Perinatal outcomes after natural conception versus in vitro fertilization (IVF) in gestational surrogates: a model to evaluate IVF treatment versus maternal effects

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Objective: To study the perinatal outcomes between singleton live births achieved with the use of commissioned versus spontaneously conceived embryos carried by the same gestational surrogate.
Design: Retrospective cohort study.
Setting: Academic in vitro fertilization center.
Patient(s): Gestational surrogate.
Intervention(s): None.
Main Outcome Measure(s): Pregnancy outcome, gestational age at birth, birth weight, perinatal complications.
Result(s): We identified 124 gestational surrogates who achieved a total of 494 pregnancies. Pregnancy outcomes for surrogate and spontaneous pregnancies were significantly different ($P<.001$), with surrogate pregnancies more likely to result in twin pregnancies: 33% vs. 1%. Miscarriage and ectopic rates were similar. Of these pregnancies, there were 352 singleton live births: 103 achieved from commissioned embryos and 249 conceived spontaneously. Surrogate births had lower mean gestational age at delivery (38.8 ± 2.1 vs. 39.7 ± 1.4), higher rates of preterm birth (10.7% vs. 3.1%), and higher rates of low birth weight (7.8% vs. 2.4%). Neonates from surrogacy had birth weights that were, on average, 105 g lower. Surrogate births had significantly higher obstetrical complications, including gestational diabetes, hypertension, use of amniocentesis, placenta previa, antibiotic requirement during labor, and cesarean section.
Conclusion(s): Neonates born from commissioned embryos and carried by gestational surrogates have increased adverse perinatal outcomes, including preterm birth, low birth weight, hypertension, maternal gestational diabetes, and placenta previa, compared with singletons conceived spontaneously and carried by the same woman. Our data suggest that assisted reproductive procedures may potentially affect embryo quality and that its negative impact can not be overcome even with a proven healthy uterine environment. (Fertil Steril® 2017;108:993–8. ©2017 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technology, in vitro fertilization, gestational surrogacy, gestational carrier, perinatal outcome, embryo culture

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Past studies have consistently demonstrated that maternal infertility and treatments for infertility are associated with adverse pregnancy outcomes in singleton pregnancies. These include preeclampsia, low birth weight, preterm delivery, placental abruption, and fetal loss (1–5). Mechanisms for the association are unknown. It is thought that poor perinatal outcomes are a manifestation of dysfunctional placentation, which in the infertile population may be attributable to the egg from an infertile woman, the laboratory manipulation of the embryo, or the altered endometrial milieu from ovarian hyperstimulation.

According to Barker's fetal origins of adult disease hypothesis the fetus drives placentation and intrauterine growth (6),

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and nonhuman animal studies suggest that this fetal programming may be influenced by the quality of the oocyte (7). The effect of poor egg quality on obstetrical outcomes is evidenced by the well documented maternal age–related increase in risk for adverse perinatal outcomes (8). We would therefore expect an improvement in perinatal outcomes in donor-oocyte in vitro fertilization (DO-IVF) cycles, which are associated with young age of the oocyte donors and good egg quality. However, epidemiologic analyses reveal perinatal complications similar to those of autologous IVF, including increased rates of gestational diabetes, hypertensive disorders, placental abnormalities, preterm delivery, and caesarean delivery for patients with DO-IVF (9–13). These observations suggest two possibilities. First, that the aging uterine environment (endometrium) plays a more critical role than previously believed. Or second, that assisted reproductive technology (ART) procedures influence the quality of the embryo and subsequent perinatal outcome, regardless of the donor's age.

To better differentiate the influence of the ART-derived embryo and endometrium on perinatal outcomes, we studied a cohort of women who achieved pregnancy via gestational-surrogacy in vitro fertilization (GS-IVF). Because traditional surrogacy (use of the surrogate's own eggs and then carried by the same woman) is rarely implemented now because of ethical and legal concerns, our use of gestational surrogate in this manuscript is interchangeable with gestational carrier. Gestational surrogates preferably have a history of uncomplicated pregnancies and therefore are known to provide a healthy uterine environment; they represent an ideal model to investigate the contribution of the ART-derived embryo to pregnancy outcomes. Furthermore, the recipient's endometrial preparation, consisting of a combination of estrogen and progesterone supplementation, is designed to mimic the natural cycle (14).

Existing literature on perinatal outcomes after GS-IVF is sparse (15, 16). Some authors report lower rates of preeclampsia, low birth weight, and placental abruption in pregnancies achieved through gestational surrogacy compared with conventional IVF (17, 18), implying a protective role of a healthy carrier. However, no studies have compared perinatal outcomes of antecedent pregnancies achieved spontaneously among gestational surrogates with those achieved via ART-derived embryos in GS-IVF (commissioned pregnancies). Use of the gestational surrogate as her own control group allows proper evaluation of the embryo's influence on perinatal outcomes, because factors such as the endometrial environment and confounders specific to the carrier are held constant. We hypothesized that if adverse perinatal outcomes after IVF are primarily due to altered embryo quality, then it should be possible to observe an increase in adverse outcomes in commissioned pregnancies when compared with antecedent pregnancies.

We conducted a retrospective cohort study of women who achieved a live birth via gestational surrogacy and compared birth outcomes with their own spontaneously conceived children.

MATERIALS AND METHODS

This was a retrospective cohort analysis of perinatal outcomes among clinical pregnancies achieved through GS-IVF. Gestational surrogates who achieved clinical pregnancies from commissioned embryos from January 1995 to December 2010 were identified at two large California-based surrogacy agencies (Surrogate Parenting Services [Laguna Niguel] and Center for Surrogate Parenting [Encino]). We also identified gestational surrogates who achieved a clinical pregnancy from January 1990 to December 2014 at the University of Southern California Fertility Center (USC Fertility).

Clinical pregnancies were defined as intrauterine pregnancies with documented cardiac motion on ultrasound. Directors of the surrogacy agencies electronically mailed the informed consent and Health Insurance Portability and Accountability Act authorization forms to all gestational surrogates who met inclusion criteria.

USC Fertility patients who agreed to participate also received a secure electronic survey link. Data on perinatal outcomes were collected both by means of the electronic survey instrument and through a detailed review of medical records. Medical records were obtained from the gestational surrogacy agencies and from USC Fertility. All antecedent pregnancies that were spontaneously achieved by these women were included.

Clinical diagnosis of the different obstetrical and perinatal complications was based on the discretion of the primary obstetrical provider. Because there was a wide range of providers, specific definitions used to establish a diagnosis of obstetrical complication was not obtained and we assumed that standard of care was practiced.

Records were excluded when data on pregnancy outcome were missing in surrogate pregnancies and for higher-order multiples, multifetal selective reduction, and singletons resulting from spontaneous "vanishing twin syndrome." Data on donor egg use also were obtained on patients that had undergone GS-IVF at USC Fertility. All gestational surrogates underwent endometrial preparation with the use of estrogen and progesterone replacement designed to mimic the natural pattern of E_2 in the circulation. Institutional Review Board approval was met before starting the study.

Sample size was calculated assuming an alpha of 0.05, a drop-out rate of 30%, and 90% power to detect a difference of 9% in rates of preeclampsia between spontaneous pregnancies and gestational surrogacy pregnancies. This was based on a rate of preeclampsia in the general population of 3% (19) compared with the published preeclampsia rate in recipients of IVF egg donation of 12% (20). The required sample size was 309 clinical pregnancies.

Statistical analysis was performed with the use of Stata 14 (Statacorp). Perinatal outcome data were compared between surrogate births and births conceived spontaneously by the same woman. To account for correlation between birth outcomes to the same woman and difference in age, we fitted random-effects regression models (linear models for continuous outcomes and logistic models for dichotomous outcomes) with an exchangeable covariance structure, using mother as the random effect and type of birth (spontaneous vs. surrogate) as the explanatory variable. All statistical tests were two sided with a P value of .05 required for statistical significance.

RESULTS

We identified 124 gestational surrogates who achieved a total of 494 pregnancies (312 spontaneous, 182 surrogate). Demographics of the gestational surrogates are summarized in Table 1. Pregnancy outcomes for surrogate and spontaneous pregnancies were significantly different ($P \leq .001$), with spontaneously pregnancies more likely to have resulted in an elective abortion, although miscarriage and ectopic rates were similar (Table 2). Of the total live births achieved, surrogate pregnancies were significantly more likely to result in twin pregnancies: 32% vs. 1%; $P \leq .001$; Supplemental Table 1 (available online at www.fertstert.org).

Of these 494 clinical pregnancies, there were 352 singleton live births with complete data on birth weight and gestational age (71.3%; Table 3). One hundred three of these were achieved with the use of commissioned embryos via gestational surrogacy, and 249 were conceived spontaneously as previous births by the same women.

Surrogate births had lower mean gestational age at delivery (38.8 ± 2.1 wk vs. 39.7 ± 1.4 wk; $P < .001$), higher rates of preterm birth (10.7% vs. 3.1%; $P = .01$), and higher rates of low birth weight (7.8% vs. 2.4%; $P = .02$). Neonates from surrogacy had birth weights that were, on average, 105 g lower ($P = .03$; Table 3).

Surrogate births had significantly more obstetrical complications, including gestational diabetes, hypertension, use of amniocentesis, placenta previa, antibiotic requirement during labor, and cesarean sections (Table 4).

To determine if the effects seen in surrogate pregnancies were due to unknown effects of the infertility condition of the donors, we attempted to compare surrogate pregnancies between patients using autologous eggs versus donor eggs. However, egg donor information was known for only 29 pregnancies (17 donor eggs, 12 autologous eggs). Gestational age was similar for the two groups (38.2 ± 1.6 wk for donor eggs, 38.3 ± 2.5 wk for autologous eggs). Birth weight was 105 g less for donor eggs (3,269 ± 164 g) than for autologous eggs (3,375 ± 530 g), but the difference was not statistically significant.

TABLE 1

Demographics of gestational surrogates (n = 92 women with complete demographics).

Variable	Data
Age (y) at time of surrogacy	33.0 ± 4.7
Gravidity	2.6 ± 1.1
No. of children	2.3 ± 0.9
Race	
White	68
Asian	2
Hispanic	21
Black	3
Other	6
Marital status	
Single	15
Married	85
Highest level of education	
High school	39
College	56
Graduate school	15

Note: Data presented as mean ± standard deviation or percent.

Woo. Gestational surrogacy perinatal outcomes. Fertil Steril 2017.

TABLE 2

Pregnancy outcomes.[a]

Outcome	Surrogacy (n = 182)	Spontaneous (n = 312)
Live birth	177 (97)	277 (89)
Miscarriage	5 (3)	12 (4)
Elective abortion	0 (0)	21 (7)
Stillbirth	0 (0)	1 (<1)
Ectopic	0 (0)	1 (<1)

Note: Data presented as n (%).
[a] Fisher exact test, $P < .001$.

Woo. Gestational surrogacy perinatal outcomes. Fertil Steril 2017.

DISCUSSION

This is the first study to compare perinatal outcomes between live births achieved via ART and gestational surrogacy versus spontaneously conceived pregnancies in the same woman. The purpose of this study was to provide better insight into the influence of ART-derived embryos on perinatal outcomes. With the use of the same woman's antecedent pregnancies as controls for the commissioned pregnancies, factors such as the uterine environment and other confounders related to the carrier are kept constant.

Notably, our study shows that the neonates born from ART-derived embryos had lower mean gestational age, higher rates of preterm birth, and lower birth weights. In addition, the women were more likely to develop gestational diabetes and placenta previa and to deliver by means of cesarean section when carrying ART pregnancies versus their own spontaneously conceived neonates. This supports the theory that the processes involved with ART may have adverse effects on the development of the fetus.

Concerns regarding the potential impact of ART manipulation of gametes and in vitro culture of embryos are not new. Since the first infant in the United States conceived through ART was born in 1981, interests about the health of these neonates have been expressed by the scientific community (21, 22). In 1996, the Centers for Disease Control and

TABLE 3

Perinatal outcomes for singleton live births.

Outcome	Surrogacy (n = 103)	Spontaneous (n = 249)	*P* value
Gestational age (wk)	38.8 ± 2.1	39.7 ± 1.4	<.001
Preterm birth	11 (10.7)	8 (3.1)	.01
Birth weight (g)	3,436 ± 696	3,541 ± 504	.03
Low birth weight	8 (7.8)	6 (2.4)	.02

Note: Data presented as mean ± standard deviation or n (%).
There were 352 singleton live births with complete information regarding birth weight and gestational age.

Woo. Gestational surrogacy perinatal outcomes. Fertil Steril 2017.

TABLE 4

Obstetrical complications for singleton live births.

Complication	Surrogacy (n = 103)	Spontaneous (n = 249)	*P* value
Preeclampsia	2 (1.9)	3 (1.2)	.59
Hypertension	7 (6.8)	7 (2.81)	.03
Gestational diabetes	7 (6.8)	3 (1.2)	.01
Placenta previa	5 (4.9)	3 (1.2)	.05
Amniocentesis	7 (6.8)	0 (0)	<.001
Vaginal bleeding	3 (2.9)	5 (2.0)	.71
Meconium	1 (1.0)	8 (3.2)	.26
Antibiotics required in labor	5 (6.2)	1 (0.5)	.02
Emergency CS	3 (3.5)	6 (2.8)	.77
Total CS	19 (19.0)	18 (8.7)	.01
Postpartum hemorrhage	2 (19.4)	0 (0)	.09

Note: Data presented as n (%).
CS = cesarean section.

Woo. Gestational surrogacy perinatal outcomes. Fertil Steril 2017.

Prevention mandated data collection on ART procedures performed in fertility clinics to monitor outcomes of infants born via ART (23). There is some evidence that laboratory or medical procedures may play a role in the adverse perinatal outcome in ART singletons (24, 25). Specific laboratory procedures, such as incubator systems, type of embryo culture media, duration of culture, intracytoplasmic sperm injection (ICSI), and cryopreservation methods, all may introduce stress to the developing embryo. For example, studies have shown that growing embryos to blastocyst stage may be associated with an increased risk of monozygotic twinning (26, 27).

Evidence also suggests an effect of ART on epigenetics and gene expression. Environmental conditions can lead to modification of gene expression through epigenetic modification of the DNA. Inherent to the use of ART is the manipulation of the microenvironment surrounding the developing embryo. Controlled ovarian stimulation occurs during gametogenesis, ICSI or IVF at fertilization, and culture media and nutrition during early embryonic development; all may alter epigenetic reprograming and affect the fate of the embryo (28). Studies have shown alterations in DNA methylation status of imprinted genes (29), with the large offspring syndrome being the most notorious alteration in phenotype seen in animals produced by IVF (30, 31).

One strength of the present study is our use of antecedent pregnancies as controls to evaluate the effects of ART on human embryos. The use of controls from the general population would not account for laboratory and medical procedures or the effects of infertility on the uterine environment. In infertile patients, undiagnosed uterine factors may contribute to the adverse perinatal outcomes. In a gestational surrogate model, the woman has carried her own healthy pregnancies and thus proved that her uterus, the embryo's microenvironment, is optimal. By means of comparing spontaneously conceived pregnancies and commissioned pregnancies carried by the same women, we can control for the uterine environment and emphasize the contribution of ART techniques used to derive the commissioned embryos.

Women who have had one adverse outcome may be at higher risk of a subsequent adverse outcome. To account for correlated birth outcomes in a single woman, we included a random-effects term for the mother (gestational carrier) in the logistic model (32). This model controls for unmeasured maternal effects that do not change over time. The most relevant time-dependent maternal factor in this study was maternal age at birth. Our results did not significantly change when maternal age was included in the model. However, because maternal age was missing for many of the spontaneous births, results are presented for age-unadjusted models.

Several limitations of our study should be considered. We did not have demographic information, including race, marital status, and education, for ~25% of our surrogates. These are important potential confounders for perinatal outcome. However, because these demographic factors are unlikely to change in a woman who first had her own births and subsequently served as a gestational carrier, we thought that we could include all of these subjects without compromising the validity of our results.

During the period of the study, our clinical practices and laboratory techniques also improved, including transition from slow freeze to vitrification for cryopreservation, sequential to monophasic media, and early two-pronuclei or cleavage transfers to more elective single-embryo transfer of blastocysts. Therefore, we were unable to look at any specific ART technique that may have contributed to the outcome.

Furthermore, it is impossible to distinguish the impact of controlled ovarian stimulation itself versus the embryology laboratory conditions and procedures, such as the culture of the eggs and embryos. Previous studies have noted that ovarian stimulation may negatively affect ART-derived embryos (33, 34), with higher FSH doses associated with lower live birth rates (35). Furthermore, infertility is assumed to be a risk factor for adverse perinatal outcomes in ART singletons (36), although one study showed that even in the same mother an ART singleton has a poorer outcome than the non-ART sibling (37). Ideally, the study of embryos that are derived from healthy egg donors and subsequently carried by a gestational surrogate may help to further isolate the effect of maternal infertility and ART procedures on perinatal outcomes. However, we had insufficient numbers of donor oocyte and surrogate pairs to make an accurate comparison.

Repeated pregnancies themselves may be a contributing factor to the adverse outcomes observed in the commissioned births, although the evidence have been controversial (38, 39). One study showed that in a sibling pair, the IVF/ICSI infant born after a previous spontaneous conception was more likely to have low birth weight and preterm birth (40). However those researchers concluded that the difference in outcomes may be statistically but not clinically relevant. Conversely, another study noted a consistent increase in birth weight from the first to second child independently from mode and order of conception (41). The unique aspect of our study is that these are not true sibling pairs because the previous pregnancies and the commissioned births are not genetically related.

Our study provides additional evidence toward the conclusion that factors related to ART procedures have an influential role in pregnancy, regardless of the carrier uterine

environment. The true physiology behind the poor perinatal outcome observed in association with ART remains unknown, and the magnitude of contribution from ART laboratory manipulation needs further study.

CONCLUSION

This is the largest study to date of gestational surrogates who have given birth to a singleton via surrogacy and the only one evaluating antecedent spontaneous pregnancies achieved by the same woman. Neonates born from commissioned embryos and carried by gestational surrogates have increased adverse perinatal outcomes, including preterm birth, low birth weight, maternal gestational diabetes, hypertension, and placenta previa, compared with the live births conceived spontaneously and carried by the same woman. Our data suggests that the etiology behind the adverse outcomes in ART conceptions is multifactorial, ART procedures may potentially affect embryo quality and/or placentation, and the negative impact can not be overcome even with a healthy proven uterine environment.

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