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.