

Winter 2-2011

Risk of Adverse Perinatal Outcomes in Dizygotic Twins After IVF Pregnancies: A Systematic Review

Fatima J. Baar

Follow this and additional works at: <http://commons.pacificu.edu/pa>

 Part of the [Medicine and Health Sciences Commons](#)

Recommended Citation

Baar, Fatima J., "Risk of Adverse Perinatal Outcomes in Dizygotic Twins After IVF Pregnancies: A Systematic Review" (2011). *School of Physician Assistant Studies*. Paper 230.

This Capstone Project is brought to you for free and open access by the Theses, Dissertations and Capstone Projects at CommonKnowledge. It has been accepted for inclusion in School of Physician Assistant Studies by an authorized administrator of CommonKnowledge. For more information, please contact CommonKnowledge@pacificu.edu.

Risk of Adverse Perinatal Outcomes in Dizygotic Twins After IVF Pregnancies: A Systematic Review

Abstract

Background: Since the birth of the first test tube baby, 25 years ago, more than three million babies have been born using assisted reproductive technologies (ART). Twin births by way of ART represent 20-30% of U.S. and European births, as compared to only 1% of natural births. The purpose of this study is to investigate the risk of adverse perinatal outcomes in ART dizygotic twins, compared with non-ART twins.

Method: A review of the medical literature available in Pub Med, EBM review, the National Clinical Trials Registry and CINAHL databases. The search was limited to English language sources between 2000 and 2010. Three cohort studies were identified for the final systematic review. The GRADE tool was used to evaluate the evidence.

Results: The three cohort studies found no higher risk of low birth weight in ART twins after stratification for maternal age and parity. Birth weight discordance and mortality rates showed similar result as low birth weight. Two of the studies found an increased risk of hospitalization and neonatal intensive care unit admissions and maintained this result after stratification for maternal factors. One study found a higher risk of prematurity in twins conceived by in vitro fertilization; no such association was found in the other study.

Conclusion: A review of the evidence found an increased risk of adverse perinatal outcome in twins conceived by in vitro fertilization, compared with twin not conceived by in vitro fertilization. However, no statistically significance differences were found after stratification for maternal confounders, with the exception of hospital and NICU admission. The grade for all outcomes was moderate.

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies

First Advisor

Mary E. Von

Second Advisor

Torry Cobb

Third Advisor

Annjanette Sommers

Keywords

in vitro fertilization, IVF, dizygotic twins, birth weight

Subject Categories

Medicine and Health Sciences

Rights

Terms of use for work posted in CommonKnowledge.

Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

NOTICE TO READERS

This work is not a peer-reviewed publication. The Master's Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.

Risk of Adverse Perinatal Outcomes in Dizygotic Twins
After IVF Pregnancies: A Systematic Review

Fatima J. Baar



A course paper presented to the College of Health Professions
in partial fulfillment of the requirements of the degree of
Master of Science

Pacific University School of Physician Assistant Studies

February, 2011

Faculty Advisor: Mary E. Von

Clinical Graduate Project Instructors: Torry Cobb, DHSc, MPH, PA-C &

Annjanette Sommers MS, PAC

Biography

Fatima Baar is a native of Ecuador. She was a Gynecologic Surgeon for over 15 years and did her postgraduate work in Management of Health Care System from 1996-2000. She was also adjunct Faculty of Medicine, Guayaquil State University from 1990-2000. She initially came to United States ten years ago, seeking medical attention for her son, who needed a surgery. As a result of her son lengthy recovery time she chose to resign from her professional life in Ecuador. She decided to start her life over at considerable cost to herself and her family, in addition to her medical career. She eventually married and had another child. However, her husband suffered a series of heart attack and as a result passed away a few months before she started the Physician Assistant Program at Pacific University.

Her previous career, in addition to work done as a Certified Nursing Assistant and a Spanish Medical Interpreter, have given her a broad understanding of a wide range of health care needs. She believes that her significant experience as a Surgeon once combined with her new career as a Physician Assistant will enable her to once again return to the medical field. Upon returning she feels she will be able to make a significant contribution in light of her diverse cultural background and the growing need in Oregon, and throughout the United States, for health care professionals who are fluent in both the language and the culture of Hispanic population.

Acknowledgements

To my Mother: There are not enough words to express all my gratitude to you for being with us and being more than just a grandmother to my children. Without your unconditional love and support I could not have made my dream a reality.

In loving memory of my Father: You taught me to not take for granted the happiness that comes with success, as it is hard earned. I miss you a SO MUCH. I am so grateful you always believed in me and supported all my dreams. Thank You for teaching me that nothing is impossible when I put forth both passion and love.

In loving memory of my Husband: I miss you Douglas, I wish you could be here with us. I miss your cooking, sense of humor, guidance, and all the long talks about our plans for the future. Thank you for being my husband, my friend – a huge part of my life.

To my kids: José and Delany thank you for your patient, and understanding. Both of you are the motive and the joy of my life. Both of you make me proud and I feel blessed for having wonderful kids.

ABSTRACT

Background: Since the birth of the first test tube baby, 25 years ago, more than three million babies have been born using assisted reproductive technologies (ART). Twin births by way of ART represent 20-30% of U.S. and European births, as compared to only 1% of natural births. The purpose of this study is to investigate the risk of adverse perinatal outcomes in ART dizygotic twins, compared with non-ART twins.

Method: A review of the medical literature available in Pub Med, EBM review, the National Clinical Trials Registry and CINAHL databases. The search was limited to English language sources between 2000 and 2010. Three cohort studies were identified for the final systematic review. The GRADE tool was used to evaluate the evidence.

Results: The three cohort studies found no higher risk of low birth weight in ART twins after stratification for maternal age and parity. Birth weight discordance and mortality rates showed similar result as low birth weight. Two of the studies found an increased risk of hospitalization and neonatal intensive care unit admissions and maintained this result after stratification for maternal factors. One study found a higher risk of prematurity in twins conceived by in vitro fertilization; no such association was found in the other study.

Conclusion: A review of the evidence found an increased risk of adverse perinatal outcome in twins conceived by in vitro fertilization, compared with twin not conceived by in vitro fertilization. However, no statistically significance differences were found after stratification for maternal confounders, with the exception of hospital and NICU admission. The grade for all outcomes was moderate.

Key words: in vitro fertilization, IVF, dizygotic twins, birth weight

TABLE OF CONTENTS

| | |
|----------------------------|----|
| INTRODUCTION | 4 |
| Background..... | 4 |
| Purpose of the Study | 7 |
| METHOD | 8 |
| RESULTS | 8 |
| DISCUSSION | 13 |
| REFERENCES | 19 |
| APPENDIX..... | 21 |
| A. Table 1: GRADE | 21 |

INTRODUCTION

Background

On the 25th of July, 1978 Professor Robert Edwards (1925), a British physiologist, and gynecologist Patrick Steptoe stunned the world with the birth of the first test tube baby through the use of a revolutionary new treatment for human infertility, in vitro fertilization (IVF) without ovarian stimulation (Aboutaleb, 2005). The first attempted IVF took place in 1960, and after six years Steptoe successfully fertilized a human egg in the laboratory. For the development of IVF procedures Edwards and Steptoe (1913-1988) were awarded the 2010 Nobel Prize for physiology and/or medicine.

According to the 2002 National Survey of Family Growth conducted by the Center for Disease Control and Prevention (CDC), in the United States about 2% of women of reproductive age were seeking medical attention for infertility. Of them 10% were treated for infertility at some point in their lives. They found that married black women had about twice the odds of infertility as married white women (CDC, 2007).

Infertility, unlike other medical conditions, affects two persons at the same time. Infertility is defined as a couple not being able to become pregnant after a year of trying, without the use of contraceptives in women less than 35 years old with the same partner. Women older than 35 years old are considered infertile after six months of regular intercourse without the use of contraceptives (Practice Committee of the American Society for Reproductive Medicine, 2008). The causes of infertility are often difficult to identify because of many interconnected factors associated with infertility. It should not be taken for granted that only the woman is the cause of infertility. This has been corroborated in the study conducted by the World Health Organization (WHO, 2002) Task Force on Diagnosis and Treatment of Infertility. In the WHO

study, a sample of 8,500 infertile couples in developed countries revealed that the female fertility factor was determined to account for 37% of the infertility, the male fertility factor for 8% of the observed infertility, and, both the female and male factors together, for 35% of the observed infertility. The author also found during the study that unexplained factors accounted for an additional 5% of the observed infertility and 15 % unexpected pregnancy.

Assisted Reproductive Technology (ART) is any fertility treatment in which both eggs and sperm are handled in a series of steps called cycles. In the USA there are 483 fertility clinics but only 430 submitted data of ART cycles and outcomes to CDC- Division of Reproductive Health (CDC, 2007), for inclusion in the database.

ART includes IVF which includes few steps: ovarian stimulation, aspiration and fertilization of one or more oocytes, then transfer of the embryos into the uterus through the cervix. Each step of the IVF cycle takes two weeks. It also includes intracytoplasmic sperm injection (ICSI) for cases of severe sperm abnormalities, in which a single sperm is injected directly into the oocyte. Gamete intrafallopian transfer (GIFT), another form of ART, uses a laparoscope to aspirate and transfer oocytes and sperm into the fallopian tube. Zygote intrafallopian transfer (ZIFT) is the use of a laparoscope to transfer an embryo into the fallopian tube if uterine deformities exist and is the third form of ART that exists currently. Artificial insemination and controlled ovarian stimulation are not considered ART.

It is estimated that more than 3 million children have been born using to in vitro fertilization (Saxena, 2006). Today in the United States and Europe, it is estimated that from 1 to 3% of live births each year occur because of a successful ART intervention (CDC, 2008).

But in spite of the increase in successful IVF pregnancies, it has still not been possible to decrease the higher risk of adverse neonatal outcomes in IVF pregnancies such as twinning, low

birth weight, preterm birth, jaundice, respiratory problems, admission to NICU, and death, which are complications similar to those in natural pregnancies but which are magnified in IVF pregnancies.

Infants delivered at a low birth weight continue to have an increased risk of mortality compared to infants born at a normal birth weight. During the neonatal phase, a time when the greatest number of infant deaths occurs, lower birth weight is one of the key factors in infant mortality (McCormick MC, 1985).

In the USA and in Europe, the risk for twinning, especially dizygotic twinning, is between 20% - 30% as a result of ART (CDC, 2007) Andersen et al., 2008) and they are more admissions to NICU during the first 3 years of life than in spontaneous pregnancies. In 2006, Australia reportedly had the lowest percentage of twin deliveries, at 11.7% (Wang et al., 2008).

Purpose of the Study

The purpose of this study is to do a systematic review of the literature on adverse perinatal outcome and potential risk in ART dizygotic twins to include an evaluation of low birth weight, birthweight discordance, admission to hospital and neonatal intensive care (NICU), prematurity, and mortality. It is difficult to analyze one outcome alone, for example birthweight because it is related to, and affected by, other major perinatal outcomes such as prematurity, morbidity and mortality. Maternal characteristics including maternal age, parity, smoking in pregnancy, and socio-economic status can also contribute to these problems. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool will be used to evaluate the quality and strength of evidence (Guyatt et al., 2008).

METHODS

An extensive literature search was performed accessing databases through The Pacific University library system. These databases were: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 2010, EBM Reviews - ACP Journal Club 1991 to November 2010, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2010, EBM Reviews- Cochrane Central Register of Controlled Trials 4th Quarter 2010, EBM Reviews Cochrane Methodology Register 4th Quarter 2010, EBM Reviews - Health Technology Assessment 4th Quarter 2010, EBM Reviews- NHS Economic Evaluation Database 4th Quarter 2010. Pub Med, web of science, CINAHL and Medline databases.

The following keywords were searched individually and in combination: in vitro fertilization or IVF, dizygotic twins, and birth weight. Searches were conducted in all fields and title field. The search was limited to human subjects, the English language and to articles published between 2000 and 2010.

This search resulted in 27 articles. After excluding duplicates, narrative review articles and singleton births, three cohort studies were left for the final systematic review. Monozygotic twins were excluded since they occur more frequently in spontaneous conception and they associated with a greater risk of poor perinatal outcomes than dizygotic twins.

RESULTS

The studies included in this systematic review included three retrospective observational studies in which five perinatal outcomes were analyzed: low birth weight (LBW), birth weight discordance (BWD), gestational age (GA), admissions to NICU or hospital, and mortality. The studies included one published in 2009 from Australia, a Danish study published in 2004 and a study from Sweden in 2010. These studies follow a large population-based cohort which

identified dizygotic twins (DZ) born as a result of ART, and compared selected neonatal outcomes with spontaneous conception (SC) dizygotic twins within a period of six, five and twenty-five years, respectively.

Kallen, et al. (2010) selected 1545 dizygotic IVF/ICSI twin pairs and 8675 dizygotic non-IVF/ICSI twin pairs. The authors followed the population for 25 years (1982-2007) using the National health register which includes the IVF clinics in Sweden, and the Medical Birth Register. Four twin pairs were excluded as data was unavailable on year of birth and two did not specify maternal age.

The authors found in the IVF group, a higher percentage of older primiparous IVF mothers between 30-39 years of age who smoked less in early pregnancy thereby differing from their counterparts. They also found a higher risk for pre-term and low birth weight that were related to the group with a maternal age that was less than 25 years of age. The researchers did not find a notable distinction in the lowest birthweight or birthweight difference in the twin pairs among IVF and non- IVF twins. Maternal confounders such as low maternal age, first parity and smoking augment the risk of LBW. According to the authors, the risk of LBW was higher in IVF twins, even though there was no significant difference between IVF twins and non-IVF twins (Odds Ratio=1.12; 95% CI, 0.88-1.42).

In evaluating birth weight discordance the authors found the risk for BWD > 500g augments with maternal age and is associated with low body mass index (BMI) (Kallen, et al. (2010). First parity had no impact on BWD. According to the authors, the risk of BWD is not augmented in IVF twins.

In terms of gestational age, low maternal age, first parity, and smoking augment the risk of preterm birth. After IVF dizygotic twins have higher risk for preterm birth. The OR for first parity and < 32 weeks of gestation was 1.29, 95% CI 0.92-1.79. The OR for parity higher or

equal to two was 2.07, 95% CI 1.37-3.12. According to the investigators, parity did not increase the risk of preterm birth outcome. After adjustment for maternal age, parity, and smoking the risk for preterm birth stays higher OR 1.52 (1.18-1.97) in IVF twins, which is statistically significant compared to non-IVF twins.

Undesirable perinatal outcomes are increased in IVF dizygotic twins. However, the statistical difference existing between IVF twins and non-IVF twins could be modified by maternal confounders.

Pinborg et al. (2004) selected 3,438, of which 3,393 were live born IVF/ICSI dizygotic twin pairs and 10,362, of which 10,239 were live-born non-IVF/ICSI dizygotic twins, from 1995 to 2000. All monozygotic twins and stillborn babies were excluded. Data collected from the Danish National Medical Birth Registry (MBR,) which monitors the health of newborns including the quality of care services during the prenatal and delivery period. People born in Denmark have a CPR number (Centralized Civil Registry) used for healthcare and social services. This is the way women are recognized in the MBR and establishes who received IVF, ICSI or no treatment. Also the authors cross reference the data with the Danish IVF Registry.

For LBW, the authors reported that the higher risk of in IVF/ICSI twins vanished after stratification for maternal age and parity. After adjusting for maternal age and parity, LBW less than 2500g was considerably less in IVF/ICSI twins compared with the control group (OR 0.88, 95% CI 0.80-0.96).

The authors reported a mean BWD of 12.5% and 11.3% in the counterpart ($p < 0.001$). Dizygotic twins in IVF/ICSI have a greater than 20 % BWD compared with control group (OR 1.29, 95 % CI 1.04-1.58). The increased risk of preterm birth was considerably higher in IVF/ICSI twins, but after adjustment for maternal age and parity, there was no difference with spontaneous conception twins, OR, 95% CI 0.94 (0.80-1.10).

The authors reported that IVF/ICSI twins have 56 % of a higher risk of admission to NICU, compared to control 52.4%. (OR 1.18, 95% CI 1.09-1.27). ULS twins in IVF/ICSI have an increased risk for NICU admission (OR 1.34, 95% CI 1.19-1.51). This result was not modified with adjusted gestational age (OR 1.30, 95% CI 1.13-1.50) and represented 1.3 fold of increased risk for this outcome in ULS twins born after IVF/ICSI. No significant difference was noted between IVF/ICSI and control group, in stillborn rate (p= 0.6), neonatal rate (p= 0.3), and infant death lower in IVF/ICSI 10/1000 compared with 15/1000 in control group (p= 0.004). The mortality rate in IVF/ICSI unlike sex twins was 12/1000 and 11/1000 for control group (p= 0.65). Unlike the first year of birth where spontaneous conception twins had an increased mortality rate (p=0.04).

The researchers found that the mean birth weight and gestational age in the IVF/ICSI twin was considerably less than in control twins (Pinborg, 2004). LBW was also associated with frequent admissions to NICU. Also the authors found that parity is the strongest influencing maternal characteristic where maternal age is the least, which explains why after adjustment for maternal age, LBW and preterm birth turn out to be higher in IVF/ICSI twins. However, these perinatal outcomes changed when parity is added, and became lower risk for LBW in IVF/ICSI.

Hansen, et al. (2009) included seven hundred children born as twins which represent 14.6% of all twins born in Western Australia as a result of ART conception (IVF-65.4 %, ICSI-25.75, and GIFT-8.9%) and 4097 children (85.4%) born after spontaneous conception (SC) in a period of 6 years from 1993 to 2000. The researchers studied low birth weight, gestational age, mortality, and NICU/hospital admission in twins under 3 years old in Western Australia. They excluded aboriginal children. The data was collected using record linkage methods.

The investigators found increased risk of LBW <2500g in IVF/ICSI twins, which represents 47.7% compared with 39.7% of all SC twins. They reported an increased risk of

preterm birth < 32 weeks in IVF/ICSI (16.3 %) compared to all SC twins (12.4 %). ORs (95% CI) 1.7 (1.2-2.4). The length of stay was considered from admission day to discharge day or death. In the first year of life it was deemed an admission after day 29. During the first year the median LOS was noted to be longer than the second and third years. The second year was statistically significant compare to control twins. In contrast, the difference in LOS for the third year did not reveal much variation. The median LOS of birth admission for ART twins was 12 days and 8 days for ULS SC twins. The authors excluded birth admissions < 29 days and social admissions. They noticed increased LOS by preterm birth, LBW and major birth defects. Admission to NICU was higher in ART twins, 34% compared with 12 % in ULS SC twins (Table 2) even after adjustment for maternal, parity, sex, and year of birth.

The authors reported the risk of perinatal death to be higher in ART twins compared to ULS in the spontaneous twins (OR 2.2, 95% CI 1.1-4.6). However, there was no difference when compared to all SC twins (OR 1.1, 95% CI 0.6-1.9). Compared with ULS in SC, the risk of stillbirth (OR 1.9, 95% CI 0.8-4.9), neonatal death (OR 2.7, 95% CI 0.8-8.5) and risk of infant death (OR 1.8, 95% CI 0.4-8.8) were higher. However, these calculations were not statistically significant.

The results were similar to other studies mentioned before in this paper where the authors found higher percentage of older primiparous mother, preterm and low birthweight lower than 2500 g in the ART conception group. Infants delivered at a low birth weight continued to have an increased risk of mortality compared to infants born at a normal birth weight. As a consequence, these infants experience more admission to NICU which lead to major medical costs. The authors suggested that the couple should contemplate the selection of one embryo instead of two embryos to reduce perinatal complications and surplus cost of ART twin delivery

in which include more days in the hospital at birth and higher risk for admission to NICU and hospital.

DISCUSSION

It is well known that poor perinatal outcome in assisted reproductive technology (ART) singletons compared with spontaneous conception (SC), as well as the increased risk of mortality and morbidity rises in multiple pregnancies. A total of three retrospective observational studies (ROS) were systematically reviewed in which the association between dizygotic (DZ) twins conceived after ART treatments and higher risk of prenatal outcomes such as low birth weight, birth weight discordance, prematurity, admission to the hospital/NICU, and mortality was established.

Limitations

Hansen et al., (2009) investigated the relationship between poor perinatal outcomes and admission to NICU and hospital in ART (IVF/ICSI/GIFT) twins from 1994 to 2000 in Western Australia. The authors found that preterm birth (less than 32 weeks), low birth weight and death were not statistically significant after adjustment for maternal characteristics maternal age, parity, and socioeconomic confounders. In addition, the authors also confirmed that ART twins have a 60% higher risk for NICU and hospital admission.

This study is limited to the investigation of the data obtained from hospital admission records. Also there is no additional information about other health care services. Some records were missing data or were lacking information on ovarian stimulation and intra-uterine insemination in the SC group. Any manipulation of the process of conception makes the pregnancy not strictly spontaneous. Again, this suggests dissimilarity in the outcomes between

the two groups. Finally, these procedures are associated with a higher risk of hospitalization due to poor prenatal outcomes.

The investigation in Hansen et al., (2009) differs from the others because it includes twins born after gamete intra-fallopian transfer (GIFT). The investigators confirm the results obtained by Pinborg et al., (2004) with respect to low birth weight, birth rate discordance, gestational age (lower than 32 weeks), and mortality.

Pinborg et al., (2004) analyzed neonatal outcomes in a Danish national cohort between 3,438 IVF/ICSI twins and 10, 362 non IVF twins from 1995 to 2000. Because it is a cohort study based on records and protocols, it suffers from the same difficulties as the study previously mentioned. For example, a short coming resulting from using the national health registry is illustrated when gestational age is not recorded in days, but only in weeks, so that the authors could not calculate an exact gestational age.

In addition to the limitations observed in the two previous studies by Pinborg et al., (2004), and Hansen et al., (2009), Kallen et al., (2010) collected data from accredited nationwide data- bases. However, like other registry systems, potential error is possible. For example, when the authors recorded the data, they failed to include information such as IVF data received from overseas. If the woman has IVF treatment outside of the country, the data base may not include her in the cohort.

Kallen et al., (2010) compared the neonatal outcomes in dizygotic twins after IVF versus non-IVF pregnancies from 1982 – 2007 in Sweden. The researchers found no differences in low birth weight or in birth weight discordance. However, they discovered a higher risk for pre-term birth at less than 32 weeks in IVF dizygotic twins. Singletons and twins born after ART

procedures tend to have worse perinatal outcomes compared to spontaneous conception singletons and twins.

GRADE

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) were used in order to analyze, evaluate, and score the quality of evidence and strength of recommendations of this systematic review. It is necessary to take into account also that the strength of recommendation is determined by the balance of desirable versus undesirable effects or benefits (Guyatt et al., 2008). This will help clinicians at the moment of making decisions involving all types of intervention, whether clinical or surgical and at the same time have a better criteria based on evidence based medicine (EBM) to be able to discuss with and to instruct the patient about the risks or benefits of medical interventions, so as to enable the patients to make better informed decisions. Whenever a strong recommendation is advisable the word recommend will be used, and if a weak recommendation is called for the word “suggest” will be used. The grading system has the following four categories:

High: Further research is very unlikely to change the confidence in the estimate of the effect or its accuracy.

Moderate: Further research is likely to have an important effect on the confidence in the estimate of effect or accuracy and is likely to change the estimate.

Low: Further research is very likely to have an important impact on our confidence in the estimate of effect or accuracy and is likely to change.

Very Low: Any estimate of effect or accuracy is very uncertain (Guyatt et al., 2008, p. 926)

The type of evidence of the three studies reviewed in this paper were ROS and therefore the quality of evidence was low (GRADE Appendix A).

Outcomes

Not all of the outcomes were analyzed in great detail in the three studies. Only low birth weight was analyzed in the all three cohort studies. Hansen et al. (2009), Pinborg et al., (2004), and Kallen et al., (2010) found no association with LBW after adjustment for maternal characteristics, including age and parity. Also, this outcome is studied together with prematurity, gestational age and associated with other maternal factors such as smoking, body mass index, and socioeconomic status.

Kallen et al., (2010) and Pinborg et al., (2004) did not find any association between birth discordance and IVF dizygotic twins after stratification for maternal confounders.

A discrepancy was found in the results of the two studies for the outcome of prematurity less than 32 weeks. Kallen et al., (2010) found a higher risk for prematurity in IVF/ICSI twins, which never change even after adjustment for maternal characteristics (positive association), while Pinborg et al., (2004) found a negative association. Kallen et al., (2010) could not find a plausible explanation for the differences, even though these studies had similar design characteristics, for example, in the size of the population, inclusion and exclusion criteria.

Hansen et al., (2009) and Pinborg et al., (2004) observed a higher rate of hospital admission and NICU ART twins, even after stratification for maternal age, parity, sex and year of birth. The combined evidence from the two ROS had a positive association for this outcome. The relationship has been analyzed for congenital defects, mobility, mortality and maternal socioeconomic status. The studies did not include a detailed diagnostic of admission.

According to Hansen et al., (2009) and Pinborg et al., (2004) there was no higher mortality rates observed in ART twins.

This systematic review was upgraded based on controlling for all possible confounders, classifying it in the overall GRADE of evidence as moderate.

CONCLUSION

In USA, the cost for a complete cycle of IVF goes from \$12,000-\$15,000 without mentioning the routine fertility work-up. In order to alleviate these costs and having a way of trying to ease the financial problem on the family, scholarships and reimbursement plans are available in fertility clinics in which the couple may qualify to receive money if the treatment is not successful in a limited or determined number of cycles. But it is necessary to make clear the definition used by the clinic as far as what exactly constitutes a successful result, because it could be that if the proof of pregnancy is positive but if a miscarriage results the clinic might not return the money to the couple.

Previously it was believed that singleton births obtained through IVF had more perinatal complications than multiple births. According to this systematic review it has been demonstrated the increased risk of undesirable perinatal outcomes in multiple pregnancies. Based on the evidence it is important to inform with clarity and precision and above all inculcate in couples who seek fertility treatments about the perinatal risks associated with ART. By stressing that one of the greatest risks is multiple pregnancies that, while appearing to be attractive for some couples due to maximize the opportunity to have a baby, still represent a higher rate of risk for mortality and morbidity which are aggravated with infertility problems of the couple, which may lead to a higher rate of NICU and hospital admissions during the first three years of life, as has

been demonstrated in these studies. Associated with this is the high cost of hospitalization and subsequent follow up appointments.

It might be possible to lessen or reduce these complications if there is an option to transfer a single embryo (SET) instead of choosing multiple embryos in order to maximize the probability of having a baby. At the present, techniques are being developed for improvement of embryo culture media in order to have high quality of embryos which would have a higher successful rate of implantation.

In conclusion, it is also necessary to carry out prospective cohort studies in which the researcher can follow the patients and record the details of the new events or factor that can affect the outcome in order to insure precise and accurate results and avoid variability in results, designing studies carefully to try to predict what data will be useful down the road.

REFERENCES

- Aboutaleb, Y. (2005). History of Medicine. How IVF became a Reality. *Ain Shams Journal of Obstetrics and Gynecology*, 2,312-313. Retrieved on January 7, 2010, from <http://www.asjog.org/journal/V2Issue1/312%20History%20of%20Medicine-iss4-stg4.pdf>
- Andersen, A., Goossens, V., Ferraretti, A., Bhattacharya, S., Felberbaum, R., and de Mouzon, J., Nygren KG. (2008). Assisted reproductive technology in Europe: results generated from European registers by ESHRE. *Human Reproduction*, 23,756-771.
- Centers for Disease Control and Prevention, (2007). Assisted Reproductive Technology Success Rates: National Summary and Fertility clinic Report. Retrieved on Jan 9, 2010, from <http://www.cdc.gov/art/ART2007/index.htm>
- Centers for Disease Control and Prevention, (2008). Assisted Reproductive Technology Success Rates: National Summary and Fertility clinic Report. Retrieved on Jan 9, 2010, from http://www.cdc.gov/art/ART2008/PDF/ART_2008_Full.pdf
- Guyatt, G., Rennie, D., Meade, M., Cook, D., (2008). *User's Guides to the Medical Literature, A manual for Evidence-Based Clinical Practice* (2th ed.). New York, McGraw-Hill
- Guyatt, G., Oxman, A. D., Vist, G., Kunz, R., Falck-Ytter, Y., Alonso Coello P. & Schunemann H. J. (2008) Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal*, 336,926. Retrieved on Jan 29, 2010 from http://www.gradeworkinggroup.org/publications/GRADE-1_BMJ2008.pdf
- Hansen, M., Colvin, L., Petterson, B., Kurinnnczzuk, J., de Klerk, N., & Bower, C. (2009). Twins born following assisted reproductive technology: perinatal outcome and admission to hospital. *Human Reproduction*, 00, 1-11. doi: 10.1093/humrep/dep173.
- Kallen, B., Finnstrom, O., Lindam, A., Nilsson, E., Nygren, K. G., & Otterblad Olausson P. (2010). Selected neonatal outcomes in dizygotic twins after IVF versus non-IVF pregnancies. *An International Journal of Obstetrics and Gynecology*, 17, 676-682. doi: 10.1111/j.1471-0528.2010.02517.x
- McCormick, M. C. (1985) The contribution of low birth weight to infant mortality and childhood morbidity. *New England Journal of Medicine*, 312, 82-90. Retrieved on Jan 19, 2010 from <http://www.nejm.org/doi/full/10.1056/NEJM198501103120204>

Pinborg, A., Loft A., Rasmussen, S., Schmidt, L., Langhoff-Roos, J., Greisen, G., & Andersen, A. (2004). 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*, 435-441. doi: 10.1093/humrep/deh063.

Practice Committee of the American Society for Reproductive Medicine, (2008). Definitions of infertility and recurrent pregnancy loss. *Fertil Steril* *90*, S60. Retrieved on January 7, 2010, from http://www.uptodate.com.proxy.lib.pacificu.edu:2048/online/content/topic.do?topicKey=r_endo_f/14648&selectedTitle=2%7E150&source=search_result

Saxena, P (2006). Three million babies born using assisted reproductive technologies. Retrieved on Jan 21, 2010 from www.rxpgnews.com/.../Three_million_babies_born_using_assisted_reproduct_4518_4518.shtml

World Health Organization, 1992. Technical Report Series. Recent Advances in Medically Assisted Conception, *820*, 1-111. Retrieved on January 7, 2010, from http://www.uptodate.com.proxy.lib.pacificu.edu:2048/online/content/topic.do?topicKey=rendof/14648&selectedTitle=2%7E150&source=search_result

APPENDIX A

Table 1 : GRADE Table

| Outcome | Quantity and type of evidence | Findings | Starting grade | Decrease GRADE | | | | | Increase GRADE | | | Grade of Evidence for Outcome | Overall GRADE of Evidence |
|---|-------------------------------|--|----------------|----------------|-------------|------------|-----------|-------------|----------------|-------|-------------|-------------------------------|---------------------------|
| | | | | Study | Consistency | Directness | Precision | Publication | Large | Dose- | Confounders | | |
| Lowest birth weight (LBW) | 3 ROS* | No association | Low | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | Moderate | Moderate |
| Birth weight discordance (BWD) | 2 ROS | No association | Low | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | Moderate | |
| Prematurity < 32 weeks | 2 ROS | No association (1) Positive association (1) | Low | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | Low | |
| Hospital Admission, NICU (Neonatal intensive care unit) | 2 ROS | Positive association | Low | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | Moderate | |
| Mortality | 2 ROS | No association | Low | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | Moderate | |

*ROS: retrospective observational study

GRADE of evidence for outcome:

High: Further research is very unlikely to change the confidence in the estimate of the effect or its accuracy.

Moderate: Further research is likely to have an important effect on the confidence in the estimate of effect or accuracy and is likely to change the estimate.

Low: Further research is very likely to have an important effect on the confidence in the estimate of effect or accuracy and is likely to change.

Very Low: Any estimate of effect or accuracy is very uncertain (Guyatt et al., 2008)