would have liked more help or information in order to make their decision about the number of embryos transferred what sort of help or information they would have liked. The second invited any further comments on their decision about embryo transfer.

The questionnaire did not ask any direct questions about possible risks associated with a multiple birth. This was because it was felt unethical to introduce any worries about such risks immediately after embryo transfer as many women were expected to have had more than one embryo transferred. This was felt to be an acceptable compromise to the outcomes

measured, in order to be able to explore these factors immediately after transfer rather than using hypothetical questions.

4.2-v Procedure

All consenting women received a pack containing a male and female questionnaire, labelled "for you" and "your partner", an information letter and a self addressed envelope immediately after the embryo transfer (see appendix five for a copy of the letter). Male and female partners completed the questionnaires independently and returned them in separate sealed envelopes.

4.2-vi Analysis

Quantitative data were analysed using SPSS version 11.5. Non-parametric statistics were used, as the data were not normally distributed.

Open questions were explored for emerging themes.

4.3 RESULTS

4.3-i Response Rate

During the study period questionnaires were distributed to 110 women and 72 were returned, a response rate of 65.5%. One of the 72 returned questionnaires was excluded because information regarding embryo transfer was missing, and a further three women were excluded because only one embryo was available for transfer making a decision about number of embryos to transfer irrelevant. This gave a final sample of 68 women. Questionnaires were returned by 60 of the women's partners.

4.3-ii Demographic and clinical characteristics

Demographic characteristics of the sample show the women were in their mid thirties, had been part of a relationship for at least two years and had

been trying to conceive for a median of 5 years. The couples were well educated with 46% of the women and 31% of the men educated to degree level or above. The male partners were significantly older than the women, median age 37 compared to 35.5 Wilcoxon matched-pairs test between men and women within a couple ($p<0.01$). Nearly half of the women in the sample were having their first embryo transfer and some had as many as 11 embryos available for transfer. (See table 24.)

Table 24: demographic and clinical characteristics for female partners

Demographic or clinical variable		Number of responses
Median age in years (inter-quartile range)	35.5 (32.25-39.0)	68
Partner's median age in years* (inter-quartile range)	37.0 (34-43)	67
Median years with partner (inter-quartile range)	9.0 (6-13)	67
Frequency educated to degree level or above (%)	30 (45.5)	66
Median years trying to conceive (inter-quartile range)	5.0 (2.63-6)	68
Frequency female partner any children (%)	14 (20.5)	68
Frequency male partner any children (%)	20 (29.9)	67
Frequency first embryo transfer	33 (48.5)	68
Median number of eggs available for transfer (range)	3.5 (2-11)	68

***** The male partners were significantly older ($Z=-3.4$, $P<0.01$)

4.3-iii The Embryo Transfer

Forty five women were less than 36 years old and had more than one embryo available for transfer and so could be considered at high risk of a multiple birth. However they all had more than one embryo transferred, 30 (88.2%) had 2 and 4 (11.8%) had 3 transferred.

A greater number of embryos available for transfer is regarded as a good predictor of successfully conceiving, so for example (Veleva, Vilska et al. 2006) used the availability of four good quality embryos as the criteria to randomize women to single or double embryo transfer in their study. Of the 34 women who had 4 or more embryos available none of the women chose to have only one transferred with 28 (82.4%) having two transferred and 6 (17.6) having three.

4.3-iv Factors Influencing the Embryo transfer decision

Respondents were asked to rate 18 factors influencing their decision about the number of embryos transferred on a Likert scale ranging from "0" not a factor to "3" a major factor as described in the method section. These responses were recoded into affirmative answers if the respondent indicated the factor was a major or strong factor in their decision, and non-affirmative if it was indicated as only a minor factor, or not a factor. The frequency and percentage of male and female partners indicating that the factor strongly influenced their decision regarding embryo transfer is displayed in table 25, ranked by importance for the women. The table shows that the women were not having two or more embryos transferred because they had a desire for twins or triplets but rather that they were influenced by the desire to increase the chance of pregnancy (92.7%), to avoid the need for further treatment (57.3%) or the cost of further treatment 38.8%). See table 25.

Table 25: frequency and (percentage) of male and female partners indicating that the factor strongly influenced their decision regarding embryo transfer

	Women (n=68)	**Men** (n=60)
Wish to increase chance of pregnancy	63 (92.6)	57 (95)
Medical advice from CARE	62 (91.2)	51 (85)
Partner's wishes	57 (83.8)	50 (83.3)
Personal wishes	57 (83.8)	43 (71.7)
Number of embryos available for transfer	46 (67.6)	34 (56.7)
Desire to avoid further treatment	39 (57.4)	30 (50)
Desire for a single birth	35 (51.5)	31 (52.5)
Desire to avoid triplet birth	30 (44.1)	24 (40)
Desire to avoid the cost of further treatment*	26 (38.8)	22 (36.7)
Desire for a twin birth	13 (19.1)	12 (20)
Discussion with CARE counsellor	13 (19.1)	18 (30)
Own research from books journals internet etc	13 (19.1)	10 (16.7)
Advice from GP*	11 (16.4)	12 (20)
Media information e.g. magazines, TV, radio etc	8 (11.8)	4 (6.70
Desire for a triplet birth*	3 (4.5)	4 (6.7)
Advice from family or friends*	3 (4.5)	5 (8.3)
Ethical or religious considerations	2 (3)	1 (1.7)
Desire to avoid twin birth	1 (1.5)	3 (5.2)

***One woman did not rate the importance of this factor

For both partners the five main factors were similar and ranked in the same order of importance, these included; wish to increase the chance of pregnancy, medical advice from CARE, partner's and personal wishes and

number of embryos available for transfer. As expected the most important factor is the wish to increase the chance of pregnancy, however it is important to note that medical advice is regarded as nearly as influential. Of interest also is the low level of importance attached to media information, advice from family and friends and ethical and religious considerations.

4.3-v Desire for a multiple birth

The majority of the couples did not wish for a triplet birth with only 4.5% of women and 6.7% of men indicating it was a factor in their decision about the number of embryos to be transferred. The desire to actively avoid a triplet birth, however is expressed by less than half the couples with only 40 and 44.1% of men and women respectively, claiming the desire to avoid a triplet birth was a factor in their decision.

The couples were not actively avoiding twins with only one woman (1.5%) and 3 (5.2%) of men saying it was a factor in their decision, and none of the women chose to only have one embryo put back. In addition 13 (19.1%) of women and 12 (20%) of the men said the desire for a twin birth strongly influenced their decision regarding the number of embryos transferred. However, agreement between couples about the desire for twins was only moderate, with 9 (15%) disagreeing on whether the desire for a twin birth was a factor, and this is also indicated by the Kappa value of 0.516. Moreover the men and women had similar levels of disagreement with 4 women (6.7%) saying the desire for a twin birth was a factor but whose partner said it was not and 5 (8.3%) men saying the desire for a twin birth was a factor but whose partner said it was not.

Women who welcomed a multiple birth and so rated the desire for twins or triplets as a strong or major factor in their decision were not significantly older, had not been infertile longer, or had more previous IVF cycles. However, women who welcomed a multiple birth did have significantly fewer children already ($Z=-2.1$, $p<0.05$). None of the women with children already reported a desire for a multiple birth (Fisher's Exact Test $p= 0.055$). Men who welcomed a multiple birth did not differ significantly in age, how long they had been trying to conceive or whether they had children already compared to men who did not welcome a multiple birth**.**

4.3-vi Making the Embryo transfer decision

The questionnaire asked about the ease of the decision, and whether respondents felt the number of embryos transferred affects the chance of having a child. Respondents were asked to select from strongly agree, moderately agree, disagree or strongly disagree for each statement. Responses were then recoded so that answers which showed strong or moderate agreement were considered affirmative answers and those which showed disagreement or strong disagreement were non-affirmative.

The decision about embryo transfer was considered 'easy' by 95.5% of the women and 93.2 % of the men.

A very large proportion of both the men (91.7%) and women (95.6%) agreed with the statement "transferring one embryo when two are available reduces the chance of having a child". The majority also agreed with the statement that "replacing three embryos when three are available increases the chance of having a child": 83.8% of the women and 86.7% of the men.

Respondents were also asked if they would have liked more help or information regarding their decision. Over a quarter of the couples would have liked more help or information regarding their decision about the number of embryos to transfer, with 26.9% of the women and 25.4% of the men indicating they would. The women who indicated they would have liked more help or information regarding their decision did not differ significantly from the women who did not in age, education, whether they had children already, or whether they had had a previous embryo transfer. Women who would have liked more information were more likely though to have had two rather than three embryos transferred (Fisher's Exact Test p = 0.050). The men who indicated they would have liked more help or information regarding their decision did not differ significantly from the men who did not in age, education, whether they had children already, whether they had had a previous embryo transfer or how many embryos their partners had transferred.

4.3-vii Open question: additional information desired

Couples were asked what sort of help or information they would have liked. This open question was responded to by 17 females and 12 males of whom 6 were couples giving the same reply, resulting in 23 replies to be coded. These replies were examined for common themes and 5 themes were identified as being raised by at least two individuals or couples. One theme clearly predominated however as it was the basis of 9 (39%) of the 23 replies, this was a desire for more statistical information, in 5 of the replies there was a specific plea for more information regarding success rates according to the number of embryos transferred as illustrated by the following quotes:

"The percentage of successful transfers to number of embryos transferred".

"More information about % success rates after embryo transfer. We transferred 2 embryos since we would be happy with twins but mainly to increase chance of success – we had little advice……".

Other themes identified were a general call for more information (n=4) for example;

"Any information at all would have been helpful".

Another theme was a call for more discussion or time to discuss the transfer decision (n=3) for example;

"More time to consider options".

A less prominent theme was a call for more information regarding egg quality and grading (n=2) for example;

"Could do with more information on grading and cell division."

A further less dominant theme was referring to experts to make the decision (n=2) for example;

"The decision regarding number of embryos transferred was a medical decision, I agreed with their expertise**".**

4.3-viii Open question: other comments

At the end of the questionnaire couples were asked if there were any other comments they would like to make regarding their decision about embryo transfer. A minority of couples did so: 10 (14.7%) of females and 8 (13.3%) of males, of these 3 were couples making the same comment and one was a couple explaining their different views, this resulted in 15 replies to be coded. Replies were again examined for themes, the most common

(n=4) was a further call for more information. More interesting was a new theme which emerged: a desire for more embryos to have been transferred (n=3) for example;

"We would prefer 3 embryos to have been transferred this time to increase chances of pregnancy but only 2 available so there was no choice".

This also accounted for the different opinions expressed by one couple, were the female explained;

"On my 2nd cycle of IV, I had 3 embryos but only 2 transferred. I wish I had been able to have the 3 embryos transferred, but medical staff weren't able to support this due to past medical reasons."

The male partner explained why he did not;

"On second IVF treatment, 3 embryos were available for transfer but only 2 put back. Partner wanted all 3 due to desire to get pregnant but only 2 put back as high risk of twin pregnancy. Myself and doctors thought that only 2 should be put back as we all agreed prior to treatment, including partner."

The final common theme identified concerned an explanation of how the quality of the embryos affected the number transferred (n=3) for example;

"We decided to put 3 back to maximize our chances as none of the embryos were good enough quality to freeze".

4.4 DISCUSSION

The primary research aim of the study reported in this chapter was to explore factors influencing couples' decisions about embryo transfer. The health belief model (HBM) and previous research informed the factors explored. The HBM stresses the importance of perceived benefits to health related decisions and behaviours and so we were interested in looking at how important the desire for a twin or triplet birth was to couples' decisions about the number of embryos to transfer. In contrast to findings by other researchers (Gleicher, Campbell et al. 1995; Grobman, Milad et al. 2001), this study did not find that couples were primarily motivated by a desire for a multiple birth with less than 10% saying the desire for a triplet birth was a factor, and only 20% saying the desire for a twin birth was a factor. However, the couples in both those studies were at all different stages of treatment and their positive attitudes towards a multiple birth may have reflected a desperate desire for a baby at any cost. A view endorsed by Leiblum and colleagues' finding that rather than have no biological children infertile women will endorse even quintuplets (Leiblum, Kemmann et al. 1990).

One study already mentioned as being published after this study was carried out also looked at factors affecting decisions about embryo transfer immediately after embryo transfer (Newton and McBride 2005). Interestingly just as in this study no women had eSET. When asked about how many embryos they had wanted transferred 75% of the women rated DET as very or extremely desirable, although only 45% rated a twin pregnancy as very or extremely desirable. The authors looked at factors affecting initial attitudes towards eSET and DET, multiple regression analyses showed that two predictors made unique contributions these were

estimate of the personal likelihood of twins and perceived increase in the chance of pregnancy with DET rather than eSET. As in the present study women appear motivated by a desire to increase their chance of pregnancy.

Couples in the present study although not actively seeking a multiple birth were also not actively trying to avoid a multiple birth, with fewer than 45% of couples saying the desire to avoid triplets was a factor in their decision. However, couples do value conception very highly with over 90% of the couples' rating the wish to increase the chance of pregnancy as the most important factor. The number of embryos actually transferred also supports this notion of wishing to increase the chance of pregnancy as none of the women with an increased likelihood of a multiple birth: those under 36 and those with more than 4 embryos, chose to have only one embryo transferred.

An article in the Guardian debating the merits of twins reported that two of the women focused on in the article who conceived twins maintained that "though they were happy to have two eggs implanted to raise the chance of a pregnancy, they would never have done it with the intention of having twins" (page 14) (Moorhead 2005). Gardner and colleagues in their prospective trial of single blastocyst transfer commented on the difficulty they had recruiting couples to the study which they maintained "was undoubtedly due to the perception by patients that eSET could result in lower pregnancy rates and that twin pregnancies are a desirable outcome" (page 554) (Gardner, Surrey et al. 2004).

The men and women in this study who rated desire for a multiple birth as a factor in their decision about the number of embryos to be transferred

were not older nor had they been trying to conceive for longer. These findings were in contrast to Gleicher and colleagues' that increasing age and length of infertility were associated with a stronger desire for multiples (Gleicher, Campbell et al. 1995). Glodfarb and colleagues also found length of infertility had no significant impact on attitudes towards a multiple pregnancy (Goldfarb, Kinzer et al. 1996). However, the study by Child and colleagues while agreeing that age of the women in their study was not a predictive factor for desire for a multiple pregnancy, increasing duration of infertility was (Child, Henderson et al. 2004). Grobman and colleagues also found that the desire for a twin pregnancy increased for older women and those being treated for infertility for longer (Grobman, Milad et al. 2001). However one study found that although longer duration of fertility was predictive of a desire for a multiple birth so too was being younger (Ryan, Zhang et al. 2004). The authors were surprised by the latter finding and debate whether this was due to younger women underestimating the difficulties of rearing multiples or older women appreciating the problem more and so avoiding them.

The questions probing couples' perception of the impact of eSET on treatment outcomes showed couples had the mistaken belief that the more embryos transferred the greater the probability of having a child. Newton and colleagues also found that women favouring DET believed the chance of a singleton pregnancy was significantly enhanced after DET (Newton and McBride 2005). However, Alper would argue we should not be surprised at this in view of the general emphasis on pregnancy rates which take no account of multiple birth rates (Alper 2004). The health belief model would suggest, that because of the influence of perceived susceptibility on health related decisions and behaviours; how and what information is presented

about the chance of a multiple or singleton birth, will be extremely important.

Couples have either not understood, or not been informed of the research showing reducing the number of embryos transferred; need not impact on the overall pregnancy rate. For example one study of the HFEA's published rates of multiple pregnancies and live births from UK clinics concluded that replacing two embryos although eliminating the chance of triplets did not lower the overall success rate (Ozturk and Templeton 2002). A Danish study came to a similar conclusion after studying the results of the Danish National IVF registry from 1994 to 1995 (Westergaard, Johansen et al. 2000). Indeed recent research from Sweden reports an unchanged clinical pregnancy rate after the recent eSET legislation (Saldeen and Sundstrom 2005). However in this study, not only did over 80% of the couples agree with the statement that "replacing three embryos when three are available increases the chance of having a child" but open comments revealed a desire for more rather than fewer embryos to be replaced.

Both men and women indicated that the second most important factor in their decision about embryo transfer was medical advice from CARE. Other studies have also found couples to be heavily reliant on medical advice. Murdoch not only describes doctors as "probably the most influential people in the decision making process about the number of embryos to be transferred" (page 92) but also found that in her survey most couples obtained their information from the doctor (Murdoch 1997). Given the importance of medical advice to couples' decisions we need to question what those who give the advice actually believe themselves. Of interest here is the report of an ESHRE consensus meeting in 2002 which recommended that all staff should be convinced of the importance of

avoiding twin pregnancies (Land and Evers 2003). Perhaps therefore we should not be surprised that the report of a meeting of international leaders in reproductive medicine sponsored by the Bertarelli Foundation did not reach agreement on whether twin pregnancy was an acceptable outcome of ART (Bertarelli group 2003).

As predicted by the health belief model perception of the severity of the risks associated with a multiple birth was found to be important in decisions about embryo transfer. Studies have shown that lack of knowledge about risks of a multiple birth was predictive of a desire for a multiple birth (Ryan, Zhang et al. 2004) and giving such information influenced how desirable couples rated a multiple birth (Newton and McBride 2005). Moreover, increased information about the risks of twins can also increase acceptance of eSET (Newton and McBride 2005; Wang, Lane et al. 2006), and could make women more risk aversive (Grobman, Milad et al. 2001). Indeed, Tiitinen and colleagues reported having difficulty recruiting women to a randomized trial of one or two embryo transfers after informing them of the risks of multiple births (Tiitinen, Unkila-Kallio et al. 2003).

Both men and women indicated they were strongly influenced by medical advice in this study. In theory therefore it should be possible for medics to better educate couples about the risks of a multiple birth. However many other factors are also likely to be important for example one study found that despite being counselled about multiple gestations women were not able to more accurately quantify the risks of a multiple birth (Grobman, Milad et al. 2001). This may have been because of the timing of when such information was given. Couples are often given such information at the start of their treatment, as was the case for 72% of the couples in

Murdoch's survey, moreover only 44% claimed to have been given information about the embryo decision at the time of transfer (Murdoch 1997).

Some researchers have questioned whether people really want probability information as they have problems interpreting it (Allegra, Marino et al. 2007). The couples in the present study did seem to want more information and their high levels of education suggest they could make use of it. However, changes in the NICE guidelines may offer infertile couples from a wider demographic profile the opportunity of an IVF birth. Scholz and colleagues reporting on their experiences of multiple births after ART in Germany cautioned against the uncritical treatment of migrant mothers who they felt were often unable to be properly informed of the economic, medical, social and psychological costs of a multiple birth (Scholz, Bartholomaus et al. 1999). A similar point was made by Powers and Wampler who in their observational study of twins concluded that although all twins are at higher risk than singletons for adverse outcomes all twins are not at equal risk with risks increased for twins born to black women (Powers and Wampler 1996).

The communication of risk involves much more than just presenting facts and figures and has become a growing topic of concern for doctors in all areas such that the BMJ in 2003 devoted a special issue to the subject. In this issue Sedgwick and Hall point out that even the framing of statistics in a negative or positive way can influence decisions about risk and the use of qualitative terms to describe probability is also fraught with problems as interpretation of such words varies widely (Sedgwick and Hall 2003). Alper talks of how the way a message is delivered will impact on a decision "We can say, 'Twins have a four-fold increase in morbidity', or we can say, 'You

have a higher risk of having a disabled child requiring long-term care' " (page 514) (Alper 2004). The emotional content of the latter description must surely influence couples more.

Alaszewski and Horlick-Jones went further and queried the assumption underpinning current approaches to the communication of risk that individuals rationally review the evidence they are presented with in order to choose the best outcome (Alaszewski and Horlick-Jones 2003). The authors go on to outline what influences responses to risk information. One such influence is what they call the 'relation to other perceived risks' it is important here to appreciate the magnitude of the other perceived risk for infertile couples: childlessness. This also relates to the perceived value of becoming pregnant. Another influence they describe is how the risk fits with previous knowledge and experience, for infertile couples this will encompass the joy they perceive other couples gaining from their children and the unhappiness they have endured without children. Their knowledge will be unlikely to encompass experience of problems with raising multiples. Moreover, if as these authors suggest we tend to underestimate risk of harm from a common cause then surely couples are likely to be biased towards underestimating the risk of such a common phenomenon as twins, with 10533 twin births in 2005 the latest year figures are available for (Multiple Birth Foundation 2007). Perhaps this issue is also confused by the fact twins do occur naturally, it is not possible to identify naturally occurring twins from ART conceived twins and so we can not determine how 'natural' they are.

A further problem with communicating risk information is pointed out by Allegra and colleagues they maintain that if people don't think they are confronted with a risk it may be hard to inform them as they will not be

receptive to risk information (Allegra, Marino et al. 2007). If infertile couples find it hard to believe they will have a baby at all they may find it impossible to consider they are at risk of twins, especially if as Paling argues peoples' assessment of risk is dominated by emotions rather than facts (Paling 2003).

A study already mentioned by Murray and colleagues explored ways of better informing couples about the risks of a multiple birth (Murray, Shetty et al. 2004). Couples attending the Aberdeen Assisted Reproduction Unit for their first IVF cycle between 2001 and 2003 were invited to take part in the study. Consenting couples were randomly allocated to a control group receiving standard clinic information about IVF, a leaflet group who received a leaflet on the foetal and neonatal risks of twin pregnancies together with the published results of eSET and a discussion group who were both given the leaflet and this information was gone over by the research nurse. Couples were then asked about the acceptability of a hypothetical policy of eSET, their knowledge of the risks associated with a twin IVF pregnancy, how many embryos they would like transferred and how they felt about a twin pregnancy. Over two thirds of the couples in all the groups said they would prefer a single baby however, over 90% of each group also said they would not mind having twins. Despite the extra information given to two of the groups when asked about how many embryos they would like transferred, over 70% of all the couples said two. However significantly fewer, 10% of the discussion group compared to 23% of the controls would have liked three or more embryos replaced. The extra information did not influence couples' acceptance of a hypothetical policy of eSET with couples only prepared to accept it if pregnancy rates were unchanged. Their study like the present one suggests couples' main aim is to achieve a pregnancy and rather than

desiring a twin birth they are prepared to accept one in order to achieve a pregnancy. The study demonstrates the difficulty of shifting couples' attitudes towards a twin pregnancy with couples more concerned about the negative effects on pregnancy rates of eSET than the complications of the treatment.

The reluctance to see a twin pregnancy as a complication was seen in the previously mentioned study by Pinborg and colleagues which found that twin IVF mothers did not see a twin pregnancy as a complication with only 3.8% saying they considered the additional risks of a twin pregnancy to be a problem (Pinborg, Loft et al. 2003)[b]. The authors debate whether this was due to insufficient information or a minimising or even denying of the risks of a twin pregnancy. The idea that risks are minimised or denied is supported by the fact they found the only significant predictor of acceptance of single embryo transfer was delivery of a child with very low birth weight; these mothers had been forced to experience the possible complications of a multiple pregnancy and indeed 82% of the 34 women with very low birth weight babies were mothers of twins. The study again highlights the difficulties of conveying risk information so that it changes attitudes and behaviour.

The finding that couples reported media information and advice from family and friends had little impact on their decision about the number of embryos to be transferred also suggests a denial or minimising of risk information. Further evidence of the impact of actual experience was also provided by the fact the only difference between the mothers wanting a multiple or singleton birth was none of the mothers wanting a multiple birth had children already, although this did not quite reach significance. Child and colleagues also found in their study that couples with children were less

likely to want a multiple birth (Child, Henderson et al. 2004). However, as they point out it could be that these couples feel they only need one other child to complete their family rather than that they have recognised the difficulties of rearing multiples.

The couples in this study were very considerate of their partners' wishes with 83% of both the men and women saying their partner's wishes were a factor. The men were slightly less likely to see their own wishes as important compared to the women 70% compared to 80%. This probably reflects the males' acknowledgement of the fact the physical risks of the pregnancy will be carried by the woman. Other researchers have found some gender differences in attitudes towards multiple births with Goldfarb and colleagues finding women assigned significantly higher favourability ratings to twins than their partners (Goldfarb, Kinzer et al. 1996). Newton and colleagues found that the women in their study were less risk aversive than the men (Newton and McBride 2005) and a similar finding was reported by Kalra and colleagues who also found that in 21% of couples one partner desired twins but not the other (Kalra, Milad et al. 2003). This finding may also reflect the man's desire to protect his partner while the women appear prepared to be pregnant at any cost. Indeed one study found that women rated a twin pregnancy as more risky than their partners; and that infertile women expressed more concern about losing a pregnancy compared to non-infertile women who were more concerned about potential consequences to their own health (Leiblum, Kemmann et al. 1990).

In the present study 11 (15%) of the couples disagreed in whether they saw the desire for a twin birth as a factor in their decision, and the open comments as has already been described illustrated this point with one

woman who despite knowing the risks involved still would have preferred three rather than two embryos transferred. This desperate drive for a baby at all costs may explain the surprising finding by some researchers that infertile couples are prepared to consider a multifetal reduction of a multiple birth (Gleicher, Campbell et al. 1995; Goldfarb, Kinzer et al. 1996; Murdoch 1997). They may perceive that only by accepting this as a possibility will they be allowed to increase as they see it, their chances of a pregnancy by having multiple embryos transferred.

Findings such as those discussed above: that infertile women appear to pay little regard to their own health, suggest little opportunity for health motivation to influence their decisions about how many embryos to transfer. Providing additional information about the risks of a multiple pregnancy to the mother also appears unlikely to influence her decision. One study looking at factors influencing consumer dietary health preventative behaviours also found that long term health benefits were often traded for short term benefits (Petrovici and Ritson 2006). Infertile women often appear willing to trade the possible risks of a multiple pregnancy with the short term benefits of an increased chance of getting pregnant.

Over 90% of the men and women in this study found the decision about how many embryos to transfer easy. This finding suggests how much work is going to be needed if they are to be better educated about the risks of a multiple birth. At present their decision is dominated by a desire for a baby with little understanding of the real costs and benefits of that decision. The whole area is further complicated by the different laws and regulations as already discussed in section 4.1-vi of this chapter. For example America has only guidelines about the number of embryos which

should be transferred in contrast to Israel which as The Times reported in 2004 allows women up to the age of 45 as many attempts at IVF as they wish, and couples only pay a percentage of the costs (Blackburn 2004).

The second aim of this study was to explore the information needs of couples undergoing embryo transfer. This was explored explicitly by two questions. These asked couples if they would have liked more information or help regarding their decision about embryo transfer and, if so, they were invited to comment on what they would have liked. Over a quarter of both the men and women replied that they would have liked more information or help regarding their decision about embryo transfer. The only characteristic or factor which differentiated the men or women indicating they would have liked more information was that women who wanted more information were more likely to have had two rather than three embryos transferred. Their replies to the open question focus on a desire for more statistics about the chance of conception and the expressed desire for more embryos to be transferred. The extra information they wanted appears to have been to support a decision to have more embryos transferred.

Some of the other factors explored provide insight into couples' information needs and how these might be met. For example, both men and women rated the wish to increase the chance of pregnancy as the most important factor in their decision about embryo transfer. This coupled with some misconceptions about eSET and DET suggest scope for providing information. Conveying information about the risks of a multiple birth will as already discussed be more difficult.

With reference to how information should be provided we were surprised by the low level of importance couples attached to information they

received from the media, family and friends. Some explanation seems to be offered in the answers to the open questions where one theme identified was 'referring to experts to make the decision'. The reply to the invitation for further comments by one woman seems to sum up this attitude;

"I value the calm, balanced advice of the team we chose to try with – I chose not to surf the web for information as I feel that is inaccurate. I prefer science to be left to the experts!"

However, the importance couples placed on advice from the medical tem at CARE suggests a valuable means of conveying information.

4.4-i Strengths and weaknesses of the study

One limitation of this study was that couples in this sample came from only one private fertility centre and may not be representative of all women undergoing embryo transfer. However the centre does draw from a wide referral base and in compariason to other studies of couples undergoing IVF treatment this sample does appear comparable in demographic profile. Women seeking infertility treatment have been found typically to be in their mid thirties as in this study (Leiblum, Kemmann et al. 1990; Goldfarb, Kinzer et al. 1996; Kalra, Milad et al. 2003). Other studies have also found the men to be older (Wischmann, Stammer et al. 2001; Child, Henderson et al. 2004). The average duration of the partnership was also similar to that found by other studies (Wischmann, Stammer et al. 2001). The couples in the study were well educated with over 30% being educated to degree level or above which may have implications for their understanding of the risks of a multiple birth, however other studies have also found patients seeking fertility treatment to be highly educated (Grobman, Milad et al. 2001; Ryan, Zhang et al. 2004).

At present only one other study (Newton and McBride 2005) has assessed the factors couples identified as important in their decision about the number of embryos immediately after embryo transfer. In this study it was felt that to explore couples' perceptions of risk associated with a multiple birth at this time point would be unethical. This meant no information was gathered on this issue in contrast to Newton and colleagues' study which did not share such reticence. Although as they point out just because it was possible to alter couples' perceptions does not necessarily mean their future behaviour would be different. We might also question whether some couples will have been made more anxious about their forthcoming pregnancy as a result of the information they were given. This study was strengthened by the use of an anonymous questionnaire at the point of embryo transfer thus ensuring honest and accurate answers whilst minimising any recall bias.

4.5 CONCLUSIONS

Exploring the factors involved in couples' decisions about embryo transfer revealed infertile couples are desperate for a baby and make their decision about the number of embryos to transfer based on what they believe will most increase their chance of a live birth. They mistakenly believe they can increase their chance of a pregnancy by increasing the number of embryos transferred. The health belief model provides a useful rationale for looking at aspects of the decision process such as perceived threat and costs and benefits of the decision. Providing more information about risks to the mother's health may be less successful than information about the

risks to the baby and more accurate information about chances of conception after eSET and DET.

Although the medical establishment is resolved to reduce the number of multiple births it is not yet united in a condemnation of twins and appears sometimes even to collude with the idea of twins as an acceptable risk and a natural solution to an instant family. In the present study couples reported being influenced by medical advice, were well educated, and some expressed a desire for more information on the probability of conception and a multiple birth. This suggests it should be possible to better inform them of the risks of a multiple birth. Further ideas about how to better inform couples' about the risks of a multiple birth and how to minimise the risks to the mother's mental health and the mother-infant interaction will be explored in the final discussion of this thesis.

CHAPTER FIVE - Discussion

In order to reduce the number of multiple births to something closer to the naturally occurring rate of 1.2% seen in 1938 (National Statistics 2006) before the introduction of ART, we would have to see a complete inversion of the results found in study III chapter 4 such that the vast majority of embryo transfers were single and none were three embryos. To achieve this changes in attitudes and expectations, both by society and the individual, would be needed. This discussion will focus on some of those changes: changes which were suggested by a review of the literature, exploration of relevant psychological theories or models, and findings from studies conducted during this thesis. It will then explore how they might be achieved in the UK, particularly with regard to information provision.

5.1 What do we know about the impact of a multiple birth on the mother?

The evidence regarding the negative impact of a multiple compared to a singleton birth on the mother and baby's physical health is clear and unequivocal. The literature reviewed in section 1.8 of the introduction suggests elevated risks to the mother's physical health, physical well-being and even her mortality (Thorpe, Golding et al. 1991; Gleicher, Campbell et al. 1995; Senat, Ancel et al. 1998; ESHRE 2000). There is also evidence reviewed in the same section, to suggest the risks are even greater for IVF mothers of multiples (Lynch, McDuffie et al. 2002; Stone Eddleman et al. 2002; Smithers, Halliday et al. 2003). Moreover, study I described in chapter two found that IVF/ICSI mothers of multiples were more likely to deliver by emergency caesarean than mothers of singletons.

A review of the literature discussed in section 1.5 of the introduction and section 1.6 suggests a multiple birth has a negative impact on the baby's physical health as well as their cognitive and social development partly accounted for by factors associated with their increased likelihood of low birth weight and premature delivery (Wolke 1998; Bhutta, Cleves et al. 2002; Ledger, Anumba et al. 2006; Fanaroff, Stoll et al. 2007). The additional impact of an IVF multiple birth is more equivocal. As debated in section 1.7 of the introduction IVF/ICSI twins have been found to do better in terms of health outcomes than naturally conceived twins (De Sutter, Delbaere et al. 2006). However in view of the fact they are less likely to be monochorionic twins, are more likely to have mothers who are younger, better educated, of a higher social class and less likely to smoke they might have been expected to have better rather than equal outcomes. Two reviews have concluded that for those studies closely matching mothers on variables such as age and social class any advantages for the IVF/ICSI twins disappears (McDonald, Murphy et al. 2005; Pinborg 2005).

Study I (chapter two) found that compared to singletons the multiple IVF/ICSI babies were of lower birth weight, born more weeks premature, were more likely to have complications with their health and have spent longer in the special care unit. Researchers have concluded that 73 deaths could have been avoided in 2001 if all IVF infants had been born as singletons or naturally occurring monozygotic twins (Oakley and Doyle 2006). Furthermore one author has argued that current embryo transfer practices do not take proper account of the welfare of children conceived by ART (Larcher 2007)[a].

This thesis was particularly interested in the possible impact of a multiple birth on the mother's mental health and emotional well-being. Review of

the literature as discussed in chapter 2 section 2.1-i and section 2.1-iii suggested that mothers of naturally conceived multiples were at greater risk for depression than mothers of singletons (Groothuis, Altemeier et al. 1982; Haigh and Wilkinson 1989; Hay, Gleeson et al. 1990; Robin, Bydlowski et al. 1991; Thorpe, Golding et al. 1991; Garel and Blondel 1992; Ellison, Hotamisligil et al. 2005) and even that their children were at greater risk of child abuse (Groothuis, Altemeier et al. 1982).

The literature as summarised in section 2.1-v of chapter two also shows that a multiple IVF birth has a greater impact on maternal well-being in terms of higher stress scores on the PSI (Olivennes, Golombok et al. 2005; Freeman, Golombok et al. 2007) and higher scores on the EPDS than a singleton birth (Olivennes, Golombok et al. 2005). Some studies have also found greater stress and poorer well-being in mothers of IVF/ICSI conceived twins than mothers of naturally conceived twins as discussed in chapter two section 2.1-vii; (Munro, Ironside et al. 1990; Cook, Bradley et al. 1998; Colpin, Munter et al. 1999). There are however problems with recruiting a naturally conceived control group of twins, and issues about whether such a comparison is truly appropriate as discussed in section 2.4-i of chapter two, and so Study I did not recruit such a control group.

Further impetus for Study I was provided by Champion and Power's social cognitive theory of depression (Champion and Power 1995). The theory suggests that if a highly valued goal, such as motherhood in the case of previously infertile women, is threatened; the individual may be more prone to depression. A multiple birth could threaten the goal of motherhood if the baby was more likely to be, as predicted by the research literature, low birth weight, premature, more physically vulnerable or harder to care for. Review of the qualitative literature provided some

support for this theory with Beck's metasynthesis of qualitative studies on postpartum depression revealing the theme incongruity between expectations and the reality of motherhood (Beck 2002)[c].

The results from Study 1 as reported in section 2.3-ii of chapter two provide some support for this theory and evidence that mothers of multiple babies experience poorer emotional well-being postpartum. Mothers of IVF/ICSI twins had higher scores on the EPDS and were more likely to score above 12 a commonly used cut-off to indicate clinically significant psychological symptoms of depression than mothers of singletons although these differences were not statistically significant. Poorer emotional well-being for the mother as indicated by higher scores on the EPDS was correlated with the mother finding the baby more unsettled and irregular in temperament and when this was controlled for in a logistic regression a multiple birth created a significant three fold risk of an EPDS score >12.

The qualitative analysis in Study I chapter two revealed other interesting findings about the impact of a multiple birth on the mother. Mothers of multiples were more tired, were more likely to talk of having felt depressed or down emotionally and to describe their emotional well-being as linked to worry over the baby. Mothers of multiples were also more likely to question their decision about parenthood although as already discussed some might argue this was contentious as only the mother of a multiple can express doubts about having more than one baby. However, theoretically mothers of singletons can also question their decision to become a parent at all and indeed one mother did so.

Study I chapter two demonstrated the advantages of combining quantitative analyses using reliable and validated measures with qualitative

analysis. Composite analysis allowed the most interesting and potentially important finding to emerge: that mothers of singletons were significantly more likely to describe how good they felt with the theme 'feeling wonderful' emerging inductively from the data. Olivennes and colleagues also reported finding that mothers of singletons were more likely to report feelings of enormous pleasure and that mothers of twins and triplets were more likely to say they found parenting difficult (Olivennes, Golombok et al. 2005; Freeman, Golombok et al. 2007).

Given the above discussion about the consequences of a multiple birth for the mother's mental-health, and having established that the babies were more likely to be premature, this thesis went on to explore the impact of a multiple premature baby on mother-infant interaction. Research suggests that the birth of a premature baby will be stressful for the mother as described in section 3.1-i of chapter 2 (Singer, Salvator et al. 1999; Davis, Edwards et al. 2003; Holditch-Davis, Bartlett et al. 2003). There is also evidence to suggest that a premature birth impacts on the mother-infant interaction as reviewed in section 3.1-v. Mothers of premature babies seem to work harder at the interaction (Beckwith and Cohen 1978; Crnic, Ragozin et al. 1983), however studies have also found that mothers score lower on sensitive parenting and growth fostering subscales of the NCATS (Harrison and Magill-Evans 1996), suggesting they are not always sensitive to the child's needs.

Attachment theory stresses the importance of early mother-infant interaction and places the quality and nature of these early interactions as central to the quality of the child's later attachment to its mother. Carlson and colleagues describe in their review of attachment how attachment develops from a history of the caregiver's interactions (Carlson, Sampson

et al. 2003) and as already reported one measure of mother-infant interaction: the NCATS found higher scores were positively correlated with attachment security (Sumner and Spietz 1994). Given the relationship between secure attachment and later social and cognitive development as reviewed by Bee and Boyd (Bee and Boyd 2002) any disruption to the mother-infant interaction might also be presumed to affect the infant's future development. Research has shown differences in the interactions of mothers with multiple babies and mothers with a singleton and that this interaction does have an effect on their infants' subsequent development (Holditch-Davis, Bartlett et al. 2000; Feldman and Eidelman 2005). Despite one early study finding no differences in security of attachment between premature twins and singletons, mothers whose infants were classified as securely attached were rated as more responsive to their infants (Goldberg, Perrotta et al. 1986). Moreover a more recent study, looking at the additional disadvantage of a premature and twin birth found poorer frequency and quality of maternal interaction for mothers of twins (Ostfeld, Smith et al. 2000). Furthermore, measures of mother-infant interaction were significantly correlated with lower cognitive development in the premature twins. Together attachment theory and these findings provided the impetus for Study II.

Study II was unable to explore attachment directly as the infants were only three months old, instead interaction was focused on as an important precursor to attachment. The measure of interaction used in this study: the NCATS has been shown to correlate positively with attachment security (Sumner and Spietz 1994). The use of standardised and validated measures, closely matched mothers and infants, and larger samples added rigor to earlier studies. Results showed that mothers of twins were not less responsive or stimulating when interacting with their infants during a

standardised task: the NCATS. However, they were less responsive during day to day interactions with their infants as shown by their significantly lower scores on the HOME Responsivity subscale. Mothers of twins had higher levels of parenting stress than mothers of singletons and scored significantly higher on the parent child dysfunctional interaction scale suggesting they found interacting with their infant particularly difficult and demanding. Additionally, despite the lack of any obvious disadvantage, twin premature infants had significantly lower total child scores on the NCATS at three months than singleton premature infants. This suggests that when interacting with their mothers in a one to one task they provide less clear cues and are less responsive to their mothers. The study concluded that twin status does represent an additional risk independent of prematurity.

In summary the research reviewed and undertaken during the writing of this thesis suggests a multiple birth will have a significant impact on the mother. More research is still needed on the longer term effects of a multiple birth and how this will affect the mother and infant and their interaction. Previous research studies exploring mother-infant interaction and attachment have found a combination of preterm birth and sub-clinical depressive symptoms predicted attachment (Poehlman and Fiese 2001)[a] and associations between mother's depression, attachment security, mother-infant interaction and infant social and cognitive development (Wille 1991; Field 1995; Laucht, Esser et al. 2002.) Findings which suggest there may well be long term consequences for these infants. Ellison and Hall suggested that mothers of iatrogenic multiples often felt unable to complain of tiredness or exhaustion (Ellison and Hall 2003). We might question whether, with increasing debate about the number of

embryos to be transferred mothers who transfer more than one embryo and deliver twins will feel even less able to complain or seek help.

An observation was made during the study of mother-infant interaction (Study II) that, contrary to expectations, more of the singleton premature babies in the study were conceived after ART than were the twin babies. It was speculated that one reason for this could have been because IVF mothers with twins were more reluctant to take part due to feelings of guilt or because of the excess stress they were under. Another point to consider is whether mothers of multiples will find the process of their children leaving home and creating independent lives harder as they have, of necessity, invested more in the relationship. Mothers report they had neither the time nor energy to invest in their own interests (Munro, Ironside et al. 1992), and were less likely to return to work (Glazebrook, Sheard et al. 2004; Olivennes, Golombok et al. 2005).

5.2 What do we know about the impact of a multiple birth on the father?

Although studies I and II focused on mothers, this is not to negate the potential impact of a multiple birth on the father. The difficulty of recruiting and maintaining contact with fathers has meant that their voices have often gone unheard. Partners had, in fact, been recruited at the outset of the original study on which Study I is based. Quantitative data were collected from them at various time points but data were less complete and, unlike mothers, they did not participate in the in-depth interviews. In Study II only mothers were recruited to the original study of outcomes of very premature birth. This thesis has therefore focused on maternal outcomes but acknowledges the need for further research to explore the paternal role following a twin birth. Some preliminary findings

published from the large prospective cohort study, of which Study I formed a part, showed that fathers of IVF singletons had significantly lower rates of postpartum depression than mothers (6.4% vs 16.5%), however IVF/ICSI fathers of multiples had similar rates of depression to the mothers (Glazebrook, Cox et al. 2000). The authors suggested this was related to the stress of their increased involvement in parenting multiples. The increased involvement of fathers of multiples was also found in a qualitative study, for some couples this strained the marriage while for others it strengthened the marriage (Ellison and Hall 2003). A qualitative study of the psychological consequences of having triplets also found that for mothers help and support from the father was very important to their well-being. Eight of the 11 mothers interviewed complained they did not get enough help or support while all the mothers in the study complained of emotional distress and four were taking medication for their depression (Garel, Salobir et al. 1997).

Golombok and colleagues longitudinal study of assisted reproduction families in Europe found some interesting results: assisted reproduction fathers interacted more with their child and contributed more to parenting than fathers of naturally conceived children but they did not have significantly higher stress scores (Golombok, Brewaeys et al. 1996). These families were later followed up when the children were 11-12 years old at this time assisted reproduction fathers were found to show greater expressed warmth towards their children and higher ratings of emotional involvement than fathers of adopted or naturally conceived children. In addition the assisted reproduction children perceived less criticism by their father, and more lenient discipline than the adopted and naturally conceived children (Golombok, Brewaeys et al. 2002).

In contrast to these findings a study comparing families of IVF and naturally conceived twins found fathers of IVF twins, as well as mothers reported higher levels of stress. Fathers also reported more dysfunctional interaction with their children and found them more difficult (Cook, Bradley et al. 1998). The authors debate whether these findings were a result of, increased parental expectations among the IVF parents, the increased demands of twins, or lack of experience as a parent given more of the IVF parents were first time parents. Whatever the reasons they do show parenting a multiple also impacts on the father. However, a study by Colpin and colleagues, which controlled for first time parenthood, found no significant differences in parenting stress scores between fathers of IVF and control group fathers (Colpin, Munter et al. 1999). Munro and colleagues found that although neither fathers nor mothers scored significantly differently on the GHQ compared to the control group's fathers, fathers as well as mothers were found to report poorer social relationships in terms of size and affective quality (Munro, Ironside et al. 1992). A study looking at the impact of triplets also found fathers of triplets scored significantly higher than fathers of twins and singletons on the total Parenting Stress Index-short form and the parenting distress subscale (Feldman, Eidelman et al. 2004). In a further article exploring the social and emotional development of triplets the authors postulate that trying to parent three children between two parents may upset a critical and delicate balance such that there is insufficient uninterrupted parenting available for three children's optimal social and emotional development (Feldman and Eidelman 2004).

Although Study II described in chapter three did not recruit fathers, a few studies of parental interactions with premature infants have included fathers. The study by Harrison and Magill-Evans discussed in that chapter

looked at both mothers and fathers interacting with their premature and term infants at three and 12 months corrected age (Harrison and Magill-Evans 1996). The study found that fathers as well as mothers of premature infants had lower scores on the NCATS in relation to responding to their child's distress and fostering socio-emotional and cognitive growth than fathers of term infants. Fathers also reported more stress than mothers on four of the six child domain subscales of the Parenting Stress Index, however there were no significant differences between fathers of premature and term infants. At three months the fathers of term infants were more likely to spend more than thirty minutes a day playing with their infant during the week than the fathers of premature infants. These findings suggest both fathers and mothers interact differently with a premature infant, compared to a term baby and one might speculate that the fathers of premature infants were less confident with their infants and so spent less time playing with them at three months.

Another more insidious way in which a multiple birth will impact on the father is the finding already mentioned that mothers of multiples are less likely to return to work (Glazebrook, Sheard et al. 2004; Olivennes, Golombok et al. 2005). This is likely to place increased financial pressures on the father and perhaps also emotional pressure if the mother has been unable to return because of the extra demands and childcare costs of a multiple. One study looking at depressed mood in first time fathers reported that fathers with less financial resources were more depressed (Bielawska-Batorowicz and Kossakowska-Petrycka 2006).

To conclude, the evidence from research does suggest that a multiple IVF/ICSI birth will have a significant effect on the father both directly and, indirectly through the effect on the mother. However, this is an area

requiring more research, with further studies needed to look at the longer term impact on the assisted conception father, father-infant interaction and infant development. A study of first time naturally conceiving fathers found their psychological well-being was influenced not only by their partner's emotional well-being but also by a mismatch between their expectations and the reality of parenthood (Bielawska-Batorowicz and Kossakowska-Petrycka 2006), an area explored in this thesis only with respect to mothers. The available evidence needs to be more widely known and debated by both prospective couples and clinicians because both partners will be actively involved in the decision about how many embryos to transfer. Traditionally the practice of transferring more than one embryo has been justified by the claim that couples want a multiple birth and clinicians are merely respecting that preference.

5.3 What do clinicians need to know about prospective parents attitudes towards a multiple birth?

This thesis has sought to question the assumption stated above that couples want and prefer a multiple birth. Questioning such an assumption was important not only because it has been used, as stated above, as justification for transferring more embryos but also because the health belief model places perceived value as a very important component of the decision process. The findings from Study III (chapter 4) carried out immediately after embryo transfer had taken place clearly show that the factor rated most frequently by women (92.6%) and men (95%) as having a strong or major influence on their decision regarding the number of embryos to transfer was the wish to increase the chance of pregnancy. The desire for a twin birth was rated as a strong or major influence by only 19.1% of women and 20% of men. Couples responses to the statements about chance of pregnancy after transferring one or three embryos also

supports the idea that couples are motivated by a desire to increase the chance of a successful conception with over 90% of both the men and women agreeing with the statement "transferring one embryo when two are available reduces the chance of having a child", and over 80% agreeing that "replacing three embryos when three are available increases the chance of having a child".

Support for this finding is also shown in the recent study by Newton and colleagues who found women who favoured DET thought the chance of a singleton pregnancy was significantly increased by DET compared to eSET (Newton and McBride 2005). The importance of success rates and increasing the chance of a pregnancy by DET to couples has been shown in a number of studies (Hartshorne 2002; Murray, Shetty et al. 2004; Porter and Bhattacharya 2005). Further evidence of the importance of maximising the chance of conceiving for couples was found by the HFEA's expert group on multiple births who reported on results generated by the HFEA's patient panel (Braude 2006). These included the findings that 72% of patients said they were given information about the risks of a multiple birth to the mother and baby but only 9% changed their attitude towards a multiple birth as a result. Over half would not agree to one embryo being transferred even if so advised by medical staff. Clinicians need to be aware that prospective parents do not value a multiple pregnancy highly rather they value any pregnancy so highly they are prepared to accept many of the risks associated with a multiple birth.

5.4 The role of clinicians

The importance of giving more and better information about the risks of a multiple birth has already been discussed, however in order to achieve this

change in the information provided clinicians' attitudes need to change also. The importance and impact of such a change in direction and policy was described in a recent study outlined in chapter 4 section 4.1-viii which found that such changes resulted in an increase of eSET from 13.9% to 49% over one year (Coetzee, Stewart et al. 2007).

Clinicians need to be aware of the important role they play in helping couples make decisions. The influence medical advice had on the couples' decision in the study described in chapter three has already been mentioned but clinicians need also to appreciate the value to patients of their involvement in the decision process. For example, one study found that the higher women rated their influence in the decision about number of embryos transferred the greater was their satisfaction; with the reverse being true of their rating of their physician's influence (Newton and McBride 2005).

Prospective parents' active participation in this decision may also affect their adjustment to parenthood. Research has found that patients with the chronic condition rheumatoid arthritis who believed their condition to be curable and to some extent "their own fault" reported higher feelings of depression (Schiaffino, Shawaryn et al. 1998). This suggests parents who have actively been involved with the decision to transfer more than one embryo may be particularly vulnerable if there are problems after the birth, particularly with increasing media coverage of these risks. Furthermore health professionals working with IVF parents have noted that these parents, with their tendency to be older, well educated and with established careers, are used to feeling in control and so may be particularly at risk if they feel out of control as a result of their decision (Leonard 1998).

Another issue clinicians need to be aware of is that women are not always good at understanding risk and the implications for themselves even if they are aware of them. An example of this is an American telephone survey of 1967 adults' perceptions about prematurity (Massett, Greenup et al. 2003). The study found that most women understood the condition was quite common in the USA and was a serious threat to the baby however they did not see it as a serious health problem and almost three quarters of women thought a woman who delivers prematurely could have done something about it. The finding that many women believe the mother can avoid a premature birth suggests another area of guilt for a mother prematurely giving birth to twins or triplets.

The decision about how many embryos to transfer involves what Deber and colleagues describe as decision making where the individual makes a choice often requiring trade-offs from among a number of alternatives (Deber, Kraetschmer et al. 1996). These authors explored the issue of problem solving and decision making in a survey of patients undergoing angiogram. The study was not about how these patients had reached decisions about their own care but instead presented them with different medical conditions and questioned them about how treatment options should be decided. Of interest is their finding that patients did show a high desire for information and that although they wanted problem solving tasks to be performed by or shared with their physician when it came to decision making they wanted to be involved. This illustrates the potential importance of the clinician as information provider and facilitator in the decision.

An editorial by Hallenbeck provides a helpful illustration of the differences between clinician and patient decision making describing how "the cultural divide here is between clinicians living in a medical world, which values rational, "evidence-based" medicine, and patients struggling with decisions that are as intensely personal as they are medical' (page 73) (Hallenbeck 2002). An example here is the different attitudes clinicians have towards what is a successful outcome for ART, as illustrated by a very recent study in Scotland of women waiting to undergo IVF. The women preferred the outcome of a child with a disability to not having a child at all (Scotland, McNamee et al. 2007). This can be seen as further evidence of the need to consider perceived value when seeking to influence health related decisions. In contrast clinicians argue in favour of eSET because of the complications of twins. A further problem is one pointed out by Cook and Golombok in an overview of an IVF symposium back in 1990. They suggested that technology had developed at such a pace ethical and psychological aspects of fertility treatments had been left behind so that the clinicians themselves did not always have sufficient information (Cook and Golombok 1990), a proposition probably as true today as it was then.

However, the expert group on multiple births reported to the HFEA that some clinicians still do not acknowledge the risks of a multiple birth (Braude 2006). Indeed chapter four section 4.1-vii suggested that some clinicians disagree that twins should be seen as a complication (van Wely, Twisk et al. 2006; Belaisch-Allart 2007). An ongoing study in Nottingham has been developing a measure to assess attitudes towards twin births: the Attitudes to twin IVF Pregnancies scales (ATIPS) among health professionals and couples undergoing IVF treatment (Rai and Glazebrook in press). Preliminary analyses exploring health professionals attitudes using this scale found that 34% agreed the best outcome of IVF treatment was a

twin birth and 41% agreed that the rewards associated with a twin pregnancy are worth any risk to the babies (personal communication from the author). The expert group on multiple births suggested these views may be partly explained by lack of contact across services and proposed tours of neonatal wards for fertility consultants and nurses might be of benefit as introduced in Finland (Braude 2006).

5.5 How can we better inform couples about the impact of a multiple birth?

Couples who seem intent on a multiple birth need to be encouraged to explore the impact a multiple birth will have on themselves in terms of their emotional and financial resources as well as on their relationship. The health belief model would predict the importance of considering costs and barriers when making health decisions. Prospective fathers for example should be urged to consider the greater involvement they will need to commit to and the importance of this to the success of their subsequent relationship (Fisher and Stocky 2003). An editorial by Redshaw and van den Akker suggests that researchers should be aware of the role social support and financial resources can play in contributing to a positive experience of fatherhood for first time naturally conceiving fathers (Redshaw and van den Akker 2006). This issue may be even more relevant for IVF/ICSI fathers of multiples especially if ART becomes more widely available to possibly less well resourced couples. Collins in a paper looking at the health economics of IVF/ICSI reported that in 2001 the cost of a single IVF cycle was 10% of total household expenditure and that a 10% decrease in cost could increase utilisation by 30% (Collins 2002).

Couples in Study III (chapter four) reported in over 90% of cases that they found the decision about embryo transfer 'easy', one can only argue that

this implies they did not understand the full complexities of the decision they were making, and take it as an invitation to try and provide them with more detailed information. Particularly as 91.2% of women and 85% of men said medical advice was a strong influence on their decision. The impact of giving more information about the risks of a multiple pregnancy has been well documented. One study reported problems in randomising patients to a study of eSET in Australia after more information on risks was given (Wang, Lane et al. 2006). Others have shown that more information about the risks of twins made couples hypothetically more risk averse to a multiple pregnancy (Grobman, Milad et al. 2001; Newton and McBride 2005).

However, research already discussed looking at the importance of perceptions about the chance of a successful pregnancy shows couples are highly motivated by their desire for a successful pregnancy; and to achieve this they are often prepared to accept risks. In the study by Murdoch, previously mentioned, the majority of couples were prepared to consider selective reduction of higher order multiple pregnancies so that more embryos could be replaced to increase the chance of pregnancy (Murdoch 1997). Moreover the study by Scotland and colleagues found that women waiting to undergo IVF viewed having a child with a severe disability after DET as more desirable than having no child at all (Scotland, McNamee et al. 2007). A qualitative study of women's accounts of the experience of treatment for infertility describes women using a gambling metaphor and seeing their successful pregnancy in terms of winning which suggests they are likely to accept risks in order to 'win' a baby (Redshaw, Hockley et al. 2007).

These findings and a consideration of the health belief model, which emphasises that perceived severity or risks of a multiple birth will be balanced with costs or barriers and benefits, suggest simply informing a woman about risk is unlikely to convince her to reduce the number of embryos she transfers. Abraham and Sheeran in their review of the health belief model discuss the complexities of assessing severity and argue studies have found visible immediate consequences are more important (Abraham and Sheeran 2005). For couples finding it hard to believe they will actually achieve a live birth asking them to appreciate the consequences of a multiple birth may be a step too far. A meta-analysis of studies of the health belief model in adults, found larger effect sizes for benefits and costs and smaller effect sizes for severity in retrospective studies compared to prospective studies. This would fit with the finding in Study III that couples regarded "wish to increase chances of getting pregnant" as the most important factor affecting their decision. A better approach may be to frame information for prospective parents in terms of the positive outcomes or value associated with a singleton baby.

The different attitudes clinicians and prospective parents seem to have towards a multiple birth may make achieving patient involvement in decision making about embryo transfer difficult. The most important way to actively involve patients in decision making is by communicating evidence. One paper describes how 'communicating evidence can transform a physician- dominated relationship into one that is relationship-centered' (page 2359) (Epstein, Alper et al. 2004). This paper goes on to describe a systematic review of articles published between 1966 and 2003 which dealt with communication between clinicians and patients and how to present clinical evidence. Only eight articles were found and methods of communicating evidence included using non quantitative general terms,

numerical translation of clinical evidence, graphical representations and decision aids.

Although a search of the literature shows no evidence yet of decision aids being used during consultations about ART, they may be a useful tool and research looking at them may provide useful insight into the processes involved in the decision. A paper by Bekker and colleagues evaluated the results of a randomised control trial comparing routine with decision–aided consultations for women deciding on a diagnostic test option following a screen positive result for Down's syndrome, (Bekker, Hewison et al. 2003). The decision analysis consultation included, in addition to the routine information, a decision tree representation of the testing choice. Women were also asked about utilities in terms of when they were unable to decide on whether to continue with, or terminate the pregnancy according to the risk of having a Down's Syndrome baby and were shown a threshold graph prompt which integrated this figure with the woman's actual risk. The authors argue that the decision-aid consultation was effective in facilitating more cognitive strategies, as these women assessed more decision relevant information and evaluated it in accord with their values. Women in these consultations were also more able to verbalise their decision relevant feelings. More negative evaluations during decision making were associated with better outcomes. However, the decision–aided consultations took on average 10 minutes longer and there were more expressions of negative affect, probably because of the more realistic assessment of the decision options. These factors may well make such consultations less rewarding for the patients and professionals involved, although they did result in greater satisfaction with their decision after they had chosen the treatment option.

A more recent study looked at the use of a decision aid leaflet to facilitate women's choices between pregnancy termination methods (Wong, Thornton et al. 2006). This study found that women in the decision aid leaflet group had higher knowledge, and lower risk perception scores about the two methods: medical and surgical termination. They also had more positive attitudes about the medical method, lower decisional conflict and rated the perceived usefulness of the information more highly. However, the decision aid did not raise or alleviate anxiety associated with the procedure or change the treatment choices made.

A Cochrane review of decision aids for people facing health treatment or screening decisions concluded that they improved knowledge, created more realistic expectations and enhanced active participation and lowered decisional conflict (O'Connor, Stacey et al. 2003). Findings such as these suggest decision aids may be a useful additional tool to help couples decide about how many embryos to transfer.

The health belief model has provided a useful framework for looking at information needs and how to fulfill them and could be used to inform the content of such decision aids. The HBM does not provide a perfect or complete model to explain health related behaviour, one of the main criticisms being that it does not explain how different beliefs combine and influence each other (Rutter and Quine 2002). However, consideration of all these beliefs and a willingness to explore how they interact will help us provide more useful information and decision aids to prospective IVF parents. For example, Penning argues that couples are not choosing between no children and a multiple pregnancy but between no child now and a singleton later (Pennings 2000). Presentation of risk material in such a way might encourage couples to value eSET more highly.

5.6 The role of society

A very recent report summarising the laws, regulations and guidelines established by 57 nations to regulate and oversee ART found that more countries had adopted guidelines or legislation to reduce the number of embryos transferred by 2007 and that there was a worldwide trend for elective transfer of one embryo for the first cycle (Jones and Cohen 2007). The report still comments, though, on the need to educate the lay population and healthcare professionals that a multiple gestation is an undesirable outcome. It also maintains that a responsible attitude towards embryo transfer should include the following points: 1) the priority of eSET for women under 35 with at least one good quality embryo during their first cycle of IVF, 2) the transfer of no more than two embryos and only under exceptional circumstances, 3) the improvement of results with cryopreservation

Chapter four section 4.1-vii described in detail the ways different counties have responded to these issues. Society here in the UK has to decide what it is prepared to pay in terms not only of money but also restrictions in choice and personal freedom to achieve the goals stated above. One author has argued that society needs to accept that "Children born by ART have the right to expect that their parents received appropriate information about risks and the actions that might have been taken to prevent or reduce them, and that a fair balance was struck between their parents' liberty rights and their rights to protection" (page 669) (Larcher 2007)[b]. Only Belgium has so far introduced regulations prescriptive enough to ensure eSET in women under 36 during their first cycle of IVF, this was achieved by linking the policy to funding of up to six cycles of IVF (De Neubourg, Gerris et al. 2006). An interesting point about how a different

funding approach in America could perhaps be used to encourage eSET was made by Stillman (Stillman 2007). He argued that money back guarantees from clinics for the funding of IVF could reassure patients about having a child and so encourage them to have eSET particularly if this was accompanied by cryopreservaton of embryos.

The expert group on multiple births reporting to the HFEA stressed the international importance of the UK (Braude 2006). Given the UK'S internationally respected regulator the HFEA and a reputation as a large and diverse service provider they argued a move in the UK towards the wider use of eSET could accelerate international acceptance of eSET strategies. The report went on to outline the factors hindering progress towards eSET here in the UK. These include the lack of National Health Service funding for IVF and the inconsistent way the NICE guidelines have been implemented and the fact the majority of UK treatments are funded privately and so driven by market forces. These factors can only be overcome by changes in government policy and funding.

With regard to funding and acceptance of eSET, the HFEA's patient panel found as already mentioned that 75% of the people who said that they would not accept eSET, even if it was advised by medical staff, would be more likely to consider it if the NHS routinely funded three cycles of treatment (Braude 2006). This is a good example of how couples might be prepared to balance the costs and benefits of their decision. The expert group acknowledged that enforcing regulations here in the UK without increasing funding or availability of treatment on the NHS would just encourage couples to go abroad for treatment. As they would be likely to return to the UK for delivery and childcare the NHS and the state would still

ultimately pickup the costs of any multiple births born as a result of what it calls 'reproductive tourism'.

Other factors such as the need to maintain acceptable pregnancy rates, patients' and clinicians' views regarding eSET, the way data is collected and outcomes reported by the HFEA can be tackled without legislation. This last issue was debated by the expert group, which acknowledged how the importance to couples of successfully conceiving does influence the reporting of success rates. They concluded, however, that just reporting rates differently would not be enough to change underlying attitudes. Changing these could be more effectively tackled by exploring ways to better emphasise the desirability of a singleton birth while information about rates and risks of multiple births needs also to be increased and strengthened. Findings from Study I could as has already been suggested, be used to emphasise the increased benefits of a single baby compared to a multiple. Other findings and research reviewed in this thesis would suggest caution in just increasing risk information about twins as this may be less effective particularly with regard to risks to the mother's health.

The HFEA expert group on multiple births agreed that the overall UK twin birth rate should be brought down to below 10% which would involve halving the current rate but would still be considerably higher than the naturally occurring twin rate of between 1 and 2% (Braude 2006). They also put forward two approaches to developing HFEA guidance: firstly that a maximum multiple birth rate should be set as a new standard each year until for example a rate of less than 10% is achieved. Clinics would be required to demonstrate procedures to ensure their rate did not exceed the rate set. Secondly the development of eSET guidance in the Code of

Practice stating which groups of patients under which circumstance should have only one embryo transferred. They also called for a clear directive from the Department of Health to primary care trusts to implement the NICE guidelines.

5.7 Intervention strategies to reduce the impact of a multiple birth

One alternative to trying to reduce the number of multiple births would be to implement interventions to reduce the impact of a multiple birth. Many of these interventions have been motivated by attachment theory which emphasises the importance of responsive mother-infant interaction to the development of secure attachment and better cognitive and social development. A pilot program explored the possible benefits of an early Neonatal Intensive Care Unit (NICU) intervention with mothers (Melnyk, Alpert-Gillis et al. 2001). Forty two mothers of low birth weight premature (< 2600g and 26 to 36 weeks gestation) infants took part in the randomised clinical trial with 20 being offered the COPE program. This was an educational behavioural intervention promoting infant cognitive development and maternal coping. The mother infant dyads were followed up at 3 and 6 months corrected age and the program was found to have beneficial effects for both the mothers and their infants. Infants whose mothers' received the COPE program scored significantly higher on the Bayley Mental Development Index (MDI) at three and six months; and their mothers reported being less stressed by the sights and sounds of the NICU and felt better able to understand and interpret their baby's behaviour. The authors stress that the study should be seen as only a pilot as numbers were small and the babies were all healthy and their mothers relatively advantaged as the majority were white and had completed high school education. However these findings suggest this may be a promising

intervention for mothers of IVF/ICSI multiples especially as they are also more likely to be advantaged in terms of educational level.

The literature reviewed in chapter three section 3.1-vii suggested that for more vulnerable infants such as those born prematurely or from more disadvantaged socio-economic backgrounds the quality of mother-infant interaction was especially important (Smith, Landry et al. 1996; Laucht, Esser et al. 2002). Findings such as these lead researchers here at Nottingham to explore how mothers of premature infants felt about interacting with their babies. Semi-structured interviews with 20 mothers recruited through the research charity BLISS website revealed nine themes about their experiences of interacting with their infants. These included parental insecurity about interacting with their baby, finding the baby sleepy and unresponsive, a lack of information about interacting with their baby after discharge from hospital and finding support from health visitors to be unfulfilling (Nicolaou and Glazebrook in press). As a result of this research a new initiative is underway to develop an interactive education DVD for mothers about ways to interact with their premature babies. There are also plans to later evaluate its impact and acceptability to mothers.

A recent intervention to reduce the impact of a multiple birth was introduced in Newcastle, this intervention involved the introduction of a randomised controlled trial of a midwife led antenatal programme (Sen 2006). The intervention consisted of the allocation of a midwife advisor, an invitation to attend a series of education sessions, additional home visits and attendance at an antenatal twin clinic. Women were recruited to the study at 24 weeks of pregnancy and randomly allocated to the twin control group (n=82) or twin intervention (n=80). In addition the twin control

group women were matched to a group of women expecting singletons (n=82) matched for maternal age, consultant and previous parenting experience (parented or not). Data were collected during pregnancy and women were followed up until one year after the birth. The intervention was valued by the women and 65% attended all the sessions. The intervention was found to increase preparation for parenting and information provision but no significant differences in EPDS scores were found at any of the time points studied, although fewer women scored above the cut off (>12) at each time point and this nearly reached significance at 26 weeks postpartum. However women in the intervention group reported increased emotional well-being as measured by the maternal well-being subscale of the reaction to motherhood scale at 26 week post partum, and increased self-confidence. Findings which assume more importance when taking into account the findings that mothers of twins receiving standard care reported coping less well at 12 and 26 weeks post partum. Twin mothers who only received standard care also viewed their infants as more difficult and were less positively attached to them than mothers of singletons receiving standard care.

5.8 Improving success rates of single embryo transfer

As discussed in chapter 4 section 4.1-v, one way clinicians have sought to increase the success of single embryo transfer is to culture embryos for longer than five days, replacing them instead at the blastocyst stage. Schieve points out in an editorial in the New England Journal of Medicine that although good results from studies of women under 36 undergoing their first or second IVF cycle can not be generalised to the typical population of women undergoing IVF/ICSI (Schieve 2006). She argues

further work is needed to see whether these results can be obtained with a wider range of women seeking treatment.

5.9 Natural cycle IVF

Another way to reduce multiple births is to look for alternatives which produce fewer embryos so avoiding agonising decisions about how many should be transferred. Traditionally IVF has been performed after ovarian stimulation however natural cycle IVF practically eliminates the chance of a multiple pregnancy and so can be considered as an alternative way of reducing the number of multiple pregnancies. Natural cycle IVF could also help to reduce the psychological burden of treatment. A worrying finding already mentioned in chapter four section 4.1-i was that 54% of patients at one centre discontinued their IVF program before achieving a live birth and the most common reason for this was psychological burden (Olivius, Friden et al. 2004). These findings suggest how beneficial less psychologically burdensome protocols could be. Pelinck and colleagues have reviewed 20 studies describing natural cycle IVF and concluded that natural cycle IVF was a low-risk, low-cost and patient-friendly procedure (Pelinck, Hoek et al. 2002). The ongoing pregnancy rate from these cycles was 7.2%, and 15.8% per embryo transfer. However, over 28.9% of cycles have to be cancelled and this is the main reason why the procedure is not more popular. Moreover, Garceau and colleagues, in their review of the cost effectiveness of ART, maintain that natural cycle IVF may be less cost effective than first thought. Couples will have to have more time off work due to the lower success rates and there is also the additional expense of the extra ultrasonic and endocrine monitoring required, much of which may be outside normal working hours (Garceau, Henderson et al. 2002).

Another alternative is what is described as mild IVF and this option is explored in a recent randomised trial reported in The Lancet (Heijnen, Eijkemans et al. 2007). During the study 404 women less than 38 years old were randomised to mild ovarian stimulation (gonadotropin-releasing hormone antagonist treatment combined with single embryo transfer) or standard treatment (stimulation with gonadotropin-releasing hormone antagonist long protocol and transfer of two embryos). Over one year of treatment cumulative rates of live term births were similar, but there were significantly fewer multiple births 0.5% compared to 13.1% and the mean total costs were lower. Despite an increase in the average number of IVF cycles required the mild IVF group did not report significant differences for anxiety, depression, physical discomfort, or sleep quality. The authors suggest their findings should encourage the increased use of such strategies but warn they will need to be accompanied by counselling about success rates and the risks of multiple births as well as reimbursement systems to encourage single embryo transfer. This issue of reimbursing the costs of extra cycles of treatment is common to many of the strategies to encourage single embryo transfer. The health belief model would endorse the importance of manipulating perceptions about costs or barriers and benefits of health decisions.

CHAPTER SIX - Conclusion

In summary, therefore, this thesis has established that a single IVF birth is likely to offer significant advantages to the mother. Mothers of twins and triplets have poorer mental well-being in terms of an increased risk of experiencing clinically significant psychological symptoms of depression, increased parenting stress, and transcripts of their interviews show more negative themes including 'tiredness', 'feelings of stress or depression' and a few even 'questioning parenthood'. These findings were anticipated based on a review of the research literature and fit with the social cognitive theory of depression.

Twins and triplets are also disadvantaged themselves with studies reporting poorer health and developmental outcomes. The study of mothers' interactions with their premature twin and singleton infants reported in this thesis established mothers found interacting with their premature twins more stressful and twin infants were less responsive to their mothers. Moreover, mothers of twins were less responsive when interacting in an everyday setting than mothers of singletons. Attachment theory would suggest mothers of twins and triplets conceived through ART will need more support with the parenting role in order to minimise the developmental risks these interaction difficulties are likely to predict. These will be particularly important where there are additional disadvantages such as prematurity or difficult child temperament.

The findings in this thesis challenge the perception that twin births are highly desired by infertile couples, suggesting their prime concern is to increase the chance of pregnancy. Couples are prepared to accept risks for themselves and their children in order to increase this chance. Merely

increasing information about the risks of a multiple birth is therefore unlikely to encourage significantly higher rates of eSET. To achieve this here in the UK we can either legislate to enforce eSET or, more in accord with our respect for individual autonomy and the market driven economy of our infertility services we can produce better information to convince couples of the superiority of eSET over multiple embryo transfer. In line with the health belief model we should emphasise the value and benefits of eSET. A first step would be to highlight the social and psychological benefits of a singleton birth for the mother and the health and cognitive benefits for the infant.

REFERENCES

Abdin, R. R. (1995). Parenting Stress Index. USA, Psychological Assessment Resources.

Abraham, C. and Sheeran, P. (2005). *The Health Belief Model*. In *Predicting health behaviour.* Eds. M. Conner and P. Norman. Maidenhead, Open University Press**:** 28-80.

Abusheika, N., Salha, O., Sharma, V. and Brinsden, P. (2000). *Monozygotic twinning and IVF/ICSI treatment: a report of 11 cases and review of literature.* Human Reproduction Update **6**(4): 396-403.

Addor, V., Santos-Eggimann, B., Fawer, C.-L., Paccaud, F. and Calame, A. (1998). *Impact of infertility treatments on the health newborns.* Fertility and Sterility **69**(2): 210-215.

Alaszewski, A. and Horlick-Jones, T. (2003). *How can doctors communicate information about risk more effectively?* BMJ **327**(7417): 728-731.

Albrecht, J. and Tomich, P. (1996). *The maternal and neonatal outcome of triplet gestations.* American Journal of Obstetrics and Gynecology **174**(5): 1551-1556.

Alexander, G., Kogan, M., Martin, J. and Papiernik, E. (1998). *What Are the Fetal Growth Patterns of Singletons, Twins, and Triplets in the United States?* Clinical Obstetrics & Gynecology **41**(1): 115-125.

Alfasi, G., Schwartz, F. A., Brake, S. C., Fifer, W. P., Fleischman, A. R. and Hofer, M. A. (1985). *Mother-infant feeding interactions in preterm and full-term infants.* Infant Behavior and Development **8**: 167-180.

Allegra, A., Marino, A., Coffaro, F., Scaglione, P., Sammartano, F., Rizza, G. and Volpes, A. (2007). *GnRH antagonist-induced inhibition of the premature LH surge increases pregnancy rates in IUI-stimulated cycles. A prospective randomized trial.* Human Reproduction **22**: 101-108.

Alper, M. M. (2004). *In vitro fertilization outcomes: why doesn't anyone get it?* Fertility and Sterility **81**(3): 514-516.

Andersen, A. N., Goossens, V., Gianaroli, L., Felberbaum, R., de Mouzon, J. and Nygren, K. G. (2007). *Assisted reproductive technology in Europe, 2003. Results generated from European registers by ESHRE.* Human Reproduction **22**(6): 1513-1525.

Anderson, A. and Anderson, B. (1990). Toward a substantive theory of mother-twin attachment. MCN, American Journal of Maternal Child Nursing **15**(6): 373-7.

Armstrong, K. L., Fraser, J. A., Dadds, M. R. and Morris, J. (1999). *A randomized, controlled trial of nurse home visiting to vulnerable families with newborns.* Journal of Paediatrics and Child Health **35**(3): 237-244.

Bakeman, R. and Brown, J. V. (1980). Early interaction: consequences for social and mental development at three years. Child Development **51**: 437-447.

Bakermans-Kranenburg, M. J., Van IJzendoorn, M. H. and Juffer, F. (2003). *Less is more: meta-analyses of sensitivity and attachment interventions in early childhood*. Psychological Bulletin **129**(2): 195-215.

Barratt, M. S., Roach, M. A. and Leavitt, L. A. (1992). Early channels of mother-infant communication: preterm and term infants. Journal of Child Psychology and Psychiatry **33**(7): 1193-1204.

Barnard, K. E., Bee, H. L. and Hammond, M. A. (1984). Developmental changes in maternal interactions with term and preterm infants. Infant Behavior and Development **7**(1): 101-113.

BBC News (2003). *IVF multiples 'strain marriages'*. Retrieved 16.10.2003.

BBC News (2004). *Italy fertility treatment curbed*. Retrieved 22.03.2004, http;//newsvote.bbc.co.uk/mpapps/pagetools/print/news.bbc.co.uk/1/hi/world/europe.

BBC News (2008). *Lopez gives birth to girl and boy*

Retrieved 29.02.2008, http://news.bbc.co.uk/1/hi/entertainment/7258629.stm

Beck, C. T. (1996)[a]. *A meta-analysis of the relationship between postpartum depression and infant temperament*. Nursing Research **45**(4): 225-230.

Beck, C. T. (1996)[b]. *A Meta-Analysis of Predictors of Postpartum Depression.* Nursing Research **45**(5): 297-303.

Beck, C. T. (2001). *Predictors of Postpartum Depression: An Update*. Nursing Research **50**(5): 275-285.

Beck, C. T. (2002)[a]. *Mothering multiples: A meta-synthesis of qualitative research.* MCN: The American Journal of Maternal/Child Nursing **27**(4): 214-221.

Beck, C. T. (2002)[b]. *Releasing the Pause Button: Mothering Twins During the First Year of Life.* Qualitative Health Research **12**(5): 593-608.

Beck, C. T. (2002)[c]. *Postpartum depression: a metasynthesis*. Qualitative Health Research **12**(4): 453-472.

Becker, G., Castrillo, M., Jackson, R. and Nachtigall, R. D. (2006). *Infertility among low-income Latinos.* Fertility and Sterility **85**(4): 882-887.

Beckwith, L. and Cohen, S. E. (1978). *Preterm birth: Hazardous obstetrical and postnatal events as related to caregiver-infant behavior*. Infant Behavior and Development **1**: 403-411.

Bee, H. L., Barnard, K. E., Eyres, S. J., Gray, C. A., Hammond, M. A., Spietz, A. L., Snyder, C. and Clark, B. (1982). *Prediction of IQ and language skill from perinatal status, child performance, family characteristics, and mother-infant interaction.* Child Development **53**: 1134-1156.

Bee, H. and Boyd, D. (2002). *Lifespan Development*. Boston, Allyn and Bacon.

Beemsterboer, S. N., Homburg, R., Gorter, N. A., Schats, R., Hompes, P. G. A. and Lambalk, C. B. (2006). *The paradox of declining* fertility but increasing twinning rates with advancing maternal age. Human Reproduction **21**(6): 1531-1532.

Bekker, H. L., Hewison, J. and Thornton, J. G. (2003). *Understanding why decision aids work: linking process with outcome.* Patient Education & Counseling **50**(3): 323-9.

Belaisch-Allart, J. (2007). *Is twin pregnancy necessarily an adverse outcome of assisted reproductive technologies?* Human Reproduction **22**(5): 1495-.

Bellamy, R. (2004). An introduction to patient education: theory and practice. Medical Teacher **26**(4): 359-365.

Bergant, A. M., Heim, K., Ulmer, H. and Illmensee, K. (1999). *Early postnatal depressive mood: Associations with obstetric and psychosocial factors.* Journal of Psychosomatic Research **46**(4): 391-394.

Bergh, C. (2005). *Single embryo transfer: a mini-review*. Human Reproduction **20**(2): 323-327.

Berkowitz, R., Lynch, L., Stone, J. and Alvarez, M. (1996). *The current status of multifetal pregnancy reduction.* American Journal of Obstetrics and Gynecology **174**(4): 1265-1272.

Bernasko, J., Lynch, L., Lapinski, R. and Berkowitz, R. L. (1997). *Twin pregnancies conceived by assisted reproductive techniques: maternal and neonatal outcomes.* Obstetrics & Gynecology **89**(3): 368-72.

Bertarelli Group (2003) *Infertility therapy-associated multiple pregnancies (births): an ongoing experience. Proceedings of an expert group* Reproductive Biomedicine Online **7**(5): 515-542.

Bhattacharya, S. and Templeton, A. (2004). *What is the most relevant standard of success in assisted reproduction?: redefining success in the*

context of elective single embryo transfer: evidence, intuition and financial reality. Human Reproduction **19**(9): 1939-1942.

Bhutta, A. T., Cleves, M. A., Casey, P. H., Cradock, M. M. and Anand, K. J. S. (2002). *Cognitive and Behavioral Outcomes of School-Aged Children Who Were Born Preterm: A Meta-analysis.* Journal of the American Medical Association **288**(6): 728-737.

Bielawska-Batorowicz, E. and Kossakowska-Petrycka, K. (2006). *Depressive mood in men after the birth of their offspring in relation to a partner's depression, social support, fathers' personality and prenatal expectations.* Journal of Reproductive & Infant Psychology. **24**(1): 21-9.

Blackburn, N. (2004). *I will become a mother at any cost*. The Times Section T2 19.07.04**:** 4-6.

Blennborn, M., Nilsson, S., Hillervik, C. and Hellberg, D. (2005). *The couple's decision-making in IVF: one or two embryos at transfer?* Human Reproduction **20**(5): 1292-1297.

Blickstein, I. (2002). *Cerebral palsy in multifoetal pregnancies*. Developmental Medicine and Child Neurology **44**: 352-355.
Blondel, B. and Kaminski, M. (2002). *Trends in the occurrence, determinants, and consequences of multiple births*. Seminars in Perinatology **26**(4): 239-49.

Blondel, B., Kogan, M., Alexander, G., Dattani, N., Kramer, M., Macfarlane, A. and Wen, S. (2002). *The impact of the increasing number of multiple births on the rates of preterm birth and low birthweight: An international study.* American Journal of Public Health **92**(8): 1323-1330.

Boggio, A. (2005). *Italy enacts new law on medically assisted reproduction.* Human Reproduction **20**(5): 1153-1157.

Boulot, P., Vignal, J., Vergnes, C., Dechaud, H., Faure, J.-M. and Hedon, B. (2000). *Multifetal reduction of triplets to twins: a prospective comparison of pregnancy outcome*. Human Reproduction **15**(7): 1619-1623.

Bowlby, J. (1969). *Attachment and Loss*. New York, Basic Books.

Boyatzis, R. E. (1998). *Transforming qualitative information: thematic analysis and code development*. California, Sage.

Bozzette, M. (2007). *A review of reserach on premature infant-mother interaction.* Newborn and Infant Nursing Reviews **7**(1): 49-55.

Braude, P. (2006). *One child at a time: reducing multiple births after IVF.* Report of the Expert group on multiple births after IVF. Downloaded from http://www.hfea.gov.uk/en/483.html

Braun, V. and Clarke, V. (2006). *Using thematic analysis in psychology*. Qualitative Research in Psychology **3**: 77-101.

Bretherton, I. (1992). *The origins of attachment theory: John Bowlby and Mary Ainsworth.* Developmental Psychology **28**: 759-775.

Bryan, E. (2002). *Educating families, before, during and after a multiple birth.* Seminars in Neonatology **7**: 241-246.

Bryan, E. (2003). *The impact of multiple preterm births on the family*. BJOG: An International Journal of Obstetrics and Gynaecology **110**(SUPPL. 20): 24-28.

Buckett, W. and Tan, S. L. (2004). *What is the most relevant standard of success in assisted reproduction?: The importance of informed choice*. Human Reproduction **19**(5): 1043-1045.

Burston, A., Puckering, C. and Kearney, E. (2005). *At HOME in Scotland: validation of the home observation for measurement of the environment inventory.* Child Care, Health & Development **31**(5): 533-8.

Cahill, D. J. and Wardle, P. G. (2002). *Management of infertility*. British Medial Journal **325**(7354): 28-32.

Caldwell, B. and Bradley, R. H. (2001). *HOME Inventory Administration Manual, 3rd edition* Little Rock: University of Arkansas.

Callahan, T. L., Hall, J. E., Ettner, S. L., Christiansen, C. L., Greene, M. F. and Crowley, W. F. (1994). *The Economic Impact Of Multiple-Gestation Pregnancies And The Contribution Of Assisted-Reproduction Techniques To Their Incidence.* New England Journal of Medicine **331**(4): 244-249.

Campbell, D. M. and A. Templeton (2004*). Maternal complications of twin pregnancy.* International Journal of Gynecology & Obstetrics **84**: 71-73.

CARE. (2004). *IVF treatment and results*. Retrieved 09.06.2004, from http://www.care-ivf.com/locations/Park/Resultspark.htm.

Carlson, E., Sampson, M. and Sroufe, L. (2003). *Implications of attachment theory and research for developmental-behavioral pediatrics.* Developmental and Behavioral Pediatrics **24**(5): 364-379.

Champion, L. A. and Power, M. J. (1995). *Social and cognitive approaches to depression: towards a new synthesis*. British Journal of Clinical Psychology **34**: 485-503.

Chang, C. (1990). *Raising Twin Babies and Problems in the Family*. Acta Geneticae Medicae et Gemellologiae **39**: 501-505.

Child, T., AM, H. and SL, T. (2004). *The desire for mulitple pregnancy in male and female infertility patients*. Human Reproduction **19**(3): 558-561.

Choi, P., Henshaw, C., Baker, S. and Tree, J. (2005). *Supermum, superwife, supereverything: performing femininity in the transition to motherhood*. Journal of Reproductive and Infant Psychology **23**(2): 167-180.

Coetzee, K., Stewart, B., Peek, J. and Hutton, J. D. (2007). *Acceptance of single-embryo transfer by patients.* Fertility & Sterility **87**(1): 207-209

Cohen, J. (1977). *The significance of a Product Moment r_s.* Statistical power analysis for the behavioural sciences. New York, Academic Press**:** 79-107.

Collins, J. A. (2002). *An international survey of the health economics of IVF and ICSI.* Human Reproduction Update **8**(3): 265-277.

Colpin, H., Demyttenaere, K. and Vandemeulebroecke, L. (1995*). New reproductive technology and the family: The parent-child relationship following in vitro fertilization*. Journal of Child Psychology & Psychiatry & Allied Disciplines **36**(8): 1429-1441.

Colpin, H., Munter, A. D., Nys, K. and Vandemeulebroecke, L. (1999). *Parenting stress and psychosocial well-being among parents with twins conceived naturally or by reproductive technology*. Human Reproduction **14**(12): 3133-7.

Colpin, H., De-Munter, A., Nys, D. and Vandemeulebroecke, L. (2000). *Pre- and Postnatal Determinants of Parenting Stress in Mothers of One -Year-Old Twins*. Marriage and Family Review **30**(1-2): 99-107.

Cook, R. and Golombok, S. (1990). *Overview of IVF symposium*. Journal of Reproductive and infant psychology **8**(4): 210-212.

Cook, R., Bradley, S. and Golombok, S. (1998). *A preliminary study of parental stress and child behaviour in families with twins conceived by in-vitro fertilization.* Human Reproduction **13**(11): 3244-6.

Cooper, P. and Murray, L. (1998). *Postnatal depression*, British Medical Journal **316**(7148): 1884-6.

Cox, J., Holden, J. M. and Sagovsky, R. (1987). Detection of Postnatal Depression Development of the 10-item Edinburgh Postnatal Depression Scale. British Journal of Psychiatry **150**: 782-786.

Cox, J. (1994). *Origins and development of the 10-item Edinburgh Postnatal Depression Scale.* In: *Perinatal psychiatry - use and misuse of the Edinburgh Postnatal Depression Scale*. Eds J. Cox and J. Holden. London, Gaskell**:** 115-125.

Crawford, J. W. (1982). *Mother-infant interaction in premature and full-term infants.* Child Development **53**: 957-962.

Criniti, A., Thyer, A., Chow, G., Lin, P., Klein, N. and Soules, M. (2005). *Elective single blastocyst transfer reduces twin rates without compromising pregnancy rates*. Fertility and Sterility **84**(6): 1613-1619.

Crnic, K. A., Ragozin, A. S., Greenberg, M. T., Robinson, N. M. and B, B. R. (1983). *Social interaction and developmental competence of preterm and full-term infants during the first year of life*. Child Development **54**: 1199-1210.

Cutrona, C. E. and Troutman, B. R. (1986). *Social support, infant temperament and parenting self-efficacy: A mediational model of postpartum depression.* Child Development **57**: 1507-1518.

D'Alton, M. (2004). *Infertility and the desire for multiple births*. Fertility and Sterility **81**(3): 523-525.

Daniel, Y., Ochshorn, Y., Fait, G., Geva, E., Bar-Am, A. and Lessing, J. B. (2000). *Analysis of 104 twin pregnancies conceived with assisted reproductive technologies and 193 spontaneously conceived twin pregnancies*. Fertility and Sterility **74**(4): 683-689.

Davis, L., Edwards, H., Mohay, H. and Wollin, J. (2003). *The impact of a very premature birth on the psychological health of mothers.* Early Human Development **73**: 61-70.

Davies, M. J., Wang, J. X. and Norman, R. J. (2004). *What is the most relevant standard of success in assisted reproduction?: Assessing the BESST index for reproduction treatment.* Human Reproduction **19**(5): 1049-1051.

De Neubourg, D. and Gerris, J. (2006). *What about the remaining twins since single-embryo transfer? How far can (should) we go?* 10.1093/humrep/dei425. Human Reproduction **21**(4): 843-846.

De Neubourg, D., Gerris, J., Van Royen, E., Mangelschots, K. and Vercruyssen, M. (2006). *Impact of a restriction in the number of embryos transferred on the multiple pregnancy rate*. European Journal of Obstetrics and Gynecology and Reproductive Biology **124**: 212-215.

De Sutter, P., Gerris, J. and Dhont, M. (2002). *A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI*. Human Reproduction **17**(11): 2891-2896.

De Sutter, P., Delbaere, I., Gerris, J., Verstraelen, H., Goetgeluk, S., Van der Elst, J., Temmerman, M. and Dhont, M. (2006). *Birthweight of singletons after assisted* reproduction is higher after single- than after double-embryo transfer. Human Reproduction **21**(10): 2633-2637

Deber, R. B. P., Kraetschmer, N. M. and Irvine, J. D. (1996). *What Role Do Patients Wish to Play in Treatment Decision Making?* Archives of Internal Medicine **156**(13): 1414-1420.

Deech, R. (2001). *HFEA embryo transfer policy review*. Retrieved 13.06.2006, from http://212.49.193.187/cps/rde/xchg/SID-3F57D79B-91953691/hfea/hs.xsl/567.html.

Dell'Avvocato, L. (1998). *Do we realise the stress caused by twins?* Health Visitor **61**: 37.

Derom, C., Leroy, F., Vlietinck, R., Fryns, J.-P. and Derom, R. (2006). *High frequency of iatrogenic monozygotic twins with administration of clomiphene citrate and a change in chorionicity.* Fertility and Sterility **85**(3): 755-757.

Dhont, M., De Sutter, P., Ruyssinck, G., Martens, G. and Bekaert, A. (1999*). Perinatal outcome of pregnancies after assisted reproduction: A case-control study.* American Journal of Obstetrics and Gynecology 181 **181**(3): 688-695.

Dickey, R. P., Sartor, B. M. and Pyrzak, R. (2004). *What is the most relevant standard of success in assisted reproduction?: No single outcome measure is satisfactory when evaluating success in assisted reproduction; both twin births and singleton births should be counted as successes*. Human Reproduction **19**(4): 783-787.

Dodd, J. and Crowther, C. (2004). *Multifetal pregnancy reduction of triplet and higher-order multiple pregnancies to twins* Fertility and Sterility **81**(5): 1420-1422.

Ellison, M. A. and Hall, J. E. (2003). *Social stigma and compounded losses: Quality-of-life issues for multiple-birth families*. Fertility & Sterility **80**(2): 405-414.

Ellison, M. A., Hotamisligil, S., Lee, H., Rich-Edwards, J. W., Pang, S. C. and Hall, J. E. (2005). *Psychosocial risks associated with multiple births resulting from assisted reproduction*. Fertility and Sterility **83**(5): 1422-1428.

Elster, N. (2000). *Less is more: The risks of multiple births*. The Institute for Science, Law and Technology Working Group on Reproductive Technology. Fertility & Sterility **74**(4): 617-623.

Engmann, L., Maconochie, N., Tan, S. L. and Bekir, J. (2001). *Trends in the incidence of births and multiple births and the factors that determine the probability of multiple birth after IVF treatment.* Human Reproduction **16**(12): 2598-2605.

Epstein, R. M., Alper, B. S. and Quill, T. E. (2004). *Communicating Evidence for Participatory Decision Making.* Journal of the American Medical Association **291**(19): 2359-2366.

Ericson, A., Nygren, K. G., Olausson, P. O. and Kallen, B. (2002). *Hospital care utilization of infants born after IVF*. Human Reproduction **17**(4): 929-932.

Escalona, S. K. (1982). *Babies at Double Hazard: Early Development of Infants at Biologic and Social Risk*. Pediatrics **70**(5): 670-676.

ESHRE (2000). *Multiple gestation pregnancy*. The ESHRE Capri Workshop Group. Human Reproduction **15**: 1856-1864.

ESHRE (2001). Prevention of twin pregnancies after IVF/ICSI by single embryo transfer. Human Reproduction **16**(4): 790-800.

ESRC. (2005). *Parenting in the UK*. Retrieved 23.11.2005, from http://www.esrcsocietytoday.ac.uk/ESRCInfoCentre/facts/index33.aspx.

Evans, M. I., Kaufman, M. I., Urban, A. J., Britt, D. W. and Fletcher, J. C. (2004). *Fetal reduction from twins to a singleton: a reasonable consideration?* Obstetrics & Gynecology **104**(1): 102-109.

Evers, J. L. H. (2002). *Female Subfertility.* The Lancet **360**: 151-159.

Fanaroff, A. A., Stoll, B. J., Wright, L. L., Carlo, W. A., Ehrenkranz, R. A., Stark, A. R., Bauer, C. R., Donovan, E. F., Korones, S. B., Laptook, A. R., Lemons, J. A., Oh, W., Papile, L.-A., Shankaran, S., Stevenson, D. K., Tyson, J. E. and Poole, W. K. (2007). *Trends in neonatal morbidity and mortality for very low birthweight infants*. American Journal of Obstetrics and Gynecology **196**(2): 147.e1-147.e8.

Feldman, R. and Eidelman, A. I. (2004). *Parent-infant synchrony and the social-emotional development of triplets*. Developmental Psychology **40**(6): 1133-1147.

Feldman, R., Eidelman, A. I. and Rotenberg, N. (2004). *Parenting stress, infant emotion regulation, maternal sensitivity, and the cognitive development of triplets: a model for parent and child influences in a unique ecology.* Child Development **75**(6): 1774-1791.

Feldman, R. and Eidelman, A. I. (2005). *Does a Triplet Birth Pose a Special Risk for Infant Development? Assessing Cognitive Development in Relation to Intrauterine Growth and Mother-Infant Interaction Across the First 2 Years*. Pediatrics **115**(2): 443-452.

Fiddelers, A. A. A., van Montfoort, A. P. A., Dirksen, C. D., Dumoulin, J. C. M., Land, J. A., Dunselman, G. A. J., Janssen, J. M., Severens, J. L. and Evers, J. L. H. (2006). "Single versus double embryo transfer: cost-effectiveness analysis alongside a randomized clinical trial." Human Reproduction del112.

Field, T. (1995). *Infants of depressed mothers*. Infant Behavior and Development **18**: 1-13.

Fisher, J., Feekery, C. and Rowe-Murray, H. (2002*). Nature, severity and correlates of psychological distress in women admitted to a private mother-baby unit.* Journal of Paediatric Child Health **38**: 140-145.

Fisher, J. and Stocky, A. (2003). *Maternal Perinatal Mental Health and Multiple Births: Implications for Practice*. Twin Research **6**(6): 506-513.

Fisher, J. R. W., Hammarberg, K. and Baker, H. W. G. (2005). *Assisted conception is a risk factor for postnatal mood disturbance and early parenting difficulties.* Fertility and Sterility **84**(2): 426-430.

Fontaine, K. R. and Jones, L. C. (1997). *Self-esteem, optimism, and postpartum depression.* Journal of Clinical Psychology **53**(1): 59-63.

Forman, D. N., Videbech, P., Hedegaard, M., Salvig, J. D. and Secher, N. J. (2000). *Postpartum depression: identification of women at risk*. British Journal of Obstetrics and Gynaecology **107**: 1210-1217.

Fowles, E. R. (1998). *The relationship between maternal role attainment and postpartum depression*. Health Care for Women International **19**: 83-94.

Freeman, T., Golombok, S., Olivennes, O., Ramogida, C. and Rust, J. (2007). *Psychological assessment of mothers and their assisted reproduction triplets at age 3 years*. Reproductive BioMedicine Online 2007

Garceau, L., Henderson, J., Davis, L. J., Petrou, S., Henderson, L. R., McVeigh, E., Barlow, D. H. and Davidson, L. L. (2002). *Economic implications of assisted reproductive techniques: a systematic review*. Human Reproduction **17**(12): 3090-3109.

Gardner, D. K., Surrey, E., Minjarez, D., Leitz, A., Stevens, J. and Schoolcraft, W. B. (2004). *Single blastocyst transfer: a prospective randomized trial.* Fertility and Sterility **81**(3): 551-555.

Gardner, M. O., Goldenberg, R. L., Cliver, S. P., Tucker, J. M., Nelson, K. G. and Copper, R. L. (1995). *The Origin and Outcome of Preterm Twin Pregnancies.* Obstetrics & Gynecology **85**(4): 553-557.

Garel, M. and Blondel, B. (1992). *Assessment at 1 year of the psychological consequences of having triplets*. Human Reproduction **7**(5): 729-732.

Garel, M., Salobir, C. and Blondel, B. (1997). *Psychological consequences of having triplets: a 4-year follow-up study*. Fertility & Sterility **67**(6): 1162-5.

Garel, M., Stark, C., Blondel, B., Lefebvre, G., Vauthier-Brouzes, D. and Zorn, J. (1997). *Psychological reactions after multifetal pregnancy reduction: a 2-year follow-up study*. Human Reproduction **12**(3): 617b-622.

Garel, M., Bahuaud, M. and Blondel, B. (2004). *Consequences for the family of a very preterm birth two months after discharge. Results of the EPIPAGE qualitative study*. Archives De Pediatrie **11**(11): 1299-1307.

Garner, P. W., Landry, S. H. and Richardson, M. A. (1991). *The development of joint attention skills in very-low-birth-weight infants across the first 2 years.* Infant Behavior and Development **14**(4): 489-495.

Gerhold, M., Laucht, M., Texdorf, C., Schmidt, M. H., Esser, G., Gerhold, M., Laucht, M., Texdorf, C., Schmidt, M. H. and Esser, G. (2002). *Early mother-infant interaction as a precursor to childhood social withdrawal.* Child Psychiatry & Human Development **32**(4): 277-293

Germond, M., Urner, F., Chanson, A., Primi, M.-P., Wirthner, D. and Senn, A. (2004). *What is the most relevant standard of success in assisted reproduction? The cummulated singleton/twin delivery rates per oocyte pick-up the CUSIDERA and CUTWIDERA*. Human Reproduction **19**(11): 2442-2444.

Gerner, E. M. (1999). *Emotional interaction in a group of preterm infants at 3 and 6 months of corrected age*. Infant and Child Development **8**(3): 117-128.

Gerris, J., De Neubourg, D., Mangelschots, K., Van Royen, E., Van de Meerssche, M. and Valkenburg, M. (1999). *Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial*. Human Reproduction **14**(10): 2581-7.

Gerris, J., De Neubourg, D., Mangelschots, K., Van Royen, E., Vercruyssen, M., Barudy-Vasquez, J., Valkenburg, M. and Ryckaert, G. (2002). *Elective single day 3 embryo transfer halves the twinning rate without decrease in the ongoing pregnancy rate of an IVF/ICSI programme.* Human Reproduction **17**(10): 2626-2631.

Gerris, J. (2004). *IVF and ICSI reimbursed in Belgium*. Journal of Assisted Reproduction & Genetics **21**(5): 135

Gerris, J., De Sutter, P., De Neubourg, D., Van Royen, E., Vander Elst, J., Mangelschots, K., Vercruyssen, M., Kok, P., Elseviers, M., Annemans, L., Pauwels, P. and Dhont, M. (2004*). A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles*. Human Reproduction **19**(4): 917-923.

Gerris, J. M. R. (2005). *Single embryo transfer and IVF/ICSI outcome: a balanced appraisal.* Human Reproduction Update **11**(2): 105-121.

Gibson, F. L., Ungerer, J. A., Leslie, G. I., Saunders, D. M. and Tennant, C. C. (1998). *Development, behaviour and temperament: a prospective study of infants conceived through in-vitro fertilization*. Human Reproduction **13**(6): 1727-32.

Glazebrook, C., Cox, S., Oates, M. and Ndukwe, G. (2000). *Psychological adjustment during pregnancy and the postpartum period in single and multiple in vitro fertilization births: a review and preliminary findings from an ongoing study.* Reproductive Technologies **10**(2): 112-119.

Glazebrook, C., Sheard, C., Cox, S., Oates, M. and Ndukwe, G. (2004). "Parenting stress in first-time mothers of twins and triplets conceived after in vitro fertilization." Fertility and Sterility **81**(3): 505-511.

C. Glazebrook, C. Sheard, L. Winstanley, S. Cox and G. Ndukwe (2007) *Attitudes of Infertile coples to a multiple birth: a review of the literature and results form a survey*. Current Women's Health Reviews **3:** 1-6

Glazebrook, C., Marlow, N., Israel, C., Croudace, T., Johnson, S., White, I. R. and Whitelaw, A. (2007). *Randomised trial of a parenting intervention during neonatal intensive care* Archives of Diseases in Childhood Fetal and Neonatal Edition online 10.1136/adc.2006.103135

Gleicher, N., Campbell, D. P., Chan, C. L., Karande, V., Rao, R., Balin, M. and Pratt, D. (1995). *The desire for multiple births in couples with infertility problems contradicts present practice patterns*. Human Reproduction **10**(5): 1079 - 1084.

Gleicher, N., Weghofer, A. and Barad, D. (2006). *A formal comparison of the practice of assisted reproductive technologies between Europe and the USA*. Human Reproduction **21**: 1945-1950.

Goldberg, S., Perrotta, M. and Minde, K. (1986). *Maternal behaviour and attachment in low-birth-weight twins and singletons*. Child Development **57**: 34-46.

Goldfarb, J., Kinzer, D. J., Boyle, M. and Kurit, D. (1996). *Attitudes of in vitro fertilization and intrauterine insemination couples toward multiple gestation pregnancy and multifetal pregnancy reduction*. Fertility and Sterility **65**(4): 815-20.

Goldfarb, J. M. (2006). *Solutions to the problem of multple pregnancy with IVF: letter to the editor.* Fertility and Sterility **85**(5): e11.

Golombok, S., Brewaeys, A., Cook, R., Giavazzi, M. T., Guerra, D., Mantovani, A., van Hall, E., Crosignani, P. G. and Dexeus, S. (1996). *The European study of assisted reproduction families: family functioning and child development.* Human Reproduction **11**(10): 2324-31.

Golombok, S., Brewaeys, A., Giavazzi, M. T., Guerra, D., MacCallum, F. and Rust, J. (2002). *The European study of assisted reproduction families: the transition to adolescence*. Human Reproduction **17**(3): 830-840.

Goshen-Gottstein, E. R. (1980). *The mothering of twins, triplets and quadruplets.* Psychiatry **43**(3): 189-204.

Greenberg, M. T. and Crnic, K. A. (1988). *Longitudinal predictors of developmental status and social interaction in premature and full-term infants at age two.* Child Development **59**: 554-570.

Greene, J. G., Fox, N. A. and Lewis, M. (1983). *The relationship between neonatal characterisitcs and three month mother-infant interaction in high -risk infants.* Child Development **54**: 1286-1296.

Griesinger, G., Dafopoulos, K., Schultze-Mosgau, A., Felberbaum, R. and Diedrich, K. (2004). *What is the most relevant standard of success in assisted reproduction?: Is BESST (birth emphasizing a successful singleton at term) truly the best?* Human Reproduction **19**(6): 1239-1241.

Grobman, W. A., Milad, M. P., Stout, J. and Klock, S. C. (2001). *Patient perceptions of multiple gestations: an assessment of knowledge and risk aversion.* American Journal of Obstetrics & Gynecology **185**(4): 920-924.

Groothuis, J. R., Altemeier, W. A., Robarge, J. P. O'Connor, S., Sander, H., Vietze, P. and Lustig, J. (1982). *Increased child abuse in families with twins*. Pediatrics **70**(5): 769-773.

Hahn, C. S. (2001*). Psychosocial well-being of parents and their children born after assisted reproduction*. Journal of Pediatric Psychology **26**: 525-538.

Hahn, C. S. and DiPietro, J. A. (2001). *In Vitro Fertilization and the family: quality of parenting, family functioning, and child psychosocial adjustment*. Developmental Psychology **37**(1): 37-48.

Haigh, J. and Wilkinson, L. (1989). *Care and management of twins*. Health Visitor **62**(2): 43-45.

Hallenbeck, J. L. (2002). *What's the story--how patients make medical decisions.* The American Journal of Medicine **113**(1): 73-74.

Hamilton, B. E., Minino, A. M., Martin, J. A., Kochanek, K. D., Strobino, D. M. and Guyer, B. (2007). *Annual Summary of Vital Statistics: 2005*. Pediatrics **119**(2): 345-360.

Hankins, G. D. V., Erickson, K., Zinberg, S. and Schulkin, J. (2003). *Neonatal encephalopathy and cerebral palsy: a knowledge survey of Fellows of The American College of Obstetricians and Gynecologists*. Obstetrics & Gynecology **101**(1): 11-17.

Harrison, M. J. and Magill-Evans, J. (1996). *Mother and father interactions over the first year with term and preterm infants*. Research in Nursing & Health **19**: 451-459.

Hartshorne, G. M. (2002). *Embryology. Different perspectives of patients and health care professionals on the potential benefits and risks of blastocyst culture and multiple embryo transfer*. Human Reproduction **17**: 1023-1030.

Haskett, M. E., Ahern, L. S., Ward, C. S. and Allaire, J. C. (2006). *Factor structure and validity of the Parentng Stress Index-Short Form.* Journal of Clinical Child and Adolescent Psychology **35**(2): 302-312.

Hay, D., Gleeson, C., Davies, C., Lorden, B., Mitchell, D. and Paton, L. (1990). *What information should the multiple birth family receive before, during and after the birth?*" Acta Geneticae Medicae et Gemellologiae **39**: 259-269.

Hazekamp, J., Bergh, C., Wennerholme, U. B., Hovatta, O. and Karlstrom, A. (2000). *Avoiding multiple pregnancies in ART: consideration of new strategies.* Human Reproduction **15**(6): 1217-1219.

Healy, D. (2004). *Damaged babies from assisted reproductive technologies: focus on the BESST (birth emphasizing a successful singleton at term) outcome.* Fertility and Sterility **81**(3): 512-513.

Heijnen, E. M. E. W., Macklon, N. S. and Fauser, B. C. J. M. (2004). *What is the most relevant standard of success in assisted reproduction?: The next step to improving outcomes of IVF: consider the whole treatment.* Human Reproduction **19**(9): 1936-1938.

Heijnen, E. M., Eijkemans, M. J., De Klerk, C., Polinder, S., Beckers, N. G., Klinkert, E. R., Broekmans, F. J., Passchier, J., Te Velde, E. R., Macklon, N. S. and Fauser, B. C. (2007). *A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial.* Lancet **369**(9563):743-749

Helmerhorst, F. M., Perquin, D. A. M., Donker, D. and Keirse, M. (2004). *Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies*. British Medical Journal **328**(7434): 261-264B.

Henman, M., Catt, J. W., Wood, T., Bowman, M. C., de Boer, K. A. and Jansen, R. P. S. (2005). *Elective transfer of single fresh blastocysts and later transfer of cryostored blastocysts reduces the twin pregnancy rate and can improve the in vitro fertilization live birth rate in younger women*. Fertility and Sterility **84**(6): 1620-1627.

HFEA. (2003). *Human Fertilisation and Embryology Authority 6th Code of Practice.* Human Fertilisation and Embryology Authority, London. Retrieved from www.hfeagov.uk

HFEA. (2005). *Fertility regulator looks to reduce the risks of IVF treatment.* Retrieved 01.03.2006, from http://www.hfea.gov.uk/PressOffice/Archive/.

HFEA. (2006). *Fertility problems and treatment - facts and figures*. Retrieved 27.06.2006 from http://www.hfea.gov.uk/PressOffice//Factsandfigures/.

Hiscock, H. and Wake, M. (2001). *Infant Sleep Problems and Postnatal Depression: A Community-Based Study.* Pediatrics **107**(6): 1317-1322.

Hock, D. L. S., D.B. Kontopoulos E. and Ananth, C.V (2002). *Practice Patterns Among Board-Certified Reproductive Endocrinologists Regarding*

High-Order Multiple Gestations: A United States National Survey. Obstetrics & Gynecology **99**(5): 763-770

Hogue, C. J. R. (2002). *Successful assisted reproductive technology: the beauty of one.* Obstetrics & Gynecology **100**(5): 1017-1019.

Holditch-Davis, D., Roberts, D. and Sandelowski, M. (1999). *Early parental interactions with and perceptions of multiple birth infants.* Journal of Advanced Nursing **30**(1): 200-210.

Holditch-Davis, D., Bartlett, T. R. and Belyea, M. (2000). *Developmental problems and interactions between mothers and prematurely born children.* Journal of Pediatric Nursing **15**(3): 157-167.

Holditch-Davis, D., Docherty, S., Miles, M. S. and Burchinal, M. (2001). *Developmental outcomes of infants with bronchopulmonary dysplasia: comparison with other medically fragile infants*. Research in Nursing & Health **24**: 181-193.

Holditch-Davis, D., Bartlett, T. R., Blickman, A. L. and Miles, M. S. (2003). *Posttraumatic stress symptoms in mothers of premature infants*. Journal of Obstetric, Gynecologic, & Neonatal Nursing **32**(2): 161-71.

Holliday, A. (2002). *Qualitative Research*. London, Sage.

Horowitz, J. A., Damato, E. G., Duffy, M. E. and Solon, L. (2005). *The relationship of maternal attributes, resources, and perceptions of postpartum experiences to depression*. Research in Nursing and Health **28**: 159-171.

Huddy, C. L. J., Johnson, A. and Hope, P. L. (2001). *Educational and behavioural problems in babies of 32-35 weeks gestation*. Archives of Diseases in Childhood Fetal and Neonatal Edition **85**(1): F23-28.

Hvidtjorn, D., Grove, J., Schendel, D. E., Vaeth, M., Ernst, E., Nielsen, L. F. and Thorsen, P. (2006). *Cerebral palsy among children born after in vitro fertilization: The role of preterm delivery - A population-based, cohort study.* Pediatrics **118**(2): 475-482.

Jain, T. M., S. and Hornstein, M (2004). "Trends in Embryo-Transfer Practice and in Outcomes of the Use of Assisted Rrproductive Technology in the United States." The New England Journal of Medicine **350**: 1639-1645.

Jarvis, P. A., Myers, B. J. and Creasey, G. L. (1989*). The effects of infants' illness on mothers' interactions with prematures at 4 and 8 months*. Infant Behavior and Development **12**(1): 25-35.

Jones, H. J. (2004). *A big first step*. Human Reproduction **19**(11): 2445.

Jones, H. W., Jr. and Cohen, J. (2007). *IFFS surveillance 07*. Fertility and Sterility **87**(4 Suppl 1): S1-67.

Jones, H. W. and Schnorr, J. A. (2001). *Multiple pregnancies: a call for action.* Fertility and Sterility **75**(1): 11-13.

Kalra, S. K., Milad, M. P., Klock, S. C. and Grobman, W. A. (2003). *Infertility patients and their partners: differences in the desire for twin gestations.* Obstetrics & Gynecology **102**(1): 152-5.

Keith, L. and Oleszczuk, J. (2002). *Triplet Births in the United States An epidemic of High -Risk Pregnancies.* The Journal of Reproductive Medicine **47**(4): 259-265.

Kjellberg, A. T., Carlsson, P. and Bergh, C. (2006). *Randomized single versus double embryo transfer: obstetric and paediatric outcome and a cost-effectiveness analysis.* Human Reproduction **21**(1): 210-216*.*

Klock, S. C. (2004). Psychological adjustment to twins after infertility. Best Practice & Research Clinical Obstetrics and Gynaecology **18**(4): 645-656.

Koeppen-Schomerus, G., Eley, T. C., Wolke, D., Gringras, P. and Plomin, R. (2000). *The interaction of prematurity with genetic and environmental influences on cognitive development in twins*. Journal of Pediatrics **137**(4): 527-33.

Kogan, M., Alexander, G. R., Kotelchuck, M., MacDorman, M., Buekens, P., Martin, J. and Papiernik, E. (2000). *Trends in twin birth outcomes and*

prenatal care utilization in the United States 1981-1997. Journal of the American Medical Association **284**(3): 335-341.

Koivurova, S., Hartikainen, A.-L., Gissler, M., Hemminki, E., Sovio, U. and Jarvelin, M.-R. (2002). *Neonatal outcome and congenital malformations in children born after in-vitro fertilization*. Human Reproduction **17**(5): 1391-1398.

Koudstaal, J., Bruinse, H. W., Helmerhorst, F. M., Vermeiden, J. P., Willemsen, W. N. and Visser, G. H. (2000). *Obstetric outcome of twin pregnancies after in-vitro fertilization: a matched control study in four Dutch university hospitals.* Human Reproduction **15**(4): 935-40.

Lambalk, C. B. and van Hooff, M. (2001). *Natural versus induced twinning and pregnancy outcome: a Dutch nationwide survey of primiparous dizygotic twin deliveries*. Fertility and Sterility **75**(4): 731-736.

Land, J. A. and Evers, J. L. H. (2003). *Risks and complications in assisted reproduction techniques: Report of an ESHRE consensus meeting*. Human Reproduction **18**(2): 455-457.

Land, J. A. and Evers, J. L. H. (2004). *What is the most relevant standard of success in assisted reproduction?: Defining outcome in ART: a Gordian knot of safety, efficacy and quality.* Human Reproduction **19**(5): 1046-1048.

Landry, S. H., Chapieski, M. L., Richardson, M. A., Palmer, J. and Hall, S. (1990). *The social competence of children born prematurely: effects of medical complications and parent behaviours*. Child Development **61**: 1605-1616.

Larcher, V. (2007)[a]. *Ethical issues in respect of children born after assisted reproduction technologies.* Archives of Diseases in Childhood **92**(8): 670-671.

Larcher, V. (2007)[b]. *The health of children conceived by assisted reproduction technologies*. Archives of Diseases in Childhood **92**(8): 668-669.

Lass, A. and Brinsden, P. (2001). *How do patients choose private in vitro fertilization treatment? A customer survey in a tertiary fertility centre in the United Kingdom.* Fertility and Sterility **75**(5): 893-897.

Laucht, M., Esser, G. and Schmidt, M. H. (2002). *Vulnerability and resilience in the development of children at risk: the role of early mother-child interaction.* Revista de Psiquiatria Clinica **29**(1): 20-27.

Leavitt, L. A. (1999). *Research to practice: Emotional development and maternal/infant attachment.* Journal of Pediatric Health Care **13**(3, Part 2): S4-S7.

Ledger, W. L., Anumba, D., Marlow, N., Thomas, C. M. and Wilson, E. C. F. (2006). *The costs to the NHS of multiple births after IVF treatment in the UK.* BJOG: An International Journal of Obstetrics and Gynaecology **113**(1): 21-25.

Leiblum, S. R., Kemmann, E. and Taska, L. (1990). *Attitudes toward multiple births and pregnancy concerns in infertile and non-infertile women*. Journal of Psychosomatic Obstetrics & Gynaecology **11**(3): 197-210.

Leitch, D. (1999). *Mother-infant interaction; achieving synchrony*. Nursing Research **48**(1): 55-58.

Leonard, L. G. (1998). *Depression and Anxiety Disorders During Multiple Pregnancy and Parenthood.* Journal of Obstetric, Gynecologic and Neonatal Nursing **27**(3): 329-337.

Leondires, M., Ernst, S., Miller, B. and Scott, R. (2000). *Triplets: Outcomes of expectant management versus multifetal reduction for 127 pregnancies*. American Journal of Obstetrics and Gynecology **183**(2): 454-459.

Lewis, M. and Coates, D. L. (1980). *Mother-infant interaction and cognitive development in twelve-week-old infants.* Infant Behavior and Development **3**: 95-105.

Lukassen, H. G. M., Schonbeck, Y., Adang, E. M. M., Braat, D. D. M., Zielhuis, G. A. and Kremer, J. A. M. (2004). *Cost analysis of singleton versus twin pregnancies after in vitro fertilization.* Fertility and Sterility **81**(5): 1240-1246.

Lukassen, H. G. M., D.Braat, D., Wetzels, A. M. M., Zielhuis, G. A., Adang, E. M. M., Scheenjes, E. and Kremer, J. A. M. (2005). *Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial.* Human Reproduction **20**(3): 702-708.

Luke, B., Brown, M. B., Nugent, C., Gonzalez-Quintero, V. H., Witter, F. R. and Newman, R. B. (2004). *Risk factors for adverse outcomes in spontaneous versus assisted conception twin pregnancies*. Fertility and Sterility **81**(2): 315-319.

Lynch, A., J. McDuffie, Robert, et al. (2002). *Preeclampsia in multiple gestation: the role of assisted reproductive technologies*. Obstetrics & Gynecology **99**(3): 445-451.

Mantymaa, M., Puura, K., Luoma, I., Salmelin, R. K. and Tamminen, T. (2004). *Early mother-infant interaction, parental mental health and symptoms of behavioral and emotional problems in toddlers*. Infant Behavior and Development **27**(2): 134-149.

Marlow, N., D. Wolke, et al. (2005). *Neurological and developmental disability at six years of age after extremely preterm birth*. New England Journal of Medicine **352**(1): 9-19.

Massett, H. A., Greenup, M., Ryan, C. E., Staples, D. A., Green, N. S. and Maibach, E. W. (2003). *Public perceptions about prematurity: a national survey.* American Journal of Preventive Medicine **24**(2): 120-127.

Mays, N. and Pope, C. (2000). *Qualitative research in health care: assessing quality in qualitative research*. British Medical Journal **320**(7226): 50-52.

Multiple Birth Foundation. (2007). *UK birth figures for 2005*. Retrieved 16.07.2007. from http://www.multiplebirths.org.uk/media.asp.

McDonald, S., Murphy, K., Beyene, J. and Ohlsson, A. (2005). *Perinatal outcomes of in vitro fertilization twins: A systematic review and meta-analyses*. American Journal of Obstetrics and Gynecology **193**(1): 141-152.

McKinney, M., Downey, J. and Timor-Tritsch, I. (1995). *The psychological effects of multifetal pregnancy reduction.* Fertility and Sterility **64**(1): 51-61.

McMahon, C. A., Ungerer, J. A., Tennant, C. and Saunders, D. (1997)[a]. *Psychosocial adjustment and the quality of the mother-child relationship at four months postpartum after conception by in vitro fertilization*. Fertility and Sterility **68**(3): 492-500.

McMahon, C., Ungerer, J., Beaurepaire, J., Tennant, C. and Saunders, D. (1997)[b]. *Anxiety during pregnancy and fetal attachment after in-vitro fertilization conception*. Human Reproduction **12**(1): 176b-182.

McMahon, C. A., Barnett, B., Kowalenko, K., Tennant, C. and Don, D. (2001). *Postnatal depression, anxiety and unsettled infant behaviour*. Australian and New Zealand Journal of Psychiatry **35**: 581-588.

Melnyk, B. M., Alpert-Gillis, L., Feinstein, N. F., Fairbanks, E., Schultz-Czarniak, J., Hurst, D., Sherman, L., LeMonie, C., Moldenhauer, Z., Small, L., Bender, N. and Sinkin, R. A. (2001). *Improving cognitive development of low-birth-weight premature infants with the COPE program: a pilot study of the benefit of early NICU intervention with mothers*. Research in Nursing and Health **24**: 373-389.

Miceli, P. J., Goeke-Morey, M. C., Whitman, T. L., Kolberg, K. S., Miller-Loncar, C. and White, R. D. (2000). *Brief Report : Birth Status, Medical Complications, and Social Environment : Individual Differences in Development of Preterm, Very Low Birth Weight Infants*. Journal of Pediatric Psychology **25**(5): 353-358.

Miles, M. S. and Holditch-Davis, D. (1995). *Compensatory parenting: how mothers describe parenting their 3- year-old, prematurely born children*. Journal of Pediatric Nursing **10**(4): 243-2253.

Miles, M. S. and Holditch-Davis, D. (1997). *Parenting the prematurely born child: Pathways of influence.* Seminars in Perinatology **21**(3): 254-266.

Min, J. K., S. A. Breheny, et al. (2004). *What is the most relevant standard of success in assisted reproduction? The singleton, term gestation, live birth rate per cycle initiated: the BESST endpoint for assisted reproduction.* Human Reproduction **19**(1): 3-7.

Moise, J., Laor, A., Armon, Y., Gur, I. and Gale, R. (1998). *The outcome of twin pregnancies after IVF.* Human Reproduction **13**(6): 1702-5.

Moorhead, J. (2005). *Double trouble- and then some*. The Guardian Parents section 2.3.2005**:** 14.

Mukhopadhaya, N. and Arulkumaran, S. (2007). *Reproductive outcomes after in-vitro fertilization.* Current Opinion in Obstetrics and Gynecology **19**: 113-119.

Muller-Nix, C., Forcada-Guex, M., Pierrehumbert, B., Jaunin, L., Borghini, A. and Ansermet, F. (2004). *Prematurity, maternal stress and mother-child interactions.* Early Human Development **79**(2): 145-158.

Munro, J. M., Ironside, W. and Smith, G. C. (1990). Psychiatric morbidity in parents of twins born after in vitro fertilization (IVF) techniques. Journal of in Vitro Fertilization & Embryo Transfer **7**(6): 332-336.

Munro, J. M., Ironside, W. and Smith, G. C. (1992). *Successful parents of in vitro fertilization (IVF): The social repercussions.* Journal of Assisted Reproduction & Genetics **9**(2): 170-176.

Murdoch, A. (1997). *Triplets and embryo transfer policy*. Human Reproduction **12**(11): 88-92.

Murray, L. and Carothers, A. D. (1990). *The validation of the Edinburgh Post-natal Depression Scale on a community sample*. British Journal of Psychiatry **157**: 288-290.

Murray, L., Stanley, C., Hooper, R., King, F. and Fiori-Cowley, A. (1996). *The Role of infant factors in postnatal depression and mother-infant interactions*. Developmental Medicine and Child Neurology **38**: 109-119.

Murray, L., Cooper, P. J., Wilson, A. and Romaniuk, H. (2003). *Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression 2. Impact on the mother-child relationship and child outcome.*" British Journal of Psychiatry **182**: 420-427.

Murray, S., Shetty, A., Rattray, A., Taylor, V. and Bhattacharya, S. (2004). *A randomized comparison of alternative methods of information provision on the acceptability of elective single embryo transfer*. Human Reproduction **19**(4): 911-916.

National Institute for Clinical Excellence (2004). *New NHS guidelines on fertility treatment*. Retrieved 21.04.2004 from http://www.nice.org.uk/page.aspx?o=cg011pressrelease

National Statistics. (2001). *Maternities with multiple births: by age of mother at childbirth 2001: Social Trends 33*. Retrieved on 2.9.2004, from http://www.statistics.gov.uk/StatBase/ssdataset.asp?vlnk =6378&More=Y.

National Statistics. (2005). *Birth Statistics : Review of the Registrar General on births and patterns of family building in England and Wales 2005* Series FMI no 34. Retrieved on 3.07.2007.

National Statistics. (2006). *Births: 1938-2004, maternities with multiple births.* Retrieved on 17.7.2007, from http://www.statistics.gov.uk/StatBase/xsdataset.asp?More=Y.

Newton, C. and McBride, J. (2005). *Single embryo transfer (SET): factors affecting patient attitudes and decision-making*. Fertility and Sterility **84** (Supplement 1): S3.

Nicolaou, M. and Glazebrook, C. (in press). Conference abstract: *Mothers' experiences of interacting with their premature infants*. Society for Reproductive and Infant Psychology 27th Annual Conference.

Noble, M., Wright, G., Dibben, C., Smith, G., McLennan, D., Anttila, C., Barnes, H., Mokhtar, C., Noble, S., Avenell, D., Gardner, J., Covizzi, I. and Lloyd, M. (2004). *The English Indices of Deprivation 2004*. Wetherby, Office of the Deputy Prime Minister.

O'Connor, A. M., Stacey, D., Entwistle, V., Llewellyn-Thomas, H., Rovner, D., Holmes-Rovner, M., Tait, V., Tetroe, J., Fiset, V., Barry, M. and Jones, J. (2003). *Decision aids for people facing health treatment or screening decisions.* Cochrane Database of Systematic Reviews (2): CD001431.

Ogden, J. (2004). *Health Psychology - a text book*. Maidenhead, Open University Press.

O'Hara, M. W. and Swain, A. M. (1996). *Rates and risk of postpartum depression- a meta-analysis.* International Review of Psychiatry **8**: 37-54.

Oakley, L. and Doyle, P. (2006). *Predicting the impact of in vitro fertilisation and other forms of assisted conception on perinatal and infant mortality in England and Wales: Examining the role of multiplicity* BJOG: An International Journal of Obstetrics and Gynaecology **113**(6): 738-741.

Office of Population Census. (1990). *Standard Occupation Classification*. London, HMSO.

Olivennes, F. (2000). *Avoiding multiple pregnancies in ART: Double trouble: yes a twin pregnancy is an adverse outcome*. Human Reproduction **15**(8): 1663-1665.

Olivennes, F., Golombok, S., Ramogida, C. and Rust, J. (2005). *Behavioral and cognitive development as well as family functioning of twins conceived by assisted reproduction: findings from a large population study*. Fertility and Sterility **84**(3): 725-733.

Olivius, C., Friden, B., Borg, G. and Bergh, C. (2004). *Why do couples discontinue in vitro fertilization treatment? a cohort study*. Fertility and Sterility **81**(2): 258-261.

Ombelet, W., De Sutter, P., Van der Elst, J. and Martens, G. (2005). *Multiple gestation and infertility treatment: Registration, reflection and reaction - The Belgian project.* Human Reproduction Update **11**(1): 3-14

Ostfeld, B. M., Smith, R. H., Hiatt, M. and Hegyi, T. (2000). *Maternal behavior toward premature twins: Implications for development*. Twin Research **3**(4): 234-241.

Ozturk, O. and Templeton, A. (2002). *In-vitro fertilisation and risk of multiple pregnancy.* The Lancet **360**(9330): 414.

Paling, J. (2003). *Strategies to help patients understand risks*. British Medical Journal **327**(7417): 745-748.

Pandian, Z., Templeton, A., Serour, G. and Bhattacharya, S. (2005). *Number of embryos for transfer after IVF and ICSI: a Cochrane review*. Human Reproduction **20**(10) 2681-2687.

Papanikolaou, E. G., Camus, M., Kolibianakis, E. M., Van Landuyt, L., Van Steirteghem, A. and Devroey, P. (2006). *In vitro fertilization with single blastocyst-stage versus single cleavage-stage embryos*, Obstetrical & Gynecological Survey **61**(8): 523-525.

Parry, V. (2007). *Pointing the finger reducing multiple births could save many babies' lives* The Times Body and Soul Section 21.04.2007: 2.

Paterson-Brown, S., Fisk, N. M. a. and Wyatt, J. C. (1995). *Uptake of meta-analytical overviews of effective care in English obstetric units*. British Journal of Obstetric and Gynaecology **102**: 297-301.

Payne, J. C., Campbell, M. K., DaSilva, O. and Koval, J. (2002). *Perinatal mortality in term and preterm twin and singleton births.* Twin Research **5**(4): 260-4.

Pelinck, M. J., Hoek, A., Simons, A. H. M. and Heineman, M. J. (2002). *Efficacy of natural cycle IVF: a review of the literature*. Human Reproduction Update **8**(2): 129-139.

Pennings, G. (2000). *Avoiding multiple pregnancies in ART: Multiple pregnancies: a test case for the moral quality of medically assisted reproduction*. Human Reproduction **15**(12): 2466-2469.

Peterson, C. M., Reading, J. C., Hatasaka, H. H., Parker Jones, K., Udoff, L. C., Adashi, E. Y., Kuneck, P. H., Erickson, L. D., Malo, J. W., Campbell, B. F. and Carrell, D. T. (2004). *Use of outcomes-based data in reducing high-order multiple pregnancies: the role of age, diagnosis, and embryo score*. Fertility and Sterility **81**(6): 1534-1541.

Petrou, S. (2003). *Economic consequences of preterm and low birthweight.* BJOG: an International Journal of Obstetrics and Gynaecology **110**(suppl 20): 17-23.

Petrovici, D. A. and Ritson, C. (2006). *Factors influencing consumer dietry health preventative behaviours.* BioMed Central Public Health **6**: 222-234.

Pharoah, P. (2002). *Neurological outcome in twins.* Seminars in Neonatology **7**: 223-230.

Pinborg, A., Loft, A., Schmidt, L. and Andersen, A. N. (2003)[a]. *Morbidity in a Danish national cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI singletons: Health-related and social implications for the children and their families.* Human Reproduction **18**(6): 1234-1243.

Pinborg, A., Loft, A., Schmidt, L. and Andersen, A. (2003)[b]. *Attitudes of IVF/ICSI-twin mothers towards twins and single embryo transfer*. Human Reproduction **18**(3): 621-627.

Pinborg, A., Loft, A., Rasmussen, S., Schmidt, L., Langhoff-Roos, J., Greisen, G. and Nyboe Andersen, A. (2004)[a]. *Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10 362 non-IVF/ICSI twins born between 1995 and 2000.* Human Reproduction **19**(2): 435-441.

Pinborg, A., Loft, A. and Andersen, A. N. (2004)[b]. *Neonatal outcome in a Danish national cohort of 8602 children born after in vitro fertilization or intracytoplasmic sperm injection: the role of twin pregnancy*. Acta Obstetricia et Gynecologica Scandinavica **83**: 1071-1078.

Pinborg, A., Loft, A., Rasmussen, S. and Andersen, A. N. (2004)[c]. *Hospital care utilization of IVF/ICSI twins followed until 2-7 years of age: a controlled Danish national cohort study.* Human Reproduction **19**(11): 2529-2536.

Pinborg, A., Loft, A., Schmidt, L., Greisen, G., Rasmussen, S. and Nyobe Andersen, A. (2004)[d]. *Neurological sequelae in twins born after assisted conception: controlled national cohort study*. British Medical Journal **329**(7461): 311-316.

Pinborg, A., Loft, A., Ziebe, S. and Nyboe Andersen, A. (2004)[e]. *What is the most relevant standard of success in assisted reproduction?: Is there a single 'parameter of excellence'?* Human Reproduction **19**(5): 1052-1054.
Pinborg, A. (2005). *IVF/ICSI twin pregnancies: risks and prevention*. Human Reproduction Update **11**(6): 575-593.

Pinborg, A., Lidegaard, O., la Cour Freiesleben, N. and Andersen, A. N. (2005). *Consequences of vanishing twins in IVF/ICSI pregnancies*. Human Reproduction **20**(10): 2821-2829.

Poehlmann, J. and Fiese, B. H. (2001)[a]. *The interaction of maternal and infant vulnerabilities on developing attachment relationships.* Development & Psychopathology **13**(1): 1-11.

Poehlmann, J. and Fiese, B. H. (2001)[b]. *Parent-infant interaction as a mediator of the relation between neonatal risk status and 12-month cognitive development*. Infant Behavior & Development **24**(2): 171-188.

Pope, C. and Mays, N. (1995). *Qualitative Research: Reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research.* British Medical Journal **311**(6996): 42-45.

Porter, M. and Bhattacharya, S. (2005). *Investigation of staff and patients' opinions of a proposed trial of elective single embryo transfer*. Human Reproduction **20**(9): 2523-2530.

Powers, W. and Wampler, N. (1996). *Further defining the risks confronting twins*. American Journal of Obstetrics and Gynecology (OB) **175**(6): 1522-1528.

PregnancyMD.org. (2001) Retrieved 09.06.2004 from www.pregnancymd.org/multiple-birth.htm

Pridham, K., Lin, C.-Y. and Brown, R. (2001). *Mothers' evaluation of their caregiving for premature and full-term infants through the first year; contributing factors*. Research in Nursing and Health **24**: 157-169.

Rai, V. and Glazebrook, C. (in press). Conference abstract: *Development and preliminary vaidation of the attitudes to twin pregnancies scale*. Society for Reproductive and Infant Psychology 27th Annual Conference.

Raoul-Duval, A., Bertrand-Servais, M., Letur-Konirsch, H. and Frydman, R. (1994). *Psychological follow-up of children born after in-vitro fertilization*. Human Reproduction **9**(6): 1097-1101.

Redshaw, M. and van den Akker, O. (2006). Editorial: *Researching parenting: In prospect and in retrospect.* Journal of Reproductive & Infant Psychology. **24**(1): 1-3.

Redshaw, M., Hockley, C. and Davidson, L. L. (2007). *A qualitative study of the experience of treatment for infertility among women who successfully became pregnant*. Human Reproduction **22**: 295-304.

Reissland, N. and Stephenson, T. (1998). *Turn-taking in early vocal interaction: a comparison of premature and term infants' vocal interaction with their mothers.* Child: Care Health and Development **25**(6): 447-456.

Reissland, N., Shepherd, J. and Stephenson, T. (1999). *Maternal verbal interaction in different situations with infants born prematurely and term*. Infant and Child Development **8**: 39-48.

Reitman, D., Currier, R. O. and Stickle, T. R. (2002). *Critical evaluation of the Parenting Stress Index-Short Form (PSI-SF) in a Head Start*

Population" Journal of Clinical Child and Adolescent Psychology **31**(3): 384-392.

Remennick, L. (2000). *Childless in the Land of Imperative Motherhood: Stigma and Coping Among Infertile Israeli Women*. Sex Roles **43**(11 - 12): 821-841.

Repokari, L., Punamaki, R. L., Poikkeus, P., Vilska, S., Unkila-Kallio, L., Sinkkonen, J., Almqvist, F., Tiitinen, A. and Tulppala, M. (2005). *The impact of successful assisted reproduction treatment on female and male mental health during transition to parenthood: a prospective controlled study.* Human Reproduction **20**(11): 3238-3247.

Reynolds, M. A., Schieve, L. A., Jeng, G. and Peterson, H. B. (2003*). Does insurance coverage decrease the risk for multiple births associated with assisted reproductive technology?*" Fertility and Sterility **80**(1): 16-23.

Reynolds, M. A. and Schieve, L. A. (2006). Trends in embryo transfer practices and multiple gestation for IVF procedures in the USA, 1996-2002, Human Reproduction **21**(3): 694-700.

Robin, M., Josse, D. and Tourrette, C. (1988). *Mother-Twin Interaction During Early Childhood.* Acta Geneticae Medicae et Gemellologiae **37**: 151-159.

Robin, M., Bydlowski, M., Cahen, F. and Josse, D. (1991). *Maternal reactions to the birth of triplets.* Acta Geneticae Medicae et Gemellolgiae **40**: 41-51.

Robin, M. and Casati, I. (1994). *Are twins different from singletons during early childhood?* Early Development and Parenting **3**(4): 211-221.

Rocissano, L. and Yatchmink, Y. (1983). *Language skill and interactive patterns in prematurely born toddlers*. Child Development **54**: 1229-1241.

Rowland, C. (1991). *Family Relationships*. The Stress of Multiple Births. Eds. D. Harvey and E. Bryan. Hereford, Multiple Births Foundation.

Ruttenberg, W. B., Finello, K. M. and Cordeiro, A. K. (1997). *Interactions between depressed and nondepressed Latina mothers and their premature infants.* Infant Mental Health Journal **18**(4): 364-377.

Rutter, D. and Quine, L. (2002). *Social cognition models and changing health behaviours.* In Changing health behaviour. Eds. D. Rutter and L. Quine. Buckingham, Open University Press**:** 1-27.

Rutter, M. and Redshaw, J. (1991). *Annotation: growing up as a twin: twin-singleton differences in psychological development*. Journal of Child Psychology and Psychiatry **32**(6): 885-895.

Rutter, M., Thorpe, K., Greenwood, R., Northstone, K. and Golding, J. (2003)[a]. *Twins as a natural experiment to study the causes of mild language delay: I: Design; twin-singleton differences in language, and obstetric risks* Journal of Child Psychology and Psychiatry **44**(3): 326-341.

Rutter, M., Thorpe, K., Greenwood, R., Northstone, K. and Golding, J. (2003)[b]. *Twins as a natural experiment to study the causes of mild language delay: II: family interaction risk factors*. Journal of Child Psychology and Psychiatry **44**(3): 342-355.

Ryan, G. L., Zhang, S. H., Dokras, A., Syrop, C. H. and Van Voorhis, B. J. (2004). *The desire of infertile patients for multiple births.* Fertility and Sterility **81**(3): 500-504.

Ryan, G. L., Maassen, R. A., Dokras, A., Syrop, C. H. and Van Voorhis, B. J. (2005). *Infertile women are twice as likely to desire multiples as fertile controls.* Fertility and Sterility **84**(Supplement 1): S22-S23.

Ryan, M. (1999). *Using conjoint analysis to take account of patient preferences and go beyond health outcomes: an application to in vitro fertilisation.* Social Science & Medicine **48**(4): 535-546.

Saldeen, P. and Sundstrom, P. (2005). *Would legislation imposing single embryo transfer be a feasible way to reduce the rate of multiple pregnancies after IVF treatment?* Human Reproduction **20**(1): 4-8.

Saxon, T. F., Colombo, J., Robinson, E. L. and Frick, J. E. (2000). *Dyadic interaction profiles in infancy and preschool intelligence.* Journal of School Psychology **38**(1): 9-25.

Schachter, M., Raziel, A., Friedler, S., Strassburger, D., Bern, O. and Ron-El, R. (2001). *Monozygotic twinning after assisted reproductive techniques: a phenomenon independent of micromanipulation*. Human Reproduction **16**(6): 1264-1269.

Scher, A. I., Petterson, B. E. V., Blair, E. V. E., Ellenberg, J. H., Grether, J. K., Haan, E., Reddihough, D. S., Yeargin-Allsopp, A. M. and Nelson, K. B. (2002). *The Risk of Mortality or Cerebral Palsy in Twins: A Collaborative Population-Based Study*. Pediatric Research **52**(5):671-681.

Schiaffino, K. M., Shawaryn, M. A. and Blum, D. (1998). *Examining the impact of illness representations on psychological adjustment to chronic illnesses.* Health Psychology **17**(3): 262-268.

Schieve, L. A., Peterson, H. B., Meikle, S. F., Jeng, G., Danel, I., Burnett, N. M. and Wilcox, L. S. (1999). *Live-birth rates and multiple-birth risk using In Vitro Fertilization.* The Journal of the American Medical Association **282**(19): 1832-1838.

Schieve, L. A., Meikle, S. F., Ferre, C., Peterson, H. B., Jeng, G. and Wilcox, L. S. (2002). *Low and Very Low Birth Weight in Infants Conceived with Use of Assisted Reproductive Technology*. New England Journal of Medicine **346**(10): 731-737.

Schieve, L. A. (2006). *The promise of single-embryo transfer*, New England Journal of Medicine **354**(11): 1190-1193

Schmittlein, D. C. and Morrison, D. G. (2003). *A live baby or your money back: The marketing of in vitro fertilization procedures*. Management Science **49**(12): 1617-1635.

Schmucker, G., Brisch, K.-H., Kohntop, B., Betzler, S., Osterle, M., Pohlandt, F., Pokorny, D., Laucht, M., Kachele, H. and Buchheim, A. (2005). *The Influence of Prematurity, Maternal Anxiety, and Infants'*

Neurobiological Risk on Mother-Infant Interactions. Infant Mental Health JournaL **26**(5): 423-441.

Scholz, T., Bartholomaus, S., Grimmer, I., Kentenich, H. and Obladen, M. (1999). *Problems of multiple births after ART: medical, psychological, social and financial aspects*. Human Reproduction **14**(12): 2932-7.

Schreiner-Engel, P., Walther, V., Mindes, J., Lynch, L. and Berkowitz, R. (1995). *First-trimester multifetal pregnancy reduction: Acute and persistent psychologic reactions*. American Journal of Obstetrics and Gynecology **172**(2): 541-547.

Scotland, G. S., McNamee, P., Peddie, V. L. and Bhattacharya, S. (2007). *Safety versus success in elective single embryo transfer: women s preferences for outcomes of in vitro fertilisation*. BJOG: An International Journal of Obstetrics and Gynaecology **114**(8): 977-983.

Sedgwick, P. and Hall, A. (2003). *Teaching medical students and doctors how to communicate risk.* British Medical Journal **327**(7417): 694-695.

Sen, D. (2006). *A randomised controlled trial of* a midwife-led twin antenatal programme - the Newcastle twin study. Phd. thesis Centre for health service research and the school of surgery and reproductive science, Newcastle University.

Senat, M.-V. M., Ancel, P.-Y. M., Bouvier-Colle, M.-H. P. and Breart, G. M. (1998). *How Does Multiple Pregnancy Affect Maternal Mortality and Morbidity?*" Clinical Obstetrics and Gynecology **41**(1): 79-83.

Seoud, M., Toner, J. P., Kruithoff, C. and Muasher, S. J. (1992). *Outcome of twin triplet and quadruplet in vitro fertilization pregnancies the Norfolk experience.* Fertility and Sterility **57**(4): 825-834.

Singer, L. T., Salvator, A., Guo, S., Collin, M., Lilien, L. and Baley, J. (1999). *Maternal Psychological Distress and Parenting Stress After the Birth of a Very Low-Birth-Weight Infant*. Journal of the American Medical Association **281**(9): 799-805.

Smith, J. A. and Osborn, M. (2003*). Interpretative phenomenological analysis*. In Qualitative Psychology. Ed J. A. Smith. London, Sage**:** 53-79.

Smith, K. E., Landry, S. H., Swank, P. R., Baldwin, C. D., Denson, S. E. and Wildin, S. (1996). *The relation of medical risk and maternal stimulation with preterm infants' development of cognitive, language and daily living skills.* Journal of Child Psychology and Psychiatry **37**(7): 855-864.

Smithers, P. R., Halliday, J., Hale, L., Talbot, J. M., Breheny, S. and Healy, D. (2003). *High frequency of cesarean section, antepartum hemorrhage, placenta previa, and preterm delivery in in-vitro fertilization twin pregnancies*. Fertility and Sterility **80**(3): 666-668.

Spiker, D., Ferguson, J. and Brooks-Gunn, J. (1993). *Enhancing maternal interactive behaviour and child social competence in low birth weight premature infants.* Child Development **64**: 754-768.

Spillman, J. (1987). *Emotional aspects of experiencing a multiple birth*. Midwife Health Visitor and Community Nurse **23**: 54-55.

St. James-Roberts, I. and Wolke, D. (1988). *Convergences and discrepancies, among mothers' and professionals' assessments of difficult neonatal behaviour.* Journal of Child Psychology and Psychiatry **29**: 21-42.

Standell, A., Bergh, C. and Lundin, K. (2000). *Selection of patients suitable for one-embryo transfer may reduce the rate of multiple births by half without impairment of overall birth rates.* Human Reproduction **15**: 2520-2525.

Stern, M., Karraker, K. H., Sopko, A. M. and Norman, S. (2000). *The prematurity stereotype revisited: impact on mothers' interactions with premature and full-tem infants.* Infant Mental Health Journal **21**(6): 495-509.

Stern, M., Karraker, K. H., McIntosh, B., Moritzen, S. and Olexa, M. (2006). *Prematurity stereotyping and mothers' interactons with their premature and full-tem infants during the first year*. Journal of Pediatric Psychology **31**(6): 597-607.

Steures, P., Berkhout, J. C., Hompes, P. G. A., van der Steeg, J. W., Bossuyt, P. M. M., van der Veen, F., Habbema, J. D. F., Eijkemans, M. J. C. and Mol, B. W. J. (2005). "Patients' preferences in deciding between intrauterine insemination and expectant management." Human Reproduction **20**: 752-755.

Stillman, R. J. (2007). *A 47-year-old woman with fertility problems who desires a multiple pregnancy.* Journal of the American Medical Association **297**(8): 858-867.

Stobel-Richter, Y., Beutel, M. E., Finck, C. and Brahler, E. (2005). The *'wish to have a child', childlessness and infertility in Germany*. Human Reproduction **20**(10): 2850-2857.

Stone, J., Eddleman, K., Lynch, L. and Berkowitz, R. (2002). *A single center experience with 1000 consecutive cases of multifetal pregnancy reduction.* American Journal of Obstetrics and Gynecology **187**(5): 1163-1167.

Sumner, G. and Spietz, A. L. (1994). *NCAST caregiver/parent-child interaction teaching manual.* Seattle, NCAST Publications, University of Washington, School of Nursing

TAMBA. (2007). *Recent trends in multiple births in the UK 2005.* Retrieved 3.07.2007. from www.tamba.org.uk/downloads/Latest%20MB%20stats%20and%20trends%2005.doc -

Tang, Y., Ma, C. X., Cui, W., Chang, V., Ariet, M., Morse, S. B., Resnick, M. B. and Roth, J. (2006). *The risk of birth defects in multiple births: A population-based study.* Maternal & Child Health Journal **10**(1): 75-81.

Tarlatzis, B. C., Qublan, H. S., Sanopoulou, T., Zepiridis, L., Grimbizis, G. and Bontis, J. (2002). *Increase in the monozygotic twinning rate after intracytoplasmic sperm injection and blastocyst stage embryo transfer.* Fertility and Sterility **77**(1): 196-198.

Templeton, A. and Morris, J. K. (1998). *Reducing the risk of multiple births by transfer of two embryos after in vitro fertilization*. New England Journal of Medicine **339**(9): 573-7.

Templeton, A. (2000). *Avoiding multiple pregnancies in ART: Replace as many embryos as you like--one at a time*. Human Reproduction **15**(8): 1662.

Tesh, E. M. and Holditch-Davis, D. (1997). *HOME inventory and NCATS: relation to mother and child behaviour during naturalistic observations*. Research in Nursing & Health **20**: 295-307.

Thorpe, K., Golding, J., MacGillivray, I. and Greenwood, R. (1991). *Comparison of prevalence of depression in mothers of twins and mothers of singletons*. British Medical Journal **302**(6781): 875-878.

Thorpe, K., Greenwood, R. and Goodenough, T. (1995). *Does a twin pregnancy have a greater impact on physical and emotional well-being than a singleton pregnancy*. Birth **22**(3): 148-152.

Thorpe, K., Greenwood, R., Eivers, A. and Rutter, M. (2001). *Prevalence and developmental course of 'secret language'.* International Journal of Language and Communication Disorders **36**(1): 43-62.

Thorpe, K., Rutter, M. and Greenwood, R. (2003). *Twins as a natural experiment to study the causes of mild langauge delay: II: Family interaction risk factors.* Journal of Child Psychology and psychiatry **44**(3): 342-355.

Thurin, A., Hausken, J., Hillensjo, T., Jablonowska, B., Pinborg, A., Strandell, A. and Bergh, C. (2004). *Elective single-embryo transfer versus double embryo transfer in in vitro fertilization*. New England Journal of Medicine **351**(23): 2392-2402.

Thurin, A., Hardarson, T., Hausken, J., Jablonowska, B., Lundin, K., Pinborg, A. and Bergh, C. (2005). *Predictors of ongoing implantation in IVF in a good prognosis group of patients.* Human Reproduction **20**(7): 1876-1880.

Tiitinen, A. and Gissler, M. (2004). *Effect of in vitro fertilization practices on multiple pregnancy rates in Finland*. Fertility and Sterility **82**(6): 1689-1690.

Tiitinen, A., Unkila-Kallio, L., Halttunen, M. and Hyden-Granskog, C. (2003). *Impact of elective single embryo transfer on the twin pregnancy rate.* Human Reproduction **18**(7): 1449-1453.

Tough, S. C. P., Greene, C. A. M. D. F., Svenson, L. W. B. S. and Belik, J. M. D. F. (2000). *Effects of in vitro fertilization on low birth weight, preterm delivery, and multiple birth.* Journal of Pediatrics **136**(5): 618-622.

Tully, L. A., Moffitt, T. E. and Caspi, A. (2003). *Maternal adjustment, parenting and child behaviour in families of school-aged twins conceived after IVF and ovulation induction.* Journal of Child Psychology and Psychiatry and Allied Disciplines **44**(3): 316-325.

van Balen, F., Naaktgeboren, N. and Trimbos-Kemper, T. C. M. (1996). *In-vitro fertilization: The experience of treatment, pregnancy and delivery.* Human Reproduction **11**(1): 95-98.

van IJzendoorn, M. H., Goldberg, S., Kroonenberg, P. M. and Frenkel, O. J. (1992). *The relative effects of maternal and child problems on the quality of attachment: a meta-analysis of attachment in clinical samples.* Child Development **63**: 840-858.

van Montfoort, A. P. A., Dumoulin, J. C. M., Land, J. A., Coonen, E., Derhaag, J. G. and Evers, J. L. H. (2005). *Elective single embryo transfer (eSET) policy in the first three IVF/ICSI treatment cycles*. Human Reproduction **20**(2): 433-436.

van Montfoort, A. P. A., Fiddelers, A. A. A., Janssen, J. M., Derhaag, J. G., Dirksen, C. D., Dunselman, G. A. J., Land, J. A., Geraedts, J. P. M., Evers, J. L. H. and Dumoulin, J. C. M. (2006). *In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: A randomized controlled trial.* Human Reproduction **21**(2): 338-343.

van Montfoort, A. P. A., Fiddelers, A. A. A., Land, J. A., Dirksen, C. D., Severens, J. L., Geraedts, J. P. M., Evers, J. L. H. and Dumoulin, J. C. M. (2007). *eSET irrespective of the availability of a good-quality embryo in the first cycle only is not effective in reducing overall twin pregnancy ra*tes. Human Reproduction **22**(6): 1669-1674.

van Wely, M., Twisk, M., Mol, B. W. and van der Veen, F. (2006). *Is twin pregnancy necessarily an adverse outcome of assisted reproductive technologies?* Human Reproduction **10** 1093/humrep/del249.

Veddovi, M., Gibson, F. L., Kenny, d. t., Bowen, J. and Starte, D. (2004). *Preterm behaviour, maternal adjustment, and competencies in the newborn period: what influence do they have at 12 months postnatal age?* Infant Mental Health Journal **25**(6): 580-599.

Veleva, Z., Vilska, S., Hyden-Granskog, C., Tiitinen, A., Tapanainen, J. S. and Martikainen, H. (2006). *Elective single embryo transfer in women aged 36-39 years.* Human Reproduction **21**(8): 2098-2102.

Verstraelen, H., Goetgeluk, S., Derom, C., Vansteelandt, S., Derom, R., Goetghebeur, E. and Temmerman, M. (2005). *Preterm birth in twins after subfertility treatment: population based cohort study*. British Medical Journal **331**(7526): 1173-.

Vilska, S., Tiitinen, A., Hyden-Granskog, C. and Hovatta, O. (1999). *Elective transfer of one embryo results in an acceptable pregnancy rate and eliminates the risk of multiple birth*. Human Reproduction **14**(9): 2392-5.

Wang, Y. A., Sullivan, E. A., Black, D., Dean, J., Bryant, J. and Chapman, M. (2005). *Preterm birth and low birth weight after assisted reproductive technology-related pregnancy in Australia between 1996 and 2000.* Fertility and Sterility **83**(6): 1650-1658.

Wang, J., Lane, M. and Norman, R. J. (2006). *Reducing multiple pregnancy from assisted reproduction treatment: Educating patients and medical staff.* Medical Journal of Australia. **184**(4): 180-181.

Warner, R., Appleby, L., Whitton, A. and Faragher, B. (1996). *Demographic and obstetric risk factors for postnatal psychiatric morbidity.* British Journal of Psychiatry **168**(5): 607-11.

Weaver, S. M., Clifford, E., Gordon, A. G., Hay, D. M. and Robinson, J. (1993). *A follow up study of successful IVF/GIFT couples: Social-emotional well-being and adjustment to parenthood*. Journal of Psychosomatic Obstetrics & Gynaecology **14**(SUPPL.): 5-16.

Wennerholm, U. B. and Bergh, C. (2004). *What is the most relevant standard of success in assisted reproduction?: Singleton live births should also include preterm births*. Human Reproduction **19**(9): 1943-1945.

Westergaard, H. B., Johansen, A. M. T., Erb, K. and Anders, N. A. (2000). *Danish National IVF Registry 1994 and 1995. Treatment, pregnancy outcome and complications during pregnancy*. Acta Obstetricia et Gynecologica Scandinavica **79**(5): 384-389.

Wijnroks, L. (1999). *Maternal recollected anxiety and mother-infant interaction in preterm infants.* Infant Mental Health Journal **20**(4): 393-409.

Wille, D. E. (1991). *Relation of preterm birth with quality of infant--mother attachment at one year*. Infant Behavior and Development **14**(2): 227-240.

Wimalasundera, R. C., Trew, G. and Fisk, N. M. (2003). *Reducing the incidence of twins and triplets.* Best Practice & Research in Clinical Obstetrics & Gynaecology **17**(2): 309-329.

Wischmann, T., Stammer, H., Scherg, H., Gerhard, I. and Verres, R. (2001). *Psychosocial characteristics of infertile couples: a study by the `Heidelberg Fertility Consultation Service'* Human Reproduction **16**(8): 1753-1761.

Witsenburg, C., Dieben, S., Van Der Westerlaken, L., Verburg, H. and Naaktgeboren, N. (2005). *Cumulative live birth rates in cohorts of patients*

treated with in vitro fertilization or intracytoplasmic sperm injection Fertility and Sterility **84**(1): 99-107.

Wolke, D. (1998). *Psychological development of prematurely born children.* Archives of Diseases in Childhood **78**(6): 567-570.

Wolner-Hansen, P. a. R., H (1998). *Cost-effectiveness analysis on in-vitro fertilization: estimated costs per successful pregnancy after transfer of one or two embryos.* Human Reproduction **13**(1): 88-94.

Wong, S. S. M., Thornton, J. G., Gbolade, B. and Bekker, H. L. (2006). *A randomised controlled trial of a decision-aid leaflet to facilitate women's choice between pregnancy termination methods.* BJOG: An International Journal of Obstetrics & Gynaecology **113**(6): 688-94.

Wright, V., Chang, J., Jeng, G., Chen, M. and Macaluso, M. (2007). *Assisted reproductive technology surveillance- United States, 2004*. Retrieved 03.07.2007, 2007, from http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5606a1.htm.

Yardley, L. and Bishop, F. (2007). *Mixing qualitative and quantitative methods: a pragmatic approach.* Handbook of qualitative research methods in psychology. Eds. C. Willig and W. Stainton-Rogers. London, Sage.

Yaron, Y., Bryant-Greenwood, P., Dave, N., Moldenhauer, J., Kramer, R., Johnson, M. and Evans, M. (1999). *Multifetal pregnancy reductions of triplets to twins: Comparison with nonreduced triplets and twins*. American Journal of Obstetrics and Gynecology **180**(5): 1268-1271.

APPENDICES

Appendix One: Consent form for study I

NOTTINGHAM UNIVERSITY RESEARCH AND TREATMENT UNIT IN REPRODUCTION

CONSENT FORM

Psychological Impact of Treatment for Infertility

(Please delete any statement with which you do not agree)

- I have read and understood the information given.
- I am happy to take part in the study.
- I understand that all information given will be confidential.
- I understand that if I do not wish to take part in the study my treatment will not be affected in any way.
- I give permission for questionnaires to be sent to my home address.
- I consent to the researcher, Ms Sara Cox, obtaining relevant information from my medical notes.
- I understand that I may withdraw from the study at any time.

WIFE/FEMALE PARTNER

NAME

SIGNATURE **DATE**

HUSBAND/MALE PARTNER

NAME

SIGNATURE **DATE**

Department of Obstetrics & Gynaecology
Floor 'B', East Block,
University Hospital,
Queen's Medical Centre,
Nottingham, NG7 2UH
Telephone – (0115) 970 9490
Facsimile – (0115) 970 9492

Appendix Two: Letter inviting participation in study I

NOTTINGHAM UNIVERSITY RESEARCH AND TREATMENT UNIT IN REPRODUCTION

Psychological Impact of Treatment for Infertility

Dear

NURTURE, together with The Behavioural Sciences Section of the Department of Psychiatry, are currently carrying out a research project to assess the psychological effects of undergoing treatment for infertility and the different ways people have of coping with it. We hope to see whether these factors affect the outcome of treatment in any way. This research will benefit patients in the future by helping to determine how best to tackle this important, but often neglected, aspect of infertility treatment. It is hoped that this research will also identify ways of improving the service offered to couples by NURTURE.

One important part of this research is to assess the impact of fertility treatment, on couple's feelings during pregnancy and on their adaptation to parenthood and I would be very grateful if you would consider taking part. The research involves a short telephone interview at around the eighteenth week of pregnancy, after which you will be sent some questionnaires for you, and if possible your partner, to complete at home. A further telephone interview will be carried out towards the end of pregnancy and again after the baby is born.

If you would be prepared to help with this research I should be grateful if you could sign and return the enclosed consent form and questionnaire in the SAE. If your partner is willing to take part please could he also sign the consent form. This consent together with your name, address and telephone number will then be passed on to Dr Cris Glazebrook whose research assistant, Ms Sara Cox, will contact you in due course.

You will, of course, be free to withdraw from the study at any time. All responses will be entirely confidential and you will be identified only by a study number. Either Dr Cris Glazebrook (0115 970 9338) or myself (0115 970 9490) will be happy to answer any concerns or queries you may have regarding this research.

Sincerely,

Dr George Ndukwe

Department of Obstetrics & Gynaecology
Floor 'B', East Block,
University Hospital,
Queen's Medical Centre,
Nottingham, NG7 2UH
Telephone – (0115) 970 9490
Facsimile – (0115) 970 9492

Appendix Three: Theme analysis codebook

Theme Analysis Coding Scheme/Codebook

Theme 1

Label: Emotional well being – **Feeling wonderful**

Definition of what the theme concerns

The mother describes in response to the question "How are you feeling in yourself at the moment?" extremely positive and or euphoric feelings about her own mental state or her enjoyment of the baby.

How to know when the theme occurs

Look for use of words describing extreme enjoyment, and colloquialisms used to indicate extreme happiness mentally such as "on cloud nine".

Description of any qualifications or exclusions to the identification of the theme

Just saying happy or pleased not enough has to express greater enthusiasm or pleasure. Nor is it enough to express the feeling after other expressions of problems or worries for example coming after "other than that".

Examples of positive and negative occurrence

Example of positive coding - "Brilliant fulfilled and very happy"

Example of negative coding - "Fine you know I have sort of tearful moments but we're so pleased and we're so lucky the first time it's been successful and we've got a beautiful daughter and she's perfect , and she looks so healthy and she's happy, she's gurgling away".

Theme 2

Label: Emotional well-being- **Feeling tired**

Definition of what the theme concerns

Mother talks of having been tired or describes how she is tired at the moment

How to know when the theme occurs

Mother expresses feelings of great tiredness or exhaustion. Look for use of words describing extreme tiredness, and colloquialisms such as "shattered", or "knackered".

Description of any qualifications or exclusions to the identification of the theme

Not enough if feeling tired qualified with an explanation of how compensating for tiredness or how not affecting the mother emotionally.

Examples of positive and negative occurrence

Example of positive coding - "Fine, but just very, very, tired have so many sleepless nights."

Example of negative coding - "Fine, quite well, tired sometimes obviously with being woken up in the night, but I feel quite happy".

Theme 3

Label: Emotional well being - **Feeling emotionally labile**

Definition of what the theme concerns

Mother describes how her feelings change, sometimes feeling happy and cheerful and at others low or depressed.

How to know when the theme occurs

Important to look for evidence of changes or variation over time in how the mother feels emotionally

Description of any qualifications or exclusions to the identification of the theme

Not enough for mother to mention past feelings of low mood must be talk of fluctuations and changes in mood at the present time.

Examples of positive and negative occurrence

Example of positive coding - "I have my good days and my bad days. Some days I feel as though I'm doing everything wrong and I can't cope, other days I feel fine."

Example of negative coding - "I've had my ups and downs you know when I first had him getting into routines and sleepless nights but he's settled down lovely and I've got him into a good routine and the two of us are quite happy."

Theme 4

Label: Emotional well being- **Worry over the baby or babies**

Definition of what the theme concerns

Mother relates her emotional well being to worries over the baby, this can be in terms of the baby's health, crying, feeding or trying to care for more than one baby at a time.

How to know when the theme occurs

Mother talks in terms of the impact of how the baby is on her emotional well-being, or refers to worrying over an aspect of the baby's care.

Description of any qualifications or exclusions to the identification of the theme

Not enough if mother just talks of the impact or shock of the baby must relate it in some way to her well-being.

Examples of positive and negative occurrence

Example of positive coding - "I feel mortified if I don't know exactly why he is crying. If I can't bring his wind up I'm traumatised I think I should be able to do it. So it does feel a bit pressured."

Example of negative coding - "He's so fragile and you wonder if you can be a good mum, now after you've gone through all that hormonal thing, I feel really well really happy."

Theme 5

Label: **Expectations of motherhood – surpassed**

Definition of what the theme concerns

Mother explicitly mentions that her expectations are surpassed in terms of what she thought the experience of motherhood would be like for her, or how she would feel.

How to know when the theme occurs

Look for any mention of expectations, or comparative statements about how the mother expected to feel or find her time at home with her baby/babies. This may include the mother talking of how she expected to feel, but then did not.

Description of any qualifications or exclusions to the identification of the theme

Does not include mother comparing how she feels after the birth to how she felt when pregnant or during treatment.

Examples of positive and negative occurrence

Example of positive coding - "The tiredness is much less than I expected to feel."

Example of negative coding - "Compared to being pregnant I feel marvellous."

Theme 6

Label: **Expectations of motherhood or of self as a mother – not met**

Definition of what the theme concerns

Mother refers to how she expected to feel or to find motherhood and expresses some form of disappointment, or mother feels she is not able to meet her own expectations of herself as a mother.

How to know when the theme occurs

Look for references to expectations, or statements passing judgement about quality of parenting or the parenting experience.

Description of any qualifications or exclusions to the identification of the theme
Does not include expectations about physical health or state of body

Examples of positive and negative occurrence

Example of positive coding - "I don't think I'm going to be good enough for him."

Example of negative coding - "The other thing is and this is specifically from this lady I spoke to of course you're quite a size and you know you're expecting all problems maybe with the children or the delivery or something and this lady was in quite a shock about the state of her own body, which once again it had never been mentioned that also personally I was horrified when I saw what was left again with a singleton you can have similar problems but you know this I suppose is all to do with the multi side of it. Other than being shocked about my own body I was fine."

Theme 7

Label: **Emotional well- being linked to easy baby and feelings of confidence as a mother**

Definition of what the theme concerns

Mother's emotional well-being is linked to finding her baby easy and to her feelings of confidence as a mother.

How to know when the theme occurs

Look for mother talking of how things have improved since she has established a routine, or the baby has a more settled sleeping or eating pattern. Look also for mother describing her baby as very easy or contented

Description of any qualifications or exclusions to the identification of the theme

This theme may apply as well as theme 4 so mother may talk of past worries and difficulties but now this has eased as she feels better able to cope and manage or in some cases she may refer to how things have got worse as the baby has developed sleeping or eating problems.

Examples of positive and negative occurrence

Example of positive coding - "Wonderful for the last two nights he's slept all the way through from 10 O'clock to 8 O'clock in the morning so I'm feeling even more wonderful.

Example of negative coding
Not applicable

Theme 8

Label: Emotional well-being – **feeling fine**

Definition of what the theme concerns

Mother claims to feel fine.

How to know when the theme occurs

The most typical response to the question "how are you feeling in yourself at the moment?" was the word fine. Look for use of the words "fine" or "alright"

Description of any qualifications or exclusions to the identification of the theme

If the mother responds fine but then goes onto describe more euphoric feelings fine not recorded. If the mother describes negative feelings first and then makes a qualifying statement such as "apart from that fine", fine not counted. Look for the impression that the mother is describing herself as fine emotionally at the current time, or at 6 weeks if asked to look back to that time.

Examples of positive and negative occurrence

Example of positive coding - "I'm fine, no problems at all."

Example of negative coding - "I feel fine. I'm just so happy. I can't believe he's here all the years of waiting and disappointment."

Theme 9

Label: **Questioning parenthood**

Definition of what the theme concerns

Mother questions or displays doubts about being a parent, or the parent of multiples.

How to know when the theme occurs

This is a rare theme. Look for doubts expressed about being a parent or becoming a parent again. Also for descriptions of problems caused to the couple's relationship by the strain of the birth.

Description of any qualifications or exclusions to the identification of the theme

Does not count if the mother just describes how her life has changed compared to her husband's without actually questioning whether becoming a parent was a good decision, or describing the strain and changes it has caused to their relationship as a couple.

Examples of positive and negative occurrence

Example of positive coding - "I thought what have we done here have we done the right thing?"

Example of negative coding - "You've caught me on a day when I'm feeling very resentful of my husband playing golf all the time. If I'm being really honest it seems like his life carries on pretty much as normal and I'm the one that's made all the changes."

Theme 10

Label: Emotional well-being – **talk of having experienced 'baby blues'**

Definition of what the theme concerns

Mother talks of having experienced something that can be identified as 'baby blues' rather than depression.

How to know when the theme occurs
Look for descriptions of a period of feeling low or emotionally very labile which has now passed. Mother or others may have related it to the hormonal changes following the birth.

Description of any qualifications or exclusions to the identification of the theme
Looking only for experiences of tearfulness, or feeling emotional labile which have passed: they were transient, do not code if mother still talks of feeling that way.

Examples of positive and negative occurrence

Example of positive coding - "Sometimes I felt a bit tearful a bit emotional at the slightest thing."

Example of negative coding - "I have my good days and my bad days. Some days I feel as though I'm doing everything wrong and I can't cope, other days I feel fine."

Theme 11

Label: Emotional well-being – **Feeling down, depressed or emotionally stressed now or earlier.**

Definition of what the theme concerns

Lack of emotional well-being caused by depression, or exceptional emotional stress

How to know when the theme occurs
Look for descriptions of feeling very low or down emotionally. Can include feeling very stressed if this obviously significantly affects the mother's emotional well-being.

Description of any qualifications or exclusions to the identification of the theme

Looking for something more than mother mentioning she occasionally feels down or tearful

Examples of positive and negative occurrence

Example of positive coding - "Exhausted, a bit depressed at times because I feel that we've got so many worries and they just seem to go on and on and you know I feel really like nothing ever gets resolved."

Example of negative coding - "When I get very tired I still get a bit weepy."

Theme 12

Label: **Physical health problems or body changes**

Definition of what the theme concerns

Mother discusses her physical health or how she feels about her physical shape in response to the question.

How to know when the theme occurs

Look for talk of pain or soreness, evidence of physical ill health or mention of trouble with body image due to weight gain during pregnancy.

Description of any qualifications or exclusions to the identification of the theme

Not relevant if the ill health was related to the fertility treatment, rather than the pregnancy or birth.

Examples of positive and negative occurrence

Example of positive coding - "Physically still uncomfortable"

Example of negative coding - "Much better the fertility treatment got me run down."

Appendix Four: Copy of the Decision about Embryo Transfer Questionnaire

Decisions about Embryo Transfer Questionnaire

Number:

Please rate the importance of the following factors in your decision regarding the number of embryos to be transferred?

	Major factor	Strong factor	Minor factor	Not a factor
Number of embryos available for transfer	3	2	1	0
Medical advice from CARE	3	2	1	0
Personal wishes	3	2	1	0
Partner's wishes	3	2	1	0
Desire for triplet birth	3	2	1	0
Desire for twin birth	3	2	1	0
Advice from GP	3	2	1	0
Advice from family or friends	3	2	1	0
Discussion with CARE counsellor	3	2	1	0
Own research from books, journals, internet etc.	3	2	1	0
Media information e.g. magazines TV radio	3	2	1	0
Religious or ethical considerations	3	2	1	0
Desire to avoid triplet birth	3	2	1	0
Desire to avoid twin birth	3	2	1	0
Desire for a single birth	3	2	1	0
Desire to avoid the need for further treatment	3	2	1	0
Desire to avoid the cost of further treatment	3	2	1	0
Wish to increase chances of pregnancy	3	2	1	0
Other please specify_____ _____ _____	3	2	1	0

Please will you tell us about your embryo transfer

Number of embryos transferred _____

Number of embryos available for transfer _____

Please will you indicate below how much you agree with the following statements?

I found it easy to make a decision regarding the number of embryos to be transferred
Strongly agree Moderately agree Disagree Strongly disagree

Only transferring one embryo when two are available reduces the chance of having a child
Strongly agree Moderately agree Disagree Strongly disagree

Replacing three embryos when three are available increases the chance of having a child
Strongly agree Moderately agree Disagree Strongly disagree

Would you have liked any more information or help regarding your decision about embryo transfer? Yes / No

If yes what sort of help or information would you have liked?
_____

_____

_____

We would like to know a little more about you and your partner as some factors such as a woman's age may influence advice given regarding the number of eggs to transfer.

How old are you? _____ How old is your husband / partner? _____

How many years have you been together? _____

What is your highest educational qualification (eg GCSE, HND, degree)?_____

What is your partner's highest educational qualification (eg GCSE, HND, degree)?_____

How long have you been trying to conceive? _____

Have you any children already? Yes / No

If yes, how old are they? _____

Has your husband / partner any children already? Yes / No

If yes, how old are they? _____

Have you ever had embryos transferred successfully before? Yes / No

If yes how many times? _____

Have you ever had embryos transferred unsuccessfully before? Yes / No
If yes how many times? _____

Have you previously spoken to our researcher Charlotte Sheard on the telephone about your decision regarding embryo transfer? Yes / No

Are there any other comments you would like to make regarding your decision about embryo transfer? Please add a separate sheet or continue on the back if necessary.

_____

_____

_____

_____

_____

_____

_____

_____

_____

Appendix Five: Letter inviting participation in study III

Decisions about embryo transfer survey

Dear

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve.

What is the purpose of the study?

CARE together with the Behavioural Sciences Section of the Division of Psychiatry are carrying out a research project to explore couples' feelings concerning the decision about the number of embryos to transfer during IVF treatment. Our previous research has suggested that some couples find this decision difficult. You may also be aware of considerable media interest in the debate over the appropriate number of embryos to transfer. We hope this research will better inform us about how couples make this decision so future information and counselling can be better suited to their needs.

Why have I been chosen?

We are asking all women and their partners who have undergone embryo transfer at CARE during the period of the study to take part in this research.

What do I have to do?

We would like you to complete the enclosed questionnaire and leave it with the clinic staff, or you can return it later in the freepost envelope provided. The questionnaire is anonymous and you do not need to give your name.

Confidentiality

The questionnaire is anonymous; it is numbered to allow us to calculate how many replies we receive. We will not identify you from the information you give, and all the information will be kept confidentially.

What are the possible benefits of taking part?

There are no direct benefits to you in taking part in this study but we hope that the information which we collect in this survey will help improve the support and information provided to couples prior to embryo transfer.

Do I have to take part?

We hope you will take part in the research but if you decide not to then you should simply discard the questionnaire. If you decide not to take part then it will not affect your treatment now, or at any time in the future. If you have questions about this research please contact Dr Cris Glazebrook, 0115 924 9924 ext 4114 or email cris.glazebrook@nottingham.ac.uk.

Thank you for your help with this research

Yours sincerely

Mr George Ndukwe (Fertility Specialist CARE)

Dr Cris Glazebrook (Senior Lecturer Behavioural Sciences)

PUBLICATIONS

C. Glazebrook, **C. Sheard**, L. Winstanley, S. Cox and G. Ndukwe (2007) Attitudes of iInfertile coples to a multiple birth: a review of the literature and results form a survey. Current Women's Health Reviews **3:** 1-6

C. Sheard, S.Cox M. Oates, G. Ndukwe and C. Glazebrook (2007) Impact of a multiple, IVF birth on post-partum mental health: a composite analysis Human Reproduction **22**: 2058-2065