Assisted Reproductive Technology and Pregnancy Outcome

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OBJECTIVE: To determine whether the use of assisted reproductive technology (ART) is associated with an increase in chromosomal abnormalities, fetal malformations, or adverse pregnancy outcomes.

METHODS: A prospective database from a large multicenter investigation of singleton pregnancies, the First And Second Trimester Evaluation of Risk trial, was examined. Subjects were divided into 3 groups: no ART use, use of ovulation induction (with or without intrauterine insemination), and use of in vitro fertilization (IVF). Multivariate logistic regression analysis was used to assess association between ART and adverse pregnancy outcomes (significance of differences was accepted at $P < .05$).

RESULTS: A total of 36,062 pregnancies were analyzed : 34,286 (95.1%) were spontaneously conceived, 1,222 (3.4%) used ovulation induction, and 554 (1.5%) used IVF. There was no association between ART and fetal growth restriction, aneuploidy, or fetal anomalies after adjustment for age, race, marital status, years of education, prior preterm delivery, prior fetal anomaly, body mass index, smoking history, and bleeding in the current pregnancy. Ovulation induction was associated with a statistically significant increase in placental abruption, fetal loss after 24 weeks, and gestational diabetes after adjustment. Use of IVF was associated with a statistically significant increase in preeclampsia, gestational hypertension, placental abruption, placenta previa, and risk of cesarean delivery.

CONCLUSION: Patients who undergo IVF are at increased risk for several adverse pregnancy outcomes. Although many of these risks are not seen in patients undergoing ovulation induction, several adverse pregnancy outcomes are still increased in this group. There was no increased incidence of fetal chromosomal or structural abnormalities in the women who used any type of ART compared with the women who conceived spontaneously.
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LEVEL OF EVIDENCE: II-2

The use of assisted reproductive technology (ART) is a highly successful and widely employed modality for the treatment of infertility. In 2001, more than 40,000 infants were born as a result of ART therapy, which represents 1% of the births in the United States.[1] Despite the success of ART, there is concern regarding both the safety of ART and its effect on maternal and fetal well-being. It is well-recognized that ART procedures significantly increase the risk of multiple gestations, both monochorionic and dichorionic, with the associated risks attributed to these pregnancies.[2] Additionally, some studies have suggested an increased risk of chromosome abnormalities, low birthweight, and preterm delivery in singletons.[3–6] Small studies have also suggested an association between the use of IVF and birth defects, adverse neurodevelopmental outcomes, preeclampsia, perinatal mortality, placenta previa, and an increased rate of cesarean delivery.[7–13]

Data derived from ART registries only provide results for overall pregnancy outcomes such as birth

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weight and number of multiple gestations. Limited data are available to describe patterns of anomalies and other adverse obstetric outcomes.[10] The few studies available are retrospective registry reviews, which exclude data regarding outcome with ovulation induction. Also, many prior studies fail to control for past obstetric history or other relevant variables. Our objective was to prospectively assess the effect of ART on the outcome of singleton pregnancies and to differentiate the effect of both IVF and ovulation induction.

PATIENTS AND METHODS

The First And Second Trimester Evaluation of Risk (FASTER) trial, a National Institute of Child Health and Human Development–sponsored study, is a prospective multicenter investigation of singleton pregnancies enrolled from an unselected obstetric population. The study was undertaken from 1999 to 2002 and was approved by the institutional review boards at each of the participating centers. The study provided noninvasive assessment of Down syndrome risk using evaluation of first trimester nuchal translucency sonography, together with first and second trimester serum markers. A database was created containing detailed antenatal, birth, and pediatric outcomes on all enrolled patients.

Patients were enrolled into the FASTER trial at 10 3/7 to 13 6/7 weeks of gestation, at which time baseline demographic data and medical histories were recorded. Postdelivery follow-up was performed by telephone interview, personal interview, or medical record review by a trained research coordinator at each site. A purpose-designed computerized tracking system with up to 10 contacts per subject was used to ensure optimal outcome collection for all enrolled patients. In addition, a single perinatologist and a pediatric geneticist reviewed detailed maternal and pediatric medical records for the following patient subsets: all patients with abnormal first or second trimester screening, all pregnancies with adverse pediatric outcome, and 10% of normal subjects randomly selected at each site from the trial database.

For this analysis, women who elected to terminate their pregnancy before term for any reason were excluded. Patients were then categorized into 3 mutually exclusive groups: those who underwent an invasive ART procedure in this pregnancy, including the use of in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer or zygote intrafallopian transfer (n = 554), women who used a noninvasive ART procedure only, such as ovulation induction or intrauterine insemination (n = 1,222); and control patients who did not undergo any ART procedure (n = 34,286).

The following adverse pregnancy outcomes were then evaluated: spontaneous fetal loss before 24 weeks, fetal loss or demise after 24 weeks, fetal growth restriction (estimated fetal weight by ultrasound below the 10th centile or birthweight below the 10th centile for gestational age), low birth weight (less than 2,500 g), gestational hypertension (blood pressure > 140/90 on at least 2 occasions more than 6 hours apart without evidence of chronic hypertension), preeclampsia (criteria for gestational hypertension and significant proteinuria), preterm labor (before 37 weeks of gestation), preterm premature rupture of membranes (membrane rupture before 37 weeks of gestation), placental abruption (premature separation of a normally implanted placenta), placenta previa (placenta completely or partially covering the internal os), gestational diabetes (a minimum of 2 abnormal values on a 3-hour glucose tolerance test after a 100-g oral glucose load), cesarean delivery, fetal aneuploidy, and congenital anomalies (major or minor, confirmed at birth).

The effects of both invasive and noninvasive ART use were investigated simultaneously for each of the pregnancy outcomes. Crude and adjusted effects were estimated using multivariate logistic regression, and odds ratios (ORs), together with 95% confidence intervals (CIs), were calculated to quantify the effect.

Confounding variables for the adjusted models were selected in a 2-stage process. First, a series of statistical tests were performed to assess relationships of selected patient characteristics with ART use and each adverse pregnancy outcome. Tests included analysis of variance for continuous confounders and χ^2 tests for categorical confounders. Confounders that were significantly ($P < .05$) associated with either ART use or the given adverse outcomes were considered in the next stage. The list of potential confounders was further reduced using multivariate logistic regression modeling and a backward elimination stepwise regression approach, keeping only those variables that were significant at $P < .05$.

In the final adjusted models, the following variables were considered as confounders: maternal age, maternal race, marital status, years of education, prior preterm delivery, prior pregnancy with anomaly, body mass index, smoking history, and bleeding in the current pregnancy.

Adjusted odds ratios with 95% confidence intervals were calculated to approximate relative risks of adverse outcomes. A P value of less than .05 was considered statistically significant (ie, the 95% confi-

dence intervals were calculated, and were considered significant if they did not include 1.0). However, due to the large sample size, statistical analysis was powerful enough to detect differences in risk between the ART groups that were statistically significant but where the actual size of the difference was small. In some cases the differences might be so small that they are not clinically meaningful. Therefore, since OR describes the magnitude of the effect between groups, an odds ratio cutoff of greater than 2.0 was selected to represent clinically meaningful risk to emphasize those outcomes with a marked association with invasive or noninvasive ART. All analyses were conducted using SAS 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

Complete obstetric and pediatric outcome data were available for 36,062 pregnancies for this analysis. The control group consisted of 34,286 (95.1%) patients who did not use any form of ART. A total of 1,222 (3.4%) patients used ovulation induction, and 554 (1.5%) underwent IVF (including gamete intrafallopian transfer or gamete intrafallopian transfer and zygote intrafallopian transfer or zygote intrafallopian transfer). Because only 33 patients reported use of ICSI, this group was not examined separately. The demographic characteristics of the 3 groups are summarized in Table 1. Those patients undergoing ART were significantly older, were more likely to be married, and had more years of education.

The overall incidences of pregnancy complications in this population are shown in Table 2. Multivariate analysis was then performed to calculate adjusted odds ratios for these adverse outcomes. The obstetric outcomes for patients undergoing ovulation induction and those using IVF are compared in Table 3 to patients who did not use ART. Patients who underwent ovulation induction were 2.4 times more likely to have a placental abruption (95% CI 1.3–4.2) and 2.1 times more likely to have a fetal loss after 24 weeks (95% CI 1.3–3.6) compared with controls. A significant association between the use of IVF and several adverse pregnancy outcomes was also noted. Patients using IVF were 2.7 times more likely to develop preeclampsia (95% CI 1.7–4.4), 2.4 times more likely to have a placental abruption (95% CI 1.1–5.2), 6.0 times more likely to have a placenta previa (95% CI 3.4–10.7), and 2.3 times more likely to undergo a cesarean delivery (95% CI 1.8–2.9) compared with controls. We did not observe an increase in the incidence of aneuploidy or congenital anomalies in patients undergoing IVF.

Although a statistically significant increase in the incidence of gestational hypertension in patients undergoing IVF and in the incidence of gestational diabetes in patients undergoing ovulation induction was noted, these findings did not meet criteria for achieving clinical significance, because the odds ratios were less than 2.0.

DISCUSSION

Despite the widespread and increasing use of assisted reproductive technologies, there are few prospective

Table 1. Use of Assisted Reproductive Technology and Pregnancy Outcome: Demographics of Population

Characteristic	No ART (n = 34,286)	Ovulation Induction (n =1,222)	IVF (n = 554)	*P*
Age (y)	29.9 (±5.7)	32.6 (±5.1)	34.5 (±5.2)	< .001
Race				< .001
African American	5.3	1.6	2.7	
Hispanic	23.3	4.5	4.5	
White	66.6	88.6	86.3	
Other	4.9	5.2	6.5	
Education (y)	14.2 (±2.6)	15.6 (±1.6)	16.1 (±1.3)	< .001
Marital status				< .001
Single	21.0	7.1	3.4	
Married	77.8	92.0	96.4	
Divorced	1.2	0.7	0	
Other	0.1	0.2	0.2	
Previous pregnancy (multiparous)	55.9	37.2	26.6	< .001
Prior preterm delivery	6.8	5.4	5.1	.048
Prior pregnancy with anomaly	3.6	7.4	12.0	< .001
Body mass index	25.0 (±5.3)	25.2 (±5.4)	24.4 (±4.8)	.009
Bleeding in pregnancy	14.0	15.8	28.8	< .001
Smoking	4.9	1.6	1.4	< .001

ART, assisted reproductive technology; IVF, in vitro fertilization.
Values are % or mean (± standard deviation).

Table 2. Incidence of Pregnancy Complications and Pediatric Outcomes

Outcome	No ART (n = 34,286)	Ovulation Induction (n = 1,222)	IVF (n = 554)	*P*
Spontaneous fetal loss (< 24 wk)	0.3	0.4	0.2	.73
Fetal loss or demise (> 24 wk)	0.9	1.6	1.1	.09
Fetal growth restriction	1.1	2.1	0.9	.005
Gestational hypertension	4.6	5.8	6.4	.03
Preeclampsia	2.4	3.3	4.7	.001
Preterm labor	5.2	6.5	6.9	.03
PPROM	1.6	1.9	2.2	.42
Placental abruption	0.7	1.4	2.2	< .001
Placenta previa	0.6	0.5	3.6	< .001
Gestational diabetes	3.4	5.9	2.7	< .001
Cesarean delivery	23.6	26.2	47.2	< .001
Aneuploidy	0.4	0.3	0.4	.98
Congenital anomalies	1.9	2.3	3.5	.02
Low birth weight	5.1	7.4	5.9	.002

ART, assisted reproductive technology; IVF, in vitro fertilization; PPROM, preterm premature rupture of membranes.
Values are %.

Table 3. Adverse Pregnancy Outcomes: Comparison With Control Patients

Outcome	Ovulation Induction Compared With No ART [Adjusted OR (95%CI)]	*P*	IVF Compared With No ART [OR (95% CI)]	*P*
Spontaneous fetal loss (< 24 wk)	1.6 (0.6–4.4)	.37	0.8 (0.1–5.6)	.80
Fetal loss or demise (> 24 wk)	2.1 (1.3–3.6)	.005	0.9 (0.3–2.4)	.78
Fetal growth restriction	1.5 (0.8–2.8)	.23	0.57 (0.1–2.2)	.39
Low birthweight	1.3 (1.0–1.8)	.09	0.9 (0.5–1.5)	.64
Gestational hypertension	0.8 (0.5–1.2)	.31	1.6 (1.0–2.5)	.036
Preeclampsia	1.1 (0.6–1.8)	.85	2.7 (1.7–4.4)	< .001
Preterm labor	1.1 (0.8–1.5)	.56	1.5 (1.0–2.2)	.07
PPROM	1.0 (0.5–1.8)	.93	1.1 (0.5–2.2)	.84
Placental abruption	2.4 (1.3–4.2)	.003	2.4 (1.1–5.2)	.03
Placenta previa	0.9 (0.3–2.3)	.75	6.0 (3.4–10.7)	< .001
Gestational diabetes	1.5 (1.1–2.2)	.01	0.5 (0.2–1.0)	.06
Cesarean delivery	1.1 (0.9–1.3)	.26	2.3 (1.8–2.9)	< .001
Aneuploidy	0.7 (0.2–2.1)	.48	0.4 (0.1–2.7)	.32
Congenital anomalies	1.1 (0.6–1.8)	.78	0.9 (0.4–2.0)	.78

ART, assisted reproductive technology; OR, odds ratio; CI, confidence interval; IVF, in vitro fertilization; PPROM, preterm premature rupture of membranes.
Adjusted odds ratios calculated after multivariate logistic regression analysis represent risk of treated group to experience outcome of interest compared with patients not undergoing any therapy.

studies published addressing the obstetric and pediatric outcomes with these therapies. Additionally, studies suggesting an increase in adverse outcomes such as congenital malformations are limited by small numbers and limited information on confounding variables.[9] A recent meta-analysis of a large number of IVF pregnancies suggested that such pregnancies are at increased risk for adverse perinatal outcome, including preterm delivery, low birthweight, placenta previa, gestational diabetes, preeclampsia, and neonatal intensive care admission.[9] The main strength of our study is that it incorporated a large number of ART pregnancies and collected prospectively from the general population, with appropriate controls. Our findings corroborate those of the recent meta-analysis, demonstrating a significant increase in hypertensive disorders, placental abnormalities such as placenta previa and placental abruption, and the incidence of cesarean delivery.

We estimated a 2.7-fold increased risk of preeclampsia in IVF pregnancies compared with controls. This association between IVF and preeclampsia has also been noted by other authors, including Jackson et al[9] in 2004, Wang et al[14] in 2002, Maman et al[15] in 1998, and Tan et al[11] in 1992. We have also shown an increased incidence of abnormal placentation with IVF use, including a 2.4-fold increased risk of placental abruption and a 6.0-fold increased risk of

placenta previa noted in IVF pregnancies compared with controls. This has also been substantiated by other authors, including Verlaenen et al[16] in 1995, Li et al[17] in 1996, Tan et al[12] in 1992, and Jackson et al[9] in 2004. Preeclampsia, placental abruption, and placenta previa are all related to abnormalities of location and function of the placenta. Therefore, when pregnancy and the formation of the chorion are initiated in vitro, an inherent difference in the nature of the placenta itself may predispose the patient to develop these conditions during gestation.

Previous authors have suggested an association between IVF use and increased cesarean delivery rate.[13,18] We found greater than a two-fold increase in the incidence of cesarean delivery in patients undergoing IVF. Although studies have linked advancing maternal age to the risk of cesarean delivery, this increase remained significant in our study after adjustment for maternal age and parity. Infertile women have been reported to be more anxious about the outcome of their pregnancies compared with women who conceive spontaneously.[19] It is possible, therefore, that the apparent increase in cesarean delivery rates may reflect patient and physician choice, rather than an inherent biologic abnormality in such pregnancies.

We did not observe an increased incidence of congenital malformations or fetal aneuploidy in the women who used ART to conceive. A recent study by Zadori et al[6] in 2003 reviewed outcomes of 301 neonates born as a result of IVF in a population of more than 12,900 deliveries and found no significant increase in the number of major birth defects. Additionally, in the United States, the Society for Assisted Reproductive Technology reported a prevalence of congenital malformations of 1.9% among patients undergoing IVF, which was similar to that seen in the general population. Retzloff and Hornstein[3] in 2003 performed an analysis of 11 major studies from 1996 to 2002 and concluded that the vast majority showed neither an increase in malformations nor clustering of any single specific major malformation in ICSI pregnancies. This finding is complemented by the work done by Bonduelle et al[20] in 2002, who studied 2,840 ICSI children and 2,955 IVF children in Brussels. This study found no significant difference in the malformation rate between ICSI and IVF pregnancies. However, our study contradicts the work of Hansen et al[7] in 2002, which found an increased incidence of major birth defects in IVF pregnancies with an overall adjusted odds ratio of 2.0. This study found that infants conceived with ART were more likely to have multiple major defects and were also more likely to have chromosomal abnormalities. However, increased diagnostic vigilance of the study population may have resulted in ascertainment bias given the low-risk nature of the control population.[21]

Additionally, prior work has suggested an association between use of ICSI and an increase in both autosomal and sex chromosome abnormalities.[22,23] This apparent association may be due to the known increase in prevalence of chromosomal abnormalities in both azoospermic and oligospermic men.[3] It is possible that any association between IVF use and fetal chromosomal abnormalities may be confined only to the subgroup of patients using ICSI. Although our study found no association between ART use overall and fetal chromosomal abnormalities, we had insufficient numbers of patients using ICSI to evaluate this subgroup individually. Also, not all of the FASTER infants had a chromosome analysis performed, so it is possible that there are FASTER infants who have a sex chromosome abnormality but do not know it. In fact, most cases of sex chromosome abnormalities go undiagnosed.

A report from the Centers for Disease Control and Prevention of IVF pregnancies from 1996 to 1997 suggested a 1.8-fold increased risk of low birth weight infants.[4] This study attempted to control for the confounding effects of multiple gestation on incidence of low birth weight, and the analysis was restricted to those singletons born of pregnancies that did not originate as multiple gestations. Similar findings for IVF singletons were also reported by Bergh et al[24] in 1999, who compared 5,856 ART children to 1,505,742 children born in the general population and found an odds ratio of 4.4 for delivery of a very low birth weight singleton. However, most recently, Schieve et al[11] in 2004 found that despite the report of their findings in 2002, from 1996–2000 in 62,551 infants born of IVF, the risk for term low birth weight was found to decline, with an overall standardized risk ratio of 1.62. Our study failed to demonstrate any association between ART and low birth weight. Our population of IVF pregnancies may not have been sufficiently large to detect a difference in birth weight. Alternatively, it is possible that earlier larger studies may have demonstrated statistical significance, but without clinical significance.

The current study objectively addresses the outcome of a subgroup of patients with "subfertility," requiring only ovulation induction rather than IVF. Nuojua-Huttunen et al[25] in 1999 studied 111 patients who underwent ovulation induction and found no change in obstetric or perinatal risk compared with controls. However, in another report by Gaudoin et al[26] in 2003, ovulation induction patients were 4.85

times more likely to have a LBW infant compared with controls. Although we did not find an increased incidence of low birthweight in this population, patients undergoing ovulation induction were 2.4 times more likely to have a placental abruption, and 2.1 times more likely to suffer a fetal loss after 24 weeks. In a study undertaken by Maman et al[15] in 1998, patients undergoing ovulation induction were also found to have a greater incidence of gestational diabetes, which may reflect an increased prevalence of polycystic ovary syndrome (PCOS) requiring therapy. This underlying metabolic instability may be linked to risk of abnormal placentation (abruption) and of fetal loss. Due to limitations of data collection regarding specific underlying causes for infertility in patients requiring ovulation induction, we cannot distinguish whether some of the abnormal outcomes seen here represent a preexisting disease process, such as PCOS, or are secondary to the ovulation induction therapy itself.[27] Despite the fact that there is a slight increase in adverse outcome for patients undergoing ovulation induction, as evidenced by the increase in fetal loss after 24 weeks, there still is a striking difference between complications rates between this group and patients undergoing IVF. This might imply that perhaps the state of subfertility or infertility itself may not be the cause of these adverse outcomes, but that these risks may be related to the process of in vitro fertilization itself.

It is unlikely that a single pathophysiologic approach is responsible for the wide range of adverse obstetric outcomes noted in this study, because the causes of infertility, both identified and unidentified, are broad. Some of the risks apparently associated with ART may be confounded by the nature and presence of infertility itself or by other associated underlying conditions, such as PCOS. A limitation of our study is that no data were collected on the particular cause of infertility, and therefore we cannot comment on how these different causes may affect outcomes. However, we feel that knowledge of an association between overall ART use and adverse pregnancy outcome will be useful for practitioners. The odds remain strong that infertile couples seeking to conceive through the use of assisted reproductive technology will have relatively uncomplicated pregnancies and healthy children. Clearly, however, there is an increased risk of adverse events in a subgroup of these patients, and the information provided here should prove useful when counseling prospective patients before embarking on fertility therapy.

Additionally, an increase in antenatal surveillance may be warranted in this population, including assessment for hypertensive complications and sonographic evaluation of the placenta. The possible associations between infertility, or its therapies, with a range of adverse obstetric outcomes should be discussed with prospective patients before embarking on fertility therapy. Clinicians caring for such patients should be aware of these possible associated adverse outcomes and may need to be vigilant for additional signs or symptoms of complications during antenatal care. However, we cannot conclude from our data whether any particular program of fetal surveillance is warranted or would cause any adverse outcome. It is important, however, for patients and clinicians to realize that although an extra level of surveillance may be warranted given the additional degree of risk, their chances of having a healthy child through ART are overall extremely high.

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APPENDIX

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