14

Down Syndrome Screening in Pregnancies Conceived after Assisted Reproductive Technologies

Maarit Sahraravand and Markku Ryynanen
Department of Obstetrics and Gynecology, Oulu University Hospital
Finland

1. Introduction

Over the last three decades, prenatal screening for Down syndrome and other chromosomal abnormalities has become routine during antenatal care. Down syndrome screening has changed from the second to the first trimester of pregnancy because of the higher detection rate and earlier diagnosis. Second-trimester screening, based on the combination of maternal serum human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), and unconjugated estradiol (uE3) as a function of maternal age, yields a detection rate of 60% with a false-positive rate (FPR) of 5% (Wald et al., 1988). In standard practice, first-trimester screening, which combines maternal age, nuchal translucency thickness (NT), and maternal serum free beta-human chorionic gonadotropin (fβ-hCG), and pregnancy-associated plasma-protein-A (PAPP-A), can achieve a detection rate 90% with a FPR of 5% (Snijders et al., 1998; Nicolaides, 2004; Wojdemann et al., 2005; Spencer, 2007).

Down syndrome screening among women pregnant after assisted reproductive technologies (ART) is complicated by several factors. Pregnancies conceived after ART represent a group of high-risk pregnancies, which carry a higher psychological and financial burden compared to spontaneous pregnancies (Oddens et al., 1999). The proportion of women aged 35 years or more is higher in ART pregnancies, therefore, they a more likely to be carrying a child affected by Down syndrome (Geipel et al., 1999; Pinborg et al., 2004; Weisz and Rodeck, 2006, Gjerris et al., 2008). Studies have also shown that foetuses conceived after intracytoplasmic sperm injection (ICSI) are known to have an increased risk of chromosomal aberrations (Aboulghar et al., 2001; Bonduelle et al., 2002; Jozwiak et al., 2004; Gjerris et al., 2008). Pregnancies conceived after ART are also associated with a higher rate of multiple pregnancies (Weisz and Rodeck, 2006, Gjerris et al., 2008). Maternal and fetal complications, such as foetal growth restriction, preeclampsia, preterm birth, congenital abnormalities, and low birth weight occur more often in assisted reproduction pregnancies (Helmerhorst et al., 2004; Amor et al., 2009; Williams and Sutcliffe, 2009; Henningsen et al., 2011). Women who have conceived after assisted reproductive techniques usually prefer to avoid invasive diagnostic procedures, such as amniocentesis and villus biopsy, due to the risk of miscarriage. Rather, they choose non-invasive screening before making a decision about invasive testing (Meschede et al., 1998; Schover et al., 1998; Geipel et al., 1999; Geipel et al., 2004).

Pregnancies conceived by assisted reproduction techniques have also been reported to be associated with changes in the biochemical parameters of screening for Down syndrome,

leading to an increased false-positive rate in the second trimester (Barkai et al., 1996; Ribbert et al., 1996; Frishman et al., 1997; Wald, 1999; Raty et al., 2002: Lambert-Messerlian et al., 2005). The effect of ART on first-trimester Down syndrome screening has been examined, but the results are inconclusive. The majority of the studies have reported that nuchal translucency screening is not affected by the mode of conception (Liao et al., 2001; Nieminen et al., 2001; Wojdemann et al., 2001; Orlandi et al., 2002; Ghisoni et al., 2003; Lambert-Messerlian et al., 2006; Matilainen et al., 2011). Yet, some studies suggested that NT measurements are altered in pregnancies conceived with ART (Maymon et al., 2002; Hui et al., 2005; Amor et al., 2009; Gjerris et al., 2009). Several studies have found that serum marker levels, especially PAPP-A levels, seem to be altered in ART pregnancies, leading to the higher false-positive rate, whereas other studies have been unable to confirm this.
In this chapter, we present the recent findings of first-trimester Down syndrome screening in singleton and twin pregnancies conceived after assisted reproductive technologies.

2. The effect of ART on nuchal translucency thickness and other ultrasound markers

Measurement of nuchal translucency thickness as a single marker may be the most effective screening test, and is thought to be least affected by the mode of conception. Down syndrome screening, which combines maternal age and fetal nuchal translucency thickness measurement, can achieve a detection rate of 75 - 80% with a false-positive rate of 3 - 5% (Kagan et al., 2010). There are several studies which have been examined, whether the nuchal translucency measurements are altered in pregnancies conceived by ART.
In the study by Gjerris et al., (2009) the median NT in entire ART group (n = 992) was smaller when compared with spontaneous pregnancies (n = 2532). They also found that the mode of the conception had an effect on NT: the nuchal translucency thickness was thinner in *in-vitro* fertilization (IVF) cases when compared with intracytoplasmic sperm injection (ICSI) cases. They also found that a smaller nuchal translucency thickness was noted in pregnancies treated with a long protocol hormone treatment compared with those with the short hormone treatment protocol. There was not any obvious biological explanation for these findings; any significant differences might be due to chance as several statistical analyses were performed. Opposite findings were reported by Amor et al., (2009); they found that in ART pregnancies (n = 833) the nuchal translucency thickness was increased compared with the controls. There was no difference between IVF and ICSI group.
In our own study (Matilainen et al., 2011), we investigated 282 pregnancies conceived after assisted reproductive technologies, and in which only one fetus was noted in early ultrasound examination, and who participated in first trimester combined screening. There were 24.783 spontaneous singleton pregnancies in our control group. Patients were divided into four groups according to the type of conception, as follows: controls, hormonally stimulated *in-vitro* fertilization or intracytoplasmic sperm injection group, spontaneous non-stimulated frozen embryo transfer (FET) group, and hormonally stimulated FET group (HRT-FET). In our study population, NT or NT MoMs (multiples of the medians) were not significantly different between the different type of ART pregnancies and spontaneous pregnancies.
The majority of the studies found no difference in the size of NT in ART pregnancies compared with spontaneous pregnancies (Liao et al., 2001; Nieminen et al., 2001; Wojdemann et al., 2001; Orlandi et al., 2002; Ghisoni et al., 2003; Lambert-Messerlian et al.,

2006 and Matilainen et al. 2011), and no influence on the screening performance and the false-positive rate by compining maternal age and NT for Down syndrome risk assessment (Liao et al., 2001; Ghisoni et al., 2003; Bellver et al., 2005; Lambert-Messerlian et al., 2006; Tul and Novac-Antolic, 2006; Ancaert et al., 2008; Bender et al., 2010; Matilainen et al., 2011).
Gjerris et al. (2008) found that gestational age dating in ART pregnancies either by the date of oocyte aspiration (DOA) or by crown-rump length differed significantly by 1.5 days. The gestational age was higher when it was dated according to CRL. The study group speculated that fetuses were larger than expected at the NT scan and their real biological gestational age was lower, therefore, a smaller NT MoM values were observed in assisted reproduction pregnancies (Gjerris et al., 2009). According to a mathematical stimulation method, the use of CRL or DOA for gestational age dating did not significantly influence the detection rate for Down syndrome (Gjerris et al., 2008).
First-trimester screening, which combines maternal age, fetal nuchal translucency thickness, and maternal serum free β-hCG, and PAPP-A, can achieve the detection rate of 90% with the FPR of 5% (Snijders et al., 1998; Nicolaides, 2004; Wojdemann et al., 2005; Spencer, 2007). A further improvement in the screening performance can be achieved by including the assessment of additional, new ultrasound markers. These additional markers are the absence of the nasal bone, and the blood flow in the ductus venosus, and across the tricuspid valve. The absence of the nasal bone, reversed a-wave in the ductus venosus, and tricuspid regurgitation are observed in about 60, 65 and 55% of fetuses with Down syndrome and in 2.6, 3.2 and 0.9%, respectively, of euploid fetuses. The assessment of each of these sonographic markers into first-trimester combined screening, which uses maternal age, NT thickness, and maternal serum free β-hCG, and PAPP-A, can yields a detection rate of 93 - 96% with the false-positive rate of 2.5%. Screening for Down syndrome by maternal age, nuchal translucency thickness and either the ductus venosus, the nasal bone, or the tricuspid flow, at the risk cut-off of 1:100, identified 83, 85, and 85% of cases with false-positive rate of 2.9, 2.7 and 2.7%, respectively (Kagan et al., 2010). Unfortunately, there are no studies concerning these new ultrasound markers in pregnancies conceived after ART.

3. The effect of ART on first-trimester biochemical markers

In pregnancies affected by Down syndrome the maternal serum level of PAPP-A is reduced to about half (Brambati et al., 1993) and the level of free β-hCG is about twice as high when compared with values in chromosomally normal pregnancies (Spencer et al., 1992). Maternal serum PAPP-A and free β-hCG values are affected by many variables, therefore, to estimate accurate patient-specific risks, adjustments in the measured free β-hCG and PAPP-A levels take into account their association with gestational age, maternal weight, ethnicity, and smoking status (Spencer et al., 1999a; Spencer et al., 2003b; Avgidou et al., 2005; Nicolaides et al., 2005). In addition, the mode of conception has an effect on maternal serum screening markers.
Previous studies have shown that serum markers in ART pregnancies differ from natural conception in the second trimester, leading to an increased false-positive rate (Barkai et al., 1996; Ribbert et al., 1996; de Graaf et al., 2000; Niemimaa et al., 2003). Most of the recent studies have reported that first-trimester serum markers are altered in pregnancies conceived after assisted reproduction, when comparing with spontaneous conception. Many studies have shown a reduction, especially in the PAPP-A levels, in ART pregnancies. In our own study (Matilainen et al., 2011), we investigated 282 pregnancies conceived after ART,

and in which only one fetus was noted in early ultrasound, and who participated in first trimester combined screening. The control group was comprised of 24.783 spontaneous singleton pregnancies. We found a significant reduction in the PAPP-A concentration level in entire ART group when compared with controls. This is in agreement with most previous studies (Liao et al., 2001; Orlandi et al., 2002; Bersinger et al., 2004; Maymon et al., 2004; Hui et al., 2005; Tul and Novac-Antolic, 2006; Ancaert et al., 2008; Gjerris et al., 2009; Amor et al., 2009).

Some studies have found that PAPP-A levels are decreased in the subgroups of IVF (Liao et al., 2001; Tul and Novac-Antolic, 2006; Amor et al., 2009; Gjerris et al., 2009; Bender et al., 2010; Engels et al. 2010) or ICSI (Ancaert et al., 2008; Amor et al., 2009; Gjerris et al., 2009; Bender et al., 2010; Engels et al., 2010). However, few studies found no differences in the value of maternal serum PAPP-A levels in ART conceptions compared to controls (Ghisoni et al., 2003; Bellver et al., 2005; Lambert-Messerlian et al., 2006). The study by Kagan et al. (2008), which is the largest study so far, reported that PAPP-A levels were reduced 10% in pregnancies conceived after assisted reproduction (n = 2115), when compared to controls (n = 94.688). In our study (Matilainen et al., 2011), we found no statistically significant differences in pregnancies conceived after spontaneous FET or HRT-FET, compared with the control group. There are other studies reported that the median PAPP-A MoM level was not significantly reduced in FET pregnancies (Anckaert et al., 2008; Gjerris et al., 2009). There is also a study in which the median PAPP-A MoM levels were significantly reduced in ICSI pregnancies in the fresh and the frozen-thawed embryo subgroups and in the fresh embryo IVF subgroups as compared to controls (Hui et al., 2005). Amor et al. (2009) studied PAPP-A concentration levels in fresh embryo transfers (n = 773) and frozen embryo transfers (n = 573). PAPP-A levels were reduced in both subgroups when compared with spontaneous pregnancies. However, fresh embryo transfers were associated with significantly lower PAPP-A levels when compared with FET pregnancies.

Studies concerning about the free β-hCG concentration levels in assisted reproduction pregnancies are contradictory. In our study (Matilainen et al. 2011), we found no difference in the median free β-hCG MoM concentrations in between the ART and control groups. This is in agreement with most previous studies (Orlandi et al., 2002; Tul et al. 2006; Bellver et al., 2005; Gjerris et al., 2009; Amor et al., 2009). Yet, there are some studies which have reported the free β-hCG levels to be increased in ART pregnancies (Niemimaa et al., 2001; Liao et al., 2001; Ghisoni et al., 2003; Bersinger et al., 2004; Hui et al., 2005). One study even has reported slightly decreased free β-hCG levels in IVF pregnancies (Engels et al., 2010).

The disintegrin and metalloproteinase domain 12 (ADAM12) is a further first-trimester serum marker for Down syndrome (Laigaar et al., 2003) and other chromocomal aberrations (Spencer & Cowans, 2007). There is only one study concerning the use of ADAM12 as a first-trimester Down syndrome screening marker in ART pregnancies (Laigaard et al., 2009). Study group found no alterations in ADAM12 serum marker levels in ART pregnancies when compared with spontaneous pregnancies.

In our study, the odds ratios for a false-positive rate in the combined first-trimester screening for Down syndrome by maternal age, nuchal translucency, and PAPP-A, and free β-hCG, were not increased in women who conceived following ART, after adjustment for maternal age (Matilainen et al. 2011). This is in agreement with many other studies (Maymon and Shulman, 2001b; Liao et al., 2001; Wojdemann et al., 2001; Orlandi et al., 2002; Bellver et al., 2005). There are also studies which have reported higher FPR in the ART group even after adjustment for maternal age (Orlandi et al., 2002; Amor et al., 2009; Gjerris

et al., 2009). Tul and the study group (2006) found a higher FPR in pregnancies after ICSI. Amor et al. (2009) found that PAPP-A levels were reduced and FPR was higher, both in fresh and frozen-thawed embryos, but only in pregnancies in which the mother was administered hormone treatment around the time of embryo transfer. First-trimester Down screening which combines maternal age, NT, and biochemical markers may increase the false-positive result in ART pregnancies, therefore, it increase the likelihood of having amniocentesis or chorionic villus sampling. However, contradictory results from previous published works require larger studies. As more information accumulates on serum marker variations in ART pregnancies, procedure-specific medians for serum markers may need to correct changes in pregnancies conceived after ART. Table 1 summarizes the results of the previous studies.

4. Possible explanations for altered serum marker levels in ART pregnancies

There are many possible confounding factors, which could lead to contradictory results on maternal serum screening markers in pregnancies conceived after assisted reproductive techniques. Multiple corpora lutea and multiple implantation sites have been suggested to be the reason for either increased or decreased marker levels (Weisz et al., 2006). It has been recommended that abnormal marker levels could be due to the underlying subtle metabolic or genetic conditions that can also be the reason for infertility itself (Ribbert et al., 1996). It has also been suggested that lower PAPP-A levels in ART pregnancies might be the result of metabolic impairments related to infertility of the mother (Maymon and Shulman, 2002). However, Amor et al. (2009) found that PAPP-A levels were reduced, both in male-factor infertility, female-factor infertility, and the combination of female and male cause. Anckaert et al. (2008) found that PAPP-A values did not differ between male and female infertility. The same study group found higher median free β-hCG level values in non-male infertility compared with male infertility and spontaneous pregnancies.

Also, a functional delay in fetal and placental development and the higher risk of obstetric complications associated with ART, can lead to changes in serum marker concentrations (Maymon et al., 2004; Helmerhorst et al., 2004; Hui et al., 2005, Williams et al., 2009; Henningsen et al., 2011). Studies have shown that low first-trimester PAPP-A levels indicates placenta-related disorders, such as fetal growth restriction, low birth weight, preeclampsia (Papageorghiou et al., 2007; Gagnon et al., 2008; Pihl et al., 2008; Goetzinger et al., 2010). Studies have also shown that maternal and fetal complications occur more often in assisted reproduction pregnancies (Helmerhorst et al., 2004; Amor et al., 2009; Williams et al., 2009; Henningsen et al., 2011). However, Amor et al. (2009) found that PAPP-A levels were reduced in ART pregnancies with or without pregnancy complications (e.g., preeclampsia or low birth weight). In other study by Zhong et al. (2010), ART pregnancies with low PAPP-A level values were at higher risk for small-for-gestational-age infants or preterm delivery less than 32 weeks of gestation when compared with spontaneous pregnancies with low PAPP-A values.

Recent studies have suggested that vanishing twin might have the impact on serum marker level alterations. Spencer et al. (2010) found that in women with a second empty gestational sac, the median PAPP-A and free β-hCG values were not different from the median values in non-ART pregnancies. Yet, they found that median PAPP-A levels were significantly increased in pregnancies with a vanishing twin and a measurable crown-rump length. Median free β-hCG levels were unchanged in those pregnancies. Amor et al. (2009) found

Study	*Natural pregnancies*	*Assisted reproduction pregnancies*	*Free β-hCG*	*PAPP-A*
Liao et al. (2001)	1233	161 (OI)	←→	←→
		220 (IVF)	↑	↓
		30 (ICSI)	←→	↓
Wojdemann et al. (2001)	3026	63 (OI)	←→	←→
		47 (IVF)	←→	←→
Niemimaa et al. (2001)	4265	49 (IVF)	←→	↑
Orlandi et al. (2002)	370	32 (IVF)	←→	↓
		42 (ICSI)	←→	←→
Maymon and Shulman (2002)	285	71 (IVF)	←→	↓
Ghisoni et al. (2003)	435	145 (ART)	↑	←→
Maymon and Shulman (2004)	1781	99 (IVF)	N/A	↓
Hui et al. (2005)	401	92 (IVF)	↓	↓
		57 (ICSI)	←→	↓
		54 (FET/IVF)	←→	←→
		31 (FET/ICSI)	←→	↓
Bellver et al. (2005)	498	97 (OI)	←→	←→
		47 (IVF)	←→	←→
		222 (ICSI)	←→	←→
		71 (OD/IVF)	←→	←→
		119 (OD/ICSI)	↑	←→
Lambert-Messerlian et al. (2006)	37 070	277 (IVF)	↑	↓
Tul and Novac-Antolic (2006)	914	130 (IVF)	←→	↓
Kagan et al. (2008)	97 294	2115 (IVF)	↓	↑
Gjerris et al. (2009)	2532	992 (ALL ART)	←→	↑
		512 (IVF)	←→	↑
		396 (ICSI)	←→	↑
		84 (FET)	←→	←→
Amor et al. (2009)	50 253	1739 (ALL ART)	←→	↑
		654 (IVF)	←→	↑
		1052 (ICSI)	←→	↑
		773 (Fresh IVF/ICSI)	←→	↑
		573 (FET)	←→	↑
Matilainen et al. (2011)	24 783	176 (IVF/ICSI)	←→	↑
		87 (FET)	←→	←→
		19 (HRT-FET)	←→	←→

OI=ovulationinduction,
↓=decreased,↑=increadec,←→=not different

Table 1. Comparison of first trimester biochemical markers in singleton pregnancies achieved spontaneously and by assisted reproduction.

that in their ART population vanished twins appear to increase the PAPP-A levels rather than decrease them. Gjerris et al. (2009) found no effect on PAPP-A and free β-hCG concentration values in ART pregnancies with an early vanishing twin. It is believed that vanished twins do not decrease the PAPP-A levels, in fact, they might have the opposite effect (Amor et al., 2009).

Maymon and Shulman (2002) suggested that a reduction in PAPP-A levels in pregnancies conceived after assisted reproduction might be an artefact of testing being undertaken at an earlier gestation. Amor et al. (2009) found no difference between ART and non-ART pregnancies in the timing of ultrasound examination or blood sampling. However, they did found a slightly greater crown-grump length for frozen-thawed embryos compared to fresh embryos. They suggested that this difference may reflect a longer in-vitro culture time for frozen-thawed embryos, but the difference would not affect the median PAPP-A MoM levels because these values are adjusted for gestational age.

There are several studies that have suggested that exogenous hormone treatment is the main reason for reduced PAPP-A levels in ART pregnancies (Bersinger et al., 2004; Hui et al., 2005a; Tul and Novak-Antolic, 2006; Amor et al., 2009). Amor et al. (2009) examined the effect of hormone treatment versus no hormone treatment irrespective of FET or fresh embryo transfer and found low PAPP-A levels in transfer cycles with any hormone treatment when compared with cycles without hormone treatment. They also found that PAPP-A levels were reduced regardless of the type of ovarian stimulation. In our study, we also found that PAPP-A concentration levels were reduced in hormonally-stimulated IVF/ICSI pregnancies, but there was no statistically significant difference in spontaneous FET pregnancies (Matilainen et al., 2011). Amor et al. (2009) suggested that administration of exogenous hormones interferes with the normal endocrine changes of early pregnancy, resulting in reduced PAPP-A levels. Tul and Novak-Antolic (2006) found significantly decreased PAPP-A concentration levels with increasing numbers of transferred embryos and also with increasing numbers of retrieved oocytes. The authors hypothesized that the number of oocytes retrieved reflected the number of corpora lutea in pregnancies, supported by their other finding that inhibin A, which is secreted by corpora lutea, was increased with decreasing PAPP-A. They suggested that inhibin A inhibits the secretion of PAPP-A. However, Bender et al. (2010) found no correlation between PAPP-A and free β-hCG values and the transfer of one, two or three embryos in assisted reproduction pregnancies.

5. Down syndrome screening in multiple pregnancies

Twin pregnancies are becoming more frequent in most developed countries due to the increased use of assisted reproductive technologies and advanced maternal age (Spencer 2000). Approximately 25% of pregnancies arising from assisted reproduction are twins or higher order multiples. Despite increasing use of elective single-embryo transfer, double or more embryo transfer was in 2004 occur in more than 80% of all ART procedures (Andersen et al., 2008).

During the last three decades various methods of screening for Down syndrome were introduced in clinical practice, yet, specific problems were encountered when they were applied for twin pregnancies. Screening for Down syndrome in twin pregnancies is considered to be difficult because of the clinical, technical and ethical challenges posed for diagnosis and clinical management of such pregnancies (Cuckle, 1998; Spencer and Nicolaides, 2003).

The value of the prenatal screening for Down syndrome by biochemical test in twins is limited because of the masking effect of normal co-twins and the difficulty of pinpointing the abnormal co-twin (Cuckle, 1998); therefore the ultrasound seems to be the better method for Down syndrome screening both for spontaneous and ART twin pregnancies (Maymon et

al., 2002). On the basis of the observation that nuchal translucency thickness measurements were comparable in twins and singleton pregnancies affected by Down syndrome, the application of a combination of maternal age and NT measurement as the tool of assessing the risk of trisomy 21 has been advocated in twins (Pandya et al., 1995; Sebire et al., 1996). The same screening strategy has also been proposed for twins produced from ART pregnancies (Maymon et al. 1999). The detection rates for Down syndrome of 75 - 80% have been reported in twin pregnancies using maternal age and NT for risk calculation (Sebire et al. 1996; Kagan et al., 2007).

Chorionicity has an impact on Down screening measurements and first-trimester evaluation in twins is not completed until an accurate chorionity determination is performed (Sepulveda, 1997). The majority of twin pregnancies conceived after ART are dichorionic, yet, the incidence of monochorionic twin pregnancies after ART has increased (Wenstrom et al., 1993). Chorionicity has an impact on the nuchal translucency thickness. In monochorionic twin pregnancies mean fetal nuchal translucency thickness and inter-twin nuchal translucency thickness were larger when compared with dichorionic twin pregnancies (Cheng et al., 2010). In monochorionic twins the increased nuchal translucency thickness and discordance of NT have been associated with adverse pregnancy outcome, such as perinatal death and twin-twin transfusion syndrome (El Kateb et al., 2007; Kagan et al., 2007). Several studies have reported that the median NT measurements did not differed in twin pregnancies conceived after ART when compared to spontaneous pregnancies (Goence et al., 2005; Hui et al., 2005; Maymon et al., 2005). It is recommended that for dichorionic twins each co-twin fetus is treated as a singleton and its risk is calculated using the published distribution of NT values for singleton pregnancies (Maymon et al. 2005). In monochorionic twins, Down syndrome screening is provided by risk calculation based on the average nuchal translucency thickness measurement of two fetuses (Vandecruys et al., 2005).

Adding the PAPP-A and free β-hCG level measurements to nuchal translucency thickness in twin pregnancies may improve the detection rate about 5 - 6% (Spencer and Nicolaides, 2003), but helped mainly to reduce the higher FPR (Goence et al, 2005, Chasen et al., 2007). In twin pregnancies interpreting all the results of these screening markers is more difficult because the serum marker concentration relates to the pregnancy, while each NT measurement is fetus-specific (Maymon et al., 2005). Chorionity is suggested to have an impact on maternal serum marker levels: one study reported lower PAPP-A levels but indifferent free β-hCG values in monochorionic twin pregnancies when compared with dichorionic pregnancies (Spencer et al., 2008). In other study both markers were decreased in monochoric twin pregnancies (Liskens et al., 2009). In two studies, where no differentiation of chorionicity was made, no differences were found in maternal serum concentrations between assisted twin pregnancies and controls (Orlandi et al., 2002; Gonce et al., 2005). It is recommended that when invasive testing is indicated, NT alone is the screening method women should be counseled to choose, because ultrasound is the best mean of specifically locating the affected co-twin (Spencer and Nicolaides, 2003).

6. Conclusion

Pregnancies conceived after ART represent a group of high-risk pregnancies, which carry a higher psychological and financial burden compared to spontaneous pregnancies (Oddens et al., 1999). ART pregnancies differ from spontaneous pregnancies in many aspects,

therefore, Down screening among women pregnant after ART is more complicated. The proportion of women aged 35 years or more is higher in ART pregnancies, therefore, a risk of women having a child affected by Down syndrome is also a higher (Geipel et al., 1999; Pinborg et al., 2004; Weisz and Rodeck, 2006, Gjerris et al., 2008). Risk of chromosomal aberrations is increased in pregnancies conceived after intracytoplasmic sperm injection (Aboulghar et al., 2001; Bonduelle et al., 2002; Jozwiak et al., 2004; Gjerris et al., 2008). The proportion of multi-fetal pregnancies is higher in pregnancies conceived after assisted reproduction (Weisz and Rodeck, 2006, Gjerris et al., 2008). Also fetal and maternal complications occur more often in assisted reproduction pregnancies (Helmerhorst et al., 2004; Amor et al., 2009; Williams and Sutcliffe, 2009; Henningsen et al., 2011). The uptake of amniocentesis and villus biopsy is believed to be lower, because of the higher risk of miscarriage. Women pregnant after ART rather choose non-invasive Down screening before making a decision about invasive testing. (Meschede et al., 1998; Schover et al., 1998; Geipel et al., 1999; Geipel et al., 2004).

A number of different first-trimester ultrasound and biochemical markers have been validated in first-trimester screening for Down syndrome. Method of choice in first-trimester Down screening is combined screening, which measures maternal serum levels of free β-hCG and PAPP-A at 9 – 12 weeks of gestation and nuchal translucency by ultrasound at 11 – 13 weeks gestation. These measurements are combined with maternal age, weight, and gestational age to produce an risk estimate of fetus having a Down syndrome (Wald et al., 2003). For pregnancies with increased risk, an invasive procedure can be offered.

Measurement of fetal nuchal translucency thickness is the most investigated screening method and it is believed to be least affected screening method in ART pregnancies. Some studies have reported a small deviation of NT measurements in pregnancies conceived after assisted reproduction, but these alterations did not influence overall screening performance. The majority of the studies found no difference in NT measurements in ART pregnancies compared with spontaneous conceptions (Liao et al., 2001; Nieminen et al., 2001; Wojdemann et al., 2001; Orlandi et al., 2002; Ghisoni et al., 2003; Lambert-Messerlian et al., 2006 and Matilainen et al. 2011) and no influence on the screening performance and the false-positive rate by combining maternal age and NT for Down syndrome risk assessment (Liao et al., 2001; Ghisoni et al., 2003; Bellver et al., 2005; Lambert-Messerlian et al., 2006; Tul and Novac-Antolic, 2006; Ancaert et al., 2008; Bender et al., 2010; Matilainen et al., 2011). The use of new sonographic markers, such as the absence of the nasal bone, has not been explored in ART pregnancies.

Several studies have reported that first-trimester maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A levels are altered in ART pregnancies and might increase the false-positive rate. The reasons behind these alterations are not unambiguous. It has been suggested that e.g. exogenous hormone treatment, functional delay in fetal, and placental development and the higher risk of obstetric complications associated with ART can lead to changes in serum marker concentrations. Pre- and post-test counseling for women carrying ART-pregnancies is extremely important. Further studies should be determined the viability of altering the risk calculation for pregnancies conceived after ART.

Twin pregnancies are becoming more frequent in most developed countries due to the increased use of assisted reproductive technologies and advanced maternal age (Spencer 2000). Down screening in twin pregnancies is considered to be difficult because of the

clinical, technical and ethical challenges posed for diagnosis and clinical management of such pregnancies (Cuckle, 1998; Spencer and Nicolaides, 2003). In twin pregnancies chorionicity is an important confounding variable. It is recommended that for dichorionic twins, each co-twin fetus should be treated as a singleton and its risk should be calculated using the published distribution of NT values for singleton pregnancies (Maymon et al. 2005). In monochorionic twins, Down syndrome screening is provided by risk calculation based on the average nuchal translucency thickness measurement of two fetuses (Vandecruys et al., 2005).

7. References

Aboulghar, H., Aboulghar, M., Mansour, R., Serour, G., Amin, Y., & Al-Inany, H. (2001). A prospective controlled study of karyotyping for 430 consecutive babies conceived through intracytoplasmic sperm injection. *Fertil Steril,* Vol.76, No.2, (August 2001), pp. 249–253.

Amor, DJ., Xu, JX., Halliday, JL., Francis, I., Healy, D., Breheny, S., Baker, HW., & Jaques, AM. (2009). Pregnancies conceived using assisted reproductive technologies (ART) have low levels of pregnancy-associated plasma protein-A (PAPP-A) leading to a high rate of false-positive results in first trimester screening for Down syndrome. *Hum Reprod,* Vol.24, No.6 (June 2009), pp.1330-1338.

Anckaert, E., Schiettecatte, J., Sleurs, E., Devroey, P., & Smitz, J. (2008). First trimester screening for Down's syndrome after assisted reproductive technology: non-male factor infertility is associated with elevated free beta-human chorionic gonadotropin levels at 10-14 weeks of gestation. *Fertil Steril,* Vol.90, No.4, (October 2008), pp.1206–1210.

Andersen, AN., Goossens, V., Ferraretti, AP., Bhattacharya, S., Felberbaum, R., de Mouzon, J., & Nygren, KG,. (2008). Assisted reproductive technology in Europe, 2004: results generated from European registers by ESHRE. *Hum Reprod,*Vol. 23, No.4, (April 2008), pp. 756-771.

Avgidou, K., Papageorghiou, A., Bindra, R., Spencer, K., & Nicolaides, KH. (2005). Prospective first-trimester screening for trisomy 21 in 30 564 pregnancies. *Am J Obstet Gynecol,* Vol.192, No.6, (June 2005), pp.1761–1767.

Barkai, G., Goldman, B., Ries, L., Chaki, R., Dor, J., & Cuckle, H. (1996). Down's syndrome screening marker levels following assisted reproduction. *Prenat Diagn,* Vol.16, No.12, (December 1996), pp. 1111–1114.

Bellver, J., Lara, C., Soares, SR., Ramirez, A., Pellicer, A., Remohi, J., & Serra, V. (2005). First trimester biochemical screening for Down's syndrome in singleton pregnancies conceived by assisted reproduction. *Hum Reprod,* Vol.20, No.9, (September 2005), pp. 2623–2627.

Bender, F., Hecken, J., Reinsberg, J., Reinsberg, J., Berg, C., van der Ven, H., Gembruch, U., & Geipel, A. (2010). Altered first-trimester screening markers after IVF/ICSI: no relationship with small-for-gestational-age and number of embryos transferred. *Reprod Biomed Online.* Vol.20, No.4, (April 2010), pp. 516-22.

Bonduelle, M., Van, AE., Joris, H., Keymolen, K., Devroey, P., Van Steirteghem, A., & Liebaers, I. (2002). Prenatal testing in ICSI pregnancies: incidence of chromosomal anomalies in 1586 karyotypes and relation to sperm parameters. *Hum Reprod,* Vol.17, No.10, (October 2002), pp. 2600–2614.

Brambati, B., Macintosh, MC., Teisner, B., Maguiness, S., Shrimanker, K., Lanzani, A., Bonacchi, I., Tului, L., Chard, T., & Grudzinskas, JG. (1993). Low maternal serum levels of pregnancy associated plasma protein A (PAPP-A) in the first trimester in association with abnormal fetal karyotype. *Br J Obstet Gynaecol,* Vol.100, No.4, (April 1993), pp. 324-326.

Chasen, ST., Pernim SC., Kalish, RB., & Chervenak, FA. (2007). First-trimester risk assessment for trisomies 21 and 18 in twin pregnancy. *Am J Obstet Gynecol*, Vol.197, No.4 (October 2007), pp. 374.e1-3.

Cheng, PJ., Huang, SY., Shaw, SW., Hsiao, CH., Kao, CC., Chueh, HY., & Hsieh, TT. (2010). Difference in nuchal translucency between monozygotic and dizygotic spontaneously conceived twins. *Prenat Diagn*, Vol.30, No. 3 (March 2010), pp. 247-250.

Cuckle, H. (1998). Down's syndrome screening in twins. *J Med Screen.* Vol.5, No. 1, pp. 3-4.

de Graaf, IM., Cuckle, HS., Pajkrt, E., Leschot, NJ., Bleker, OP., & van Lith, JM. (2000). Co-variables in first trimester maternal serum screening. *Prenatal diagnostics*, Vol.20, No. 5, (May 2000), pp. 186-189.

El Kateb, A., Nasr, B., Nassar, M., Bernard, JP., & Ville, Y. (2007). First-trimester ultrasound examination and the outcome of monochorionic twin pregnancies. *Prenat Diagn*, Vol.27, No.10, (October 2007), pp. 922-5.

Engels, MA., Kooij, M., Schats, R., Twisk, JW., Blankenstein, MA., & van Vugt, JM. (2010). First-trimester serum marker distribution in singleton pregnancies conceived with assisted reproduction. *Prenat Diagn,* Vol.30, No.4, (April 2010), pp.372-7.

Frishman, GN., Canick, JA., Hogan, JW., Hackett, RJ., Kellner, LH., & Saller, DN Jr. (1997). Serum triple-marker screening in in-vitro fertilization and naturally conceived pregnancies. *Obstet Gynecol,* Vol.90, No.1, (July 1997), pp. 98–101.

Gagnon, A., Wilson, RD., & Audibert, F. (2008). Obstetrical complications associated with abnormal maternal serum markers analytes. *Journal Obstet Gynaecol Can*. Vol.30, No.10 (October 2008), pp. 918-949.

Geipel, A., Gembruch, U., Ludwig, M., Germer, U., Schwinger, E., Dormeier, A., & Diedrich, K. (1999). Genetic sonography as the preferred option of prenatal diagnosis in patients with pregnancies following intracytoplasmic sperm injection. *Hum Reprod,* Vol.14, No.10, (October 1999), pp. 2629–2634.

Geipel, A., Berg, C., Katalinic, A., Ludwig, M., Germer, U., Diedrich, K., & Gemburch, U. (2004). Different preferences for prenatal diagnosis in pregnancies following assisted reproduction versus spontaneous conception. *Reprod Biomed Online*, Vol.8, No. 1, (January 2004), pp.119-124.

Ghisoni, L., Ferrazzi, E., Castagna, C., Levi Setti, PE., Masini, AC., & Pigni, A. (2003). Prenatal diagnosis after ART success: the role of early combined screening tests in counselling pregnant patients. *Placenta*, Vol.24, No. Suppl B, (October 2003), pp.99-103.

Gjerris, AC., Loft, A., Pinborg, A., Christiansen, M., & Tabor, A. (2008). Prenatal testing among women pregnant after assisted reproductive techniques in Denmark 1995-2000: a national cohort study. *Hum Reprod*, Vol.23, No.7, (July 2008), pp. 1545-1552.

Gjerris, AC., Loft, A., Pinborg, A., Christiansen, M., & Tabor, A. (2009). First trimester screening markers are altered in pregnancies conceived after IVF/ICSI. *Ultrasound Obstet Gynecol,* Vol.33, No.1, (January 2009), pp. 8-17.

Goetzinger, KR., Cahill, AG., Macones, GA., & Odibo, AO. (2010) Association of first trimester low PAPP-A levels with pretesm birth. *Prenatal Diagnosis,* Vol.30, No.4, (April 2010), pp. 309-313.

Goncé, A., Borrell, A., Fortuny, A., Casals, E., Martínez, MA., Mercadé, I., Cararach, V., & Vanrell, JA. (2005). First-trimester screening for trisomy 21 in twin pregnancy: does the addition of biochemistry make an improvement? *Prenat Diagn.* Vol.25, No. 12, (December 2005), pp. 1156-61.

Helmerhorst, FM., Perquin, DA., Donker, D., & Keirse, MJ. (2004). Prenatal outcome of singletond and twins after assisted conception: a systematic review of controlled studies. *BMJ*, Vol. 328, No. 7434, (January 2004), pp. 261-265.

Henningsen, AK., Pinborg, A., Lidegaard, O., Vestergaard, C., Forman, JL., & Andersen, AN. (2011). Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception: Danish national sibling-cohort study. *Fertil Steril*, Vol.95, No.3, (March 2011), pp. 959-963.

Hui, PW., Lam, YH., Tang, MH., Ng, EH., Yeung, WS., & Ho, PC. (2005). Maternal serum pregnancy-associated plasma protein-A and free beta-human chorionic gonadotrophin in pregnancies conceived with fresh and frozen-thawed embryos from in vitro fertilization and intracytoplasmic sperm injection. *Prenat Diagn*, Vol.25, No.5, (May 2005), pp.390–393.

Hui, PW., Tang, MH., Ng, EH., Yeung, WS., & Ho, PC. (2006). Nuchal translucency in dichorionic twins conceived after assisted reproduction. *Prenatal Diagn,* Vol.26, No.6, (June 2006), pp.510-3.

Kagan, KO., Gazzoni, A., Sepulveda-Gonzalez, G., Sotiriadis, A., & Nicolaides, KH. (2007). Discordance in nuchal translucency thickness in the prediction of severe twin-to-twin transfusion syndrome. *Ultrasound Obstet Gynecol*, Vol.29, No.5, (June 2007), pp.527-32.

Kagan, KO., Wright, D., Spencer, K., Molina, FS., & Nicolaides, KH. (2008). First-trimester screening for trisomy 21 by free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A: impact of maternal and pregnancy characteristics. *Ultrasound Obstet Gynecol* ,Vol.31, No.6, (June 2008), pp.493-502.

Kagan, KO., Staboulidou, I., Cruz, J., Wright, D., & Nicolaides, KH. (2010). Two-stage first-trimester screening for trisomy 21 by ultrasound assessment and biochemical testing. *Ultrasound Obstet Gynecol*, Vol.36, No.5, (November 2010), pp.542-7.

Jozwiak, EA., Ulug, U., Mesut, A., Erden, HF., & Bahcecim M. (2004). Prenatal karyotypes of fetuses conceived by intracytoplasmic sperm injection. *Fertil Steril,*Vol.82, No.3, (September 2004), pp.628–633.

Laigaard, J., Sørensen, T., Fröhlich, C., Pedersen, BN., Christiansen, M., Schiøtt, K., Uldbjerg, N., Albrechtsen, R., Clausen, HV., Ottesen, B., & Wewer, UM. (2003). ADAM12: a novel first-trimester maternal serum marker for Down syndrome. *Prenat Diagn.* Vol.23, No.13, (December 2003), pp.1086-91.

Laigaard, J., Pedersen, NG., Larsen, SO., Hedley, PL., Wøjdemann, K., Gjerris, AC., Shalmi, AC., Sundberg, K., Tabor, A., & Christiansen, M. (2009). ADAM12 in first trimester maternal serum from pregnancies conceived by assisted reproduction techniques (ART). *Prenat Diagn*, Vol.29, No.6, (June 2009), pp.628-9.

Lambert-Messerlian, G., Dugoff, L., Vidaver, J., Canick, JA., Malone, FD., Ball, RH., Comstock CH., Nyberg, DA., Saade, G., & Eddleman, K., et al. (2006). First- and

second-trimester Down syndrome screening markers in pregnancies achieved through assisted reproductive technologies (ART): a FASTER trial study. *Prenat Diagn,*Vol.26, No. 8, (August 2006), pp.672–678.

Liao, AW., Heath, V., Kametas, N., Spencer, K., & Nicolaides, KH. (2001). First-trimester screening for trisomy 21 in singleton pregnancies achieved by assisted reproduction. *Hum Reprod,* Vol.16, No.7, (July 2001), pp. 1501–1504.

Linskens, IH., Spreeuwenberg, MD., Blankenstein, MA., & van Vugt, JM. (2009). Early first-trimester free beta-hCG and PAPP-A serum distributions in monochorionic and dichorionic twins. *Prenat Diagn,*Vol.29, No.1, (January 2009), pp.74-78.

Matilainen, M., Peuhkurinen, S., Laitinen, P., Jarvela, I., Morin-Papunen, L., & Ryynanen, M. (2011). In combined first-trimester Down syndrome screening, the false-positive rate is not higher in pregnancies conceived after assisted reproduction compared with spontaneous pregnancies. Fertil Steril, Vol.95, No. 1, (January 2011), pp.378-81.

Maymon, R., Dreazen, E., Tovbin, Y., Bukovsky, I., Weinraub, Z., & Herman, A. (1999). The feasibility of nuchal translucency measurement in higher order multiple gestations achieved by assisted reproduction. *Hum Reprod* Vol.14, No.8, (August 1999), pp. 2102–2105.

Maymon, R., Jauniaux, E., Holmes, A., Wiener, YM., Dreazen, E., & Herman, A. (2001). Nuchal translucency measurement and pregnancies outcomes after assisted conception versus spontaneously conceived twins. *Hum Reprod,* Vol.16: No.9, (September 2001), pp.1999-2004.

Maymon, R., & Shulman, A. (2002). Serial first- and second trimester Down's syndrome screening tests among IVF-versus naturally –conceived singletons. *Hum Reprod,* Vol.17, No.4, (April 2002), pp. 1081-1085.

Maymon, R., & Shulman, A. (2004). Integrated first- and second-trimester Down syndrome screening test among unaffected IVF pregnancies. *Prenat Diagn,* Vol.24, No.2, (February 2004), pp.125–129.

Maymon, R., Neeman, O., Shulman, A., Rosen, H., & Herman, A. (2005). Current concepts of Down syndrome screening tests in assisted reproduction twin pregnancies: another double trouble. *Prenat Diagn,* Vol.25, No.9, (September 2005), pp.746-50.

Meschede, D., Lemcke, B., Stussel, J., Louwen, F., & Horst, J. (1998). Strong preference for non-invasive prenatal diagnosis in women pregnant through intracytoplasmic sperm injection (ICSI). *Prenat Diagn*, Vol.89, No 7. (July 1998), pp.248-251.

Nicolaides KH. (2004). Nuchal translucency and other first-trimester sonographic markers on chromosomal abnormalities. *Am J Obstet Gynecol,* Vol.191, No.1 (July 2004), pp. 45-67.

Nicolaides, KH., Spencer, K., Avgidou, K., Faiola, S., & Falcon, O. (2005). Multicenter study of first-trimester screening for trisomy 21 in 75 821 pregnancies: results and estimation of the potential impact of individual risk-orientated two-stage first-trimester screening. *Ultrasound Obstet Gynecol, Vol.*25, No. 3, (March 2005), pp. 221–226.

Niemimaa, M., Heinonen, S., Seppala, M., Hippelainen, M., Martikainen, H.,& Ryynanen, M. (2001). First-trimester screening for Down's syndrome in in vitro fertilization pregnancies. *Fertility & Sterility.*Vol.76, No.6, (December 2001), pp.1282-3.

Niemimaa, M., Heinonen, S., Seppala, M., & Ryynanen, M. (2003). The influence of smoking on the pregnancy-associated plasma protein A, free beta human chorionic gonadotropin and nuchal translucency. *BJOG,* Vol.110, No.7, (July 2003), pp.664-667.

Oddens, BJ., den Tonkelaar, I., & Nieuwenhuyse, H. (1999). Psychosocial experiences in women facing fertility problems--a comparative survey. *Hum Reprod*. Vol.14, No.1, (January 1999), pp.225-61.

Orlandi, F., Rossi, C., & Allegra, A. et al. (2002). First trimester screening with free beta-hCG, PAPP-A and nuchal translucency in pregnancies conceived with assisted reproduction. *Prenat Diagn*, Vol.22, No.8, (August 2002), pp.718-721.

Pandya, PP., Hilbert, F., Snijders, RJ., & Nicolaides, KH. (1995). Nuchal translucency thickness and crown-rump length in twin pregnancies with chromosomally abnormal fetuses. *J Ultrasound Med* Vol.14, No.8, (August 1995), pp. 565–568.

Papageorghiou, AT., & Leslie, K. (2007). Uterine artery Doppler in the prediction of adverse pregnancy outcome. *Current Opinion of Obstetrics and Gynaecology.* Vol.19, No.2, (April 2007), pp. 103-109.

Pihl, K., Larsen, T., Krebs, L., & Christiansen, M. (2008). First trimester maternal serum PAPP-A, beta-hCG and ADAM12 in prediction of small-for-gestational-age foetuses. *Prenatal Diagnosis*. Vol.28, No.12, (December 2008), pp.1131-1135.

Pinborg, A., Loft, A., Rasmussen, S., Schmidt, L., Langhoff-Roos, J., Greisen, G., & Andersen, AN. (2004). Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10,362 non-IVF/ICSI twins born between 1995 and 2000. *Hum Reprod* Vol.19, No.2, (February, 2004), pp. 435–441.

Raty, R., Virtanen, A., Koskinen, P., Anttila, L., Forsstrom, J., Laitinen, P., Morsky, P., Tiitinen, A., & Ekblad, U. (2002). Serum free beta-HCG and alphafetoprotein levels in IVF, ICSI and frozen embryo transfer pregnancies in maternal mid-trimester serum screening for Down's syndrome. *Hum Reprod,* Vol.17, No.2, (February 2002), pp.481–484.

Ribbert, LS., Kornman, LH., De Wolf, BT., Simons, AH., Jansen, CA., Beekhuis, JR., & Mantingh, A. (1996). Maternal serum screening for fetal Down syndrome in IVF pregnancies. *Prenat Diagn,* Vol.16, No. 1, (January 1996), pp.35–38.

Schover, LR., Thomas, AJ., Falcone, T., Attaran, M., & Goldberg, J. (1998). Attitudes about genetic risk of couples undergoing in-vitro fertilization. *Hum Reprod*, Vol.13, No.4, (April 1998), pp.862-866.

Sebire, NJ., Snijders, RJ., Hughes, K., Sepulveda, W., & Nicolaides, KH. (1996). Screening for trisomy 21 in twin pregnancies by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation. *Br J Obstet Gynaecol* Vol.103, No.10, (October 1996), pp. 999–1003.

Sepulveda, W. (1997). Chorionity determination in twin pregnancies; double trouble. *Ultrasound Obtet Gynecol.* Vol.10, No.2, (August 1997), pp.79-81.

Snijders, RJ., Noble, P., Sebire, N., Souka, A., & Nicolaides, KH. (1998). UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. *Lancet* Vol.352, No.9125, (August 1998), pp. 343–346.

Spencer, K., Macri, JN., Aitken, DA., & Connor, JM. (1992). Free beta-hCG as first-trimester marker for fetal trisomy. *Lancet,* Vol.339, No.8807, (June 19992), pp.1480.

Spencer, K. (1999). The influence of smoking on maternal serum PAPP-A and free beta-hCG levels in the first trimester of pregnancy. *Prenatal diagnostics*, Vol.19, No.11, (November 1999), pp.1065-1066.

Spencer, K., Souter, V., Tul, N., Snijders, R., & Nicolaides, KH. (1999). A screening program for trisomy 21 at 10–14 weeks using fetal nuchal translucency, maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A. *Ultrasound Obstet Gynecol* Vol.13, No.4, (April 1999), pp. 231-237.

Spencer K. (2000). Screening for trisomy 21 in twin pregnancies in the first trimester using free *β*-hCG and PAPP-A combined with fetal nuchal translucency thickness. *Prenat Diagn,* Vol.20, No.2, (February 2000), pp.91–95.

Spencer, K., Spencer, CE., Power, M., Dawson, C., & Nicolaides, KH. (2003a). Screening for chromosomal abnormalities in the first trimester using ultrasound and maternal serum biochemistry in a one stop clinic: a review of three years prospective experience. *BJOG,* Vol.110, No.3, (March 2003), pp.281–286.

Spencer, K., Bindra, R., & Nicolaides, KH. (2003b). Maternal weight correction of maternal serum PAPP-A and free beta-hCG MoM when screening for trisomy 21 in the first trimester of pregnancy. *Prenat Diagn,Vol.*23, No. 10, (October 2003), pp. 851–855.

Spencer, K., & Nicolaides, KH. (2003c). Screening fot trisomy 21 in twins using first trimester ultrasound and maternal serum biochemistry in a one-stop clinic: a review of three years experience. Br J Obstet Gynaecol Vol.110, No.3, (March 2003), pp.276-280.

Spencer, K. (2003). Aneuploidy screening in the first trimester. *AmJ med Genet C Semin Med Genet* Vol.145, No.1, (April 2003), pp.18-32.

Spencer, K., & Cowans, NJ. (2007). ADAM12 as a marker of trisomy 18 in the first and second trimester of pregnancy. *J Mater Fetal Neonatal Med* Vol.20, No.9, (April 2007), pp.645-650.

Spencer, K., Kagan, KO., & Nicolaides, KH. (2008). Screening for trisomy 21 in twin pregnancies in the first trimester: an update of the impact of chorionicity on maternal serum markers. *Prenat Diagn.* Vol.28, No.1, (January 2008), pp.49-52.

Spencer, K., Staboulidou, I., & Nicolaides, KH. (2010). First trimester aneuploidy screening in the presence of a vanishing twin: implications for maternal serum markers. *Prenatal Diagnosis.* Vol.30, No.3, (March 2010), pp.235-240.

Tul, N. & Novak-Antolic, Z. (2006). Serum PAPP-A levels at 10-14 weeks of gestation are altered in women after assisted conception. *Prenat Diagn*, Vol.26, No.13, (December 2006), pp.1206-1211.

Vandecruys, H., Faiola, S., Auer, M., Sebire, N., & Nicolaides, KH. (2005). Screening for trisomy 21 in monochorionic twins by measurement of fetal nuchal translucency thickness. *Ultrasound Obstet Gynecol*. Vol.25, No.6, (June 2005), pp.551-3.

Wald, NJ., Cuckle, HS., Densem, JW., Nanchahal, K., Royston, P., Chard, T., Haddow, JE., Knight, GJ., Palomaki, GE., & Canick, JA. (1988). Maternal serum screening for Down's syndrome in early pregnancy. *BMJ* Vol.297, No. 6657, (October 1998), pp. 883-887.

Wald, NJ., White, N., Morris, JK., Huttly, WJ., & Canick, JA. (1999). Serum markers for Down's syndrome in women who have had in vitro fertilisation: implications for antenatal screening. *BJOG* Vol.106, No.12, (December 1999), pp.1304–1306.

Wald, NJ., Rodeck, C., Hackshaw, AK., Walters, J., Chitty, L., & Mackinson, AM. (2003). First and second trimester antenatal screening for Down's syndrome: the results of the

Serum, Urine and Ultrasound Screening Study (SURUSS*). J Med Screen.* Vol.10, No.2, pp.56-104.

Weisz, B.,& Rodeck, CH. (2006). An update on antenatal screening for Down's syndrome and specific implications for assisted reproduction pregnancies. *Hum Reprod Update* Vol.12, No.5, (September-October 2006), pp. 513-518.

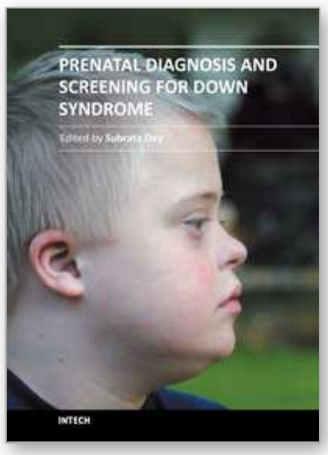
Williams, C., & Sutcliffe, A. (2009). Infant outcomes of assisted reproduction assisted repsoduction. *Early Hum Dev.* Vol.85, No.11, (November 2009), pp. 673-677.

Wenstrom, KD., Syrop, CH., Hammitt, DG., & Van Voorhis, BJ., (1993). Increased risk of monochorionic twinning associated with assisted reproduction. *Fertil Steril,* Vol. 60, No.3, (September 1993),pp.510-514.

Wojdemann, KR., Larsen, SO., Shalmi, A., Sundberg, K., Christiansen, M., & Tabor, A. (2001). First trimester screening for Down syndrome and assisted reproduction: no basis for concern. *Prenat Diagn,* Vol.21, No.7, (July 2001), pp. 563-565.

Wojdemann, KR., Shalmi, AC., Christiansen, M., Larsen, SO., Sundberg, K., Brocks, V., Bang, J., Norgaard-Pedersen, B., & Tabor, A. (2005). Improved first-trimester Down syndrome screening performance by lowering the false-positive rate: a prospective study of 9941 low risk women. *Ultrasound Obstet Gynecol* Vol.25, No.3, (March 2005), pp. 227-233.

Zhong, Y., Bradshaw, R., Stanley, AP., & Odibo, AO. (2010). The impact of assisted reproduction technology on the association between first-trimester pregnancy-associated plasma protein-A and human chorionic gonadotropin and adverse pregnancy outcomes. *Am J Perinatol* Vol.28, No.5, (May 2011), pp. 347-354).



Prenatal Diagnosis and Screening for Down Syndrome
Edited by Prof. Subrata Dey

ISBN 978-953-307-355-2
Hard cover, 232 pages
Publisher InTech
Published online 17, August, 2011
Published in print edition August, 2011

This book provides a concise yet comprehensive source of current information on Down syndrome. Research workers, scientists, medical graduates and paediatricians will find it an excellent source for reference and review. This book focuses on exciting areas of research on prenatal diagnosis - Down syndrome screening after assisted reproduction techniques, noninvasive techniques, genetic counselling and ethical issues. Whilst aimed primarily at research worker on Down syndrome, we hope that the appeal of this book will extend beyond the narrow confines of academic interest and be of interest to a wider audience, especially parents and relatives of Down syndrome patients.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen