ORIGINAL ARTICLE: EARLY PREGNANCY

Mode of conception does not appear to affect placental volume in the first trimester

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Objective: To study whether infertility treatments, including IVF and non-IVF fertility treatments, are associated with diseases of placental insufficiency in early gestation. First trimester placental volumes by ultrasound and chorionic villi weight during sampling (CVS) were performed to detect differences between pregnancies conceived spontaneously versus with fertility treatments.
Design: Retrospective cohort.
Setting: Academic tertiary center.
Patient(s): Women with singleton pregnancies undergoing CVS and first trimester ultrasound from April 2007 to November 2015.
Intervention(s): Estimated placental volume (EPV) was calculated from ultrasound images using a validated computation and CVS estimated tissue weight was performed using a validated visual analogue scale.
Main Outcome Measure(s): Adjusted linear regression was used to compare EPV and CVS weight based on mode of conception.
Result(s): A total of 1,977 spontaneous and 334 conceived with fertility treatments (133 non-IVF and 201 IVF) pregnancies were included. Significant differences in maternal age, gravidity, hypertension, and smoking status were identified. EPV and CVS weight were correlated with maternal age, gestational age, and maternal hypertension. Adjusted linear regression showed no difference in EPV in pregnancies conceived with fertility treatments versus spontaneously. The CVS weight was significantly lower in the IVF conceptions in unadjusted univariate analyses. However, after adjusted regression, this was no longer significant.
Conclusion(s): Mode of conception does not appear to affect first trimester placental size. As differences in maternal age, hypertension, and smoking status differ among the groups and are correlated to placental size, it may be the underlying patient population leading to abnormal placentation and insufficiency, not the fertility treatments used. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Infertility, IVF, placental insufficiency, estimated placental volume, CVS

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The use of assisted reproductive technology (ART) to treat infertility continues to increase substantially in the United States, accounting for approximately 1.4% of total US live births and more than four million pregnancies achieved worldwide (1, 2). In addition, these pregnancies do not account for the number of pregnancies conceived with non-IVF (NIFT) fertility treatments. There is currently no database for NIFT conceptions and they are likely under-reported. Mathematical models have proposed that NIFT accounts for approximately 4.6% of infants born in the United States (3) and contributes to adverse outcomes including the incidence of multiple births (4).

As the numbers of pregnancies are increasing with the use of NIFT and IVF, it is important to ensure the health and well-being of mother and infant. Analysis of a large meta-analysis including a review of 15 studies found an increased incidence of preeclampsia, placental abruption, preterm labor, and small for gestational age infants in pregnancies conceived by IVF, suggesting a possible association of IVF with

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placental defects (5). However, it is unclear whether these adverse outcomes result from the IVF procedures or the underlying infertility we are trying to overcome, as pregnancies conceived by couples using other types of fertility treatments are also at increased risk of adverse outcomes, including placental abruption, fetal loss, and gestational diabetes (6). We also found alterations in placentation as pregnancies conceived with IVF have a higher rate of retained placenta (7). However, it is unclear whether this is due to the fertility treatments used, the underlying infertility, or other underlying factors affecting the patients who ultimately require fertility treatments for conception.

Animal models have found significant differences in placental structure and growth in early placentation that are associated with poor pregnancy outcomes in pregnancies conceived through IVF compared with those conceived spontaneously, with molecular studies supporting a placental etiology (8–10). A placental etiology has also been suggested in human studies. Johnson et al. (11) found an association between reduced circulating placental proteins, specifically PAPP-A and SP-1 in pregnancies conceived by IVF. Decreased placental volume in the first trimester assessed by ultrasound is associated with decreased PAPP-A in pregnancies that subsequently developed growth restriction, preeclampsia, and placental abruption (12–16). Thus, placental volume may be a marker of placental insufficiency in early gestation. At present, there has only been one small study comparing first trimester placental volume based on mode of conception and although Rifouna et al. (17) found no differences in 10-week placental volumes between 84 pregnancies conceived spontaneously compared with 70 pregnancies conceived by IVF, this was largely limited by small sample size. In addition, these investigators did not address NIFT conceptions, which are also associated with increased risk of pregnancy related complications (6).

To fill this gap in knowledge, we measured first trimester placental volume in a cohort of 2,311 women who presented to our institution between 2007 and 2015. Placental weight obtained at sampling (chorionic villi weight during sampling; CVS) was used as a secondary measure of placental volume. We hypothesize that conceptions that conceive in couples with infertility are associated with a decreased placental volume and CVS weight compared with spontaneous conceptions, and those using IVF are associated with a more compromised placental volume compared with NIFT and spontaneous conceptions.

MATERIALS AND METHODS

This was a retrospective cohort study using subjects who had undergone CVS and first trimester vaginal ultrasound at an outpatient prenatal diagnostic center at an academic tertiary medical care center from April 2007 to November 2015. The Institutional Review Board of Cedars-Sinai Medical Center in Los Angeles approved the study. Women with singleton pregnancies were included.

Chart review was used to obtain patient and pregnancy characteristics, as well as mode of conception (IVF, NIFT, or spontaneous). The NIFT conceptions included those that used clomiphene citrate (CC), gonadotropin injections, and/or IUIs. Pregnancies that did not have a specific mode of conception documented were considered to be spontaneous. In spontaneous conceptions, fetal age was estimated based on last menstrual period (LMP). If there was discordancy between fetal age based on LMP and ultrasound, fetal age was adjusted to ultrasound dating. In conceptions with fertility treatments, fetal age was determined based on conception as a result of treatment. A single trained researcher measured estimated placental volumes (EPVs) using two-dimensional (2D) ultrasound images and a substantiated mathematical model. This researcher was blinded to all other subject data at the time of measurement. This model uses the linear measurements of placental width, height, and thickness to calculate the volume of an elliptical cylinder and has been correlated to placental weights (18). The EPV measurements by 2D and 3D ultrasound have been used in several studies across all gestations and have been found to correlate significantly with gestational weight at delivery (19–21).

A single expert physician performed all CVS procedures. An internally validated visual analogue scale was used to estimate tissue weight in grams. As a guide for estimating villus sample wet weight, representative samples of villus fragments were previously weighed carefully on a milligram balance, placed into 60-mm Petri dishes and photographed for comparison with the actual tissue samples (Supplemental Fig. 1, available online). This scale estimates chorionic villi weight using ordinal measurements in 5-mg increments. For example, after a CVS sample is gathered the villi tissue is visually examined and weight determined based on a visual model to be approximately 5, 10, 15, 20 mg, or more (22). Patients were excluded from analysis for missing data.

Statistical analysis was performed using SPSS for Windows. The statistical level of significance was $P<.05$. Baseline characteristics were calculated as mean ± SD for continuous variables and proportions for categorical data. Differences between groups were detected using analysis of variance (ANOVA) for normally distributed continuous variables and χ^2 and Fisher's exact tests for categorical variables. The Kruskal-Wallis test was used when data failed tests of normal distribution. Pearson's correlation coefficient was used to calculate correlations between maternal, fetal, and placental factors and EPV and CVS weights. A power calculation was performed and we were adequately powered (>90%) to detect a mean difference in EPV of anywhere between 1 and 15 cm^3 with our sample size. We selected the EPV between 1 and 15 cm^3 because fetal growth restriction has been associated with fertility treatments and an EPV of 15 cm^3 is a predictor of fetal growth restriction based on a study by Schwartz et al. (19).

Linear and logistic regression models were used to compare EPVs and CVS weights based on mode of conception. Models were adjusted for confounders of maternal age, race, gravidity, hypertension, smoking status, and gestational age.

RESULTS

Our final analysis included 2,311 subjects who underwent CVS and first trimester ultrasound. Of these, 1,977 subjects