Mode of conception does not affect fetal or placental growth parameters or ratios in early gestation or at delivery

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Abstract

Purpose Ratio of fetal weight to placenta size varies by mode of conception (fertility treatments utilized) in animals. Our objective was to assess whether fertility treatments also affect these ratios in humans.

Methods In this retrospective study, we assessed two cohorts: (a) early gestation cohort, women with singleton pregnancies who underwent first trimester vaginal ultrasound and (b) delivered cohort, women who delivered a live-born, singleton infant with placenta disposition to pathology. Crown rump length (CRL) and estimated placental volume (EPV) were calculated from first trimester ultrasound images using a validated computation. Infant birth weight (BW), pregnancy data, placental weight (PW), and placental histopathology were collected. Fetal growth-to-placental weight ratios (CRL/EPV; BW/PW) and placentas were compared by mode of conception. Linear regression was used to adjust for confounding variables.

Results Two thousand one hundred seventy patients were included in the early gestation cohort and 1443 in the delivered cohort. Of the early gestation cohort (a), 85.4% were spontaneous conceptions, 5.9% Non-IVF Fertility (NIFT), and 8.7% IVF. In the delivered cohort (b), 92.4% were spontaneous, 2.1% NIFT, and 80 5.5% IVF. There were no significant differences between fetal growth-to-placental weight parameters, ratios, and neonatal birth measurements based on mode of conception. Placenta accreta was significantly higher in the patients receiving fertility treatments (1.2 versus 3.6%, $p < 0.05$).

Conclusions Mode of conception does not appear to influence fetal growth-to-placental weight ratios throughout gestation. In addition, findings in animal models may not always translate into human studies of infertility treatment outcomes.

Keywords Fertility treatment · Crown rump length · Estimated placental volume · Birth weight · Placental weight

Introduction

The number of infants born with use of fertility treatments is on the rise. Recent estimates find that 1.6% of all infants born in the USA each year are conceived using assisted reproductive technology (ART), most commonly via in vitro fertilization (IVF)

[1]. When considering the approximate 4.6% of infants conceived with use of non-IVF (NIFT) fertility treatments [2], including ovulation induction, controlled ovarian hyperstimulation, and intrauterine insemination, this number is even greater.

Pregnancies conceived using ART are at increased risk for low birth weight and small for gestational age babies, pre-eclampsia, placental abruption, placenta previa, retained placenta, and preterm labor and delivery compared to pregnancies conceived spontaneously [3–10]. In addition, NIFT pregnancies are also at increased risk of adverse outcomes, including placental abruption, fetal loss, gestational diabetes, and outcomes related to placentation [4, 11]. As the numbers of pregnancies from IVF and NIFT are increasing, it is important to determine if any of these adverse outcomes can be predicted and/or prevented. However, the point at which pathology begins to lead to these adverse outcomes is unknown.

Animal models evaluating IVF and spontaneous pregnancies have found significant differences in placental structure

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and growth in early placentation that are associated with poor pregnancy outcomes; molecular studies support a placental etiology [12–14].

Human studies have also found relationships with decreased placental proteins, such as pregnancy-associated plasma protein-A (PAPP-A), in IVF conceptions [15–20] while more recent studies have shown no difference [21]. Decreased PAPP-A is associated with decreased placental volume in the first trimester and subsequent growth restriction, preeclampsia, and placental abruption [16–20]. While PAPP-A is not necessarily a reliable marker for placental insufficiency in early gestation, placental volume may be.

Animal studies after delivery have found that IVF offspring have increased placental size compared to fetal size leading to discordant birth weight (BW) to placental weight (PW) ratios (BW/PW) [22]. This suggests that the proportions of growth parameters may influence pregnancy outcomes.

We and others have previously demonstrated that placental volume in the first trimester does not vary by mode of conception [23, 24]. PW after delivery also does not differ in IVF compared to spontaneous conceptions [25, 26]. While studies have evaluated growth of fetuses and infants conceived via different modes of conception, fetal growth-to-placental weight ratios have not been evaluated [27–29]. The objective of this study is to assess whether infertility treatments influence fetal growth and placenta-size ratio differences in early gestation and at delivery.

Materials and methods

This is a retrospective cohort study analyzing two groups of patients: (a) an early gestation cohort and (b) a delivered cohort. The Institutional Review Board of Cedars-Sinai Medical Center in Los Angeles approved the study. Subjects in the early gestation cohort were women with singleton pregnancies who underwent chorionic villus sampling (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 delivered cohort of patients included women who delivered at our institution a live-born, singleton infant at ≥ 24 weeks from January through December 2012, with whose placenta was sent for pathologic analysis at the discretion of the delivering provider.

A systematic chart review was performed to obtain patient, pregnancy, delivery, and infant characteristics. Included in this review was mode of conception (spontaneous, NIFT, or IVF). The NIFT conceptions encompassed use of clomiphene citrate, letrozole, gonadotropin injections, and/or intrauterine insemination. 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 a discordant fetal

age based on LMP and ultrasound, fetal age was adjusted to ultrasound dating by crown rump length (CRL). 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 (EPV) using two-dimensional (2D) ultrasound images and a substantiated mathematical model [30]. This researcher was blinded to all other subject data at the time of measurement. The 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. 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 [31–33]. All placental characteristics were obtained from histopathology reports issued after analysis and weight by the pathology department.

Baseline characteristics were calculated as mean $\pm$ standard deviations (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. A power calculation was performed individually for the early gestation cohort and the delivered cohort. We were adequately powered ($>90\%$) to detect a mean difference in EPV between 1 and 15 cm³ with our sample size. We selected the EPV between 1 and 15 cm³ because fetal growth restriction has been associated with fertility treatments and an EPV of 15 cm³ is a predictor of fetal growth restriction based on a study by Schwartz et al. [31]. For the delivered cohort, a power calculation using the ratio difference detected in de Waal et al. [22] found that we have $>80\%$ power to detect this difference in our sample size, at an alpha of 0.05. Linear regression models were used to compare CRL, EPV, and CRL/EPV ratios, and BW, PW, and BW/PW ratios based on mode of conception. Models were adjusted for confounders of maternal age, race, gravidity, hypertension, smoking status, and gestational age. Statistical analysis was performed using STATA 13 (College Station, TX). The statistical level of significance was $p < 0.05$.

Results

A total of 8996 patients were evaluated and 3614 were analyzed. Two thousand two hundred eighty-five patients were included in the early gestation cohort and 1443 in the delivered cohort. Patients were excluded from analysis in the early gestation cohort if they did not have documented CRL and EPV at the time of CVS. Of the 6711 deliveries in the delivered cohort, only the 1443 with placenta disposition to pathology were included in analysis. Overall, the early gestation

cohort included 1853 (85.4%) spontaneous conceptions and 317 that received fertility treatment {infertility = [128 (5.9%) NIFT] + [189 (8.7%) IVF]}. In the delivered cohort, 1333 (92.4%) were spontaneous conceptions and 110 that had received infertility treatment {[30 (2.1%) NIFT] + [80 (5.5%) IVF]} (Fig. 1).

Early gestation cohort

First, we evaluated the early gestation cohort (a); patients were predominantly white and with non-obese pre-pregnancy body mass index (BMI). Mean maternal age was higher in the conceptions conceived with fertility treatments and lower in spontaneous conceptions (38.0 ± 3.4 versus 39.3 ± 3.2 years, $p < 0.001$). Infertility patients were less likely to be current smokers (2.5 versus 5.2%, $p = 0.03$), but more likely to have a diagnosis of hypertension (3.8 versus 1.8%, $p = 0.03$) compared to spontaneous (Table 1). Mean gestational age at CVS was not different between groups (83.9 days for spontaneous and infertility, $p = 0.97$).

Outcomes measured were not significantly different between spontaneous and infertility groups for CRL (54.8 versus 54.8 mm, $p = 0.92$), EPV (55.2 versus 56.6 cm³, $p = 0.48$), or CRL/EPV ratios (1.37 versus 1.34, $p = 0.65$) (Table 2). Subgroup analysis looking at NIFT and IVF conceptions individually also did not reveal a difference in CRL, EPV, or CRL/EPV ratios (Fig. 2).

Linear regression was performed to adjust for confounding variables of maternal age, maternal race, maternal pre-pregnancy BMI, hypertension, and current smoking status. Adjusted linear regression suggested no significant difference in CRL/EPV ratio in infertility compared to spontaneous conceptions (beta coefficient -0.57 , 95% CI $-2.17 - 1.04$, $p =$

Table 1 Early gestation cohort baseline demographics

	Spontaneous <i>N</i> = 1853	Infertility (NIFT + IVF) <i>N</i> = 317	<i>p</i> value
Maternal age, years*	38.0 ± 3.4	39.3 ± 3.2	< 0.001
Maternal race, <i>n</i> (%)			0.026
White	1088 (58.7%)	212 (66.9%)	
African-American	59 (3.2%)	4 (1.3%)	
Asian	219 (11.8%)	42 (13.2%)	
Other	118 (6.4%)	10 (3.2%)	
Maternal pre-pregnancy BMI kg/m ²	24.7 ± 4.8	25.2 ± 4.8	0.06
Current smoking, <i>n</i> (%)	96 (5.2%)	8 (2.5%)	0.03
Hypertension, <i>n</i> (%)	33 (1.8%)	12 (3.8%)	0.03
Gestational age at CVS, days	83.9 ± 7.1	83.9 ± 6.6	0.97

* Continuous variables are represented as mean $\pm$ standard deviation. Categorical variables are represented as frequency

0.49). Linear regression to evaluate growth trajectory also found that regardless of gestational age, the CRL and EPV did not vary by mode of conception.

Delivered cohort

Next, we evaluated the delivered cohort (b). Like the early gestation cohort, most participants were white and with non-obese pre-pregnancy BMI. Maternal age was higher in infertility patients and lower in spontaneous (38.7 versus 32.4 years, $p < 0.001$), (Table 3). Infertility patients were more likely to deliver via cesarean delivery compared to spontaneous (59.0 versus 45.2%, $p = 0.005$), but the gestational age at

Fig. 1 Flow diagram of patient cohorts

Table 2 Early gestation cohort outcomes

	Spontaneous <i>N</i> = 1853	Infertility (NIFT + IVF) <i>N</i> = 317	<i>p</i> value
Crown rump length (CRL), mm	54.8 ± 12.5	54.8 ± 11.68	0.92
Estimated placental volume (EPV), cm ³	55.2 ± 32.6	56.6 ± 32.9	0.48
Crown rump length/estimated placental volume (CRL/EPV) ratio, mm/cm ³	1.37 ± 0.97	1.34 ± 1.0	0.65

delivery was not different between groups (38.1 versus 38.5 weeks for infertility and spontaneous, respectively, $p = 0.26$). BW (3104 versus 3090 g, $p = 0.61$), PW (456 versus 460 g, $p = 0.61$), and BW/PW ratios (7.0 versus 6.8, $p = 0.36$) were not different between spontaneous and infertility conceptions (Table 4, Fig. 3).

After adjusting for gestational age and maternal age, there was no difference in PW or BW/PW ratios. Spontaneous conception, however, was a significant predictor for BW after controlling for gestational age and maternal age (beta coefficient 52.5, 95% CI 9.1–94.9, $p = 0.018$). Growth trajectory linear regression demonstrates that regardless of gestational age, the BW and PW do not vary by mode of conception (Fig. 4).

Fig. 2 Crown rump length (CRL) to estimated placental volume (EPV) ratios by **a** spontaneous conception versus patients receiving fertility treatment and **b** subgroup analysis by type of fertility treatment

Table 3 Delivered cohort baseline demographics

	Spontaneous <i>N</i> = 1333	Infertility (NIFT + IVF) <i>N</i> = 110	<i>p</i> value
Maternal age, years*	32.4 ± 5.5	38.7 ± 5.5	< 0.001
Maternal race, <i>n</i> (%)			0.026
White	864 (64.8%)	73 (66.4%)	
African-American	161 (12.1%)	5 (4.6%)	
Asian	199 (14.9%)	25 (22.7%)	
Other	104 (7.8%)	7 (6.4%)	
Maternal pre-pregnancy BMI, kg/m ²	23.9 (5.4)	23.1 (4.6)	0.19

* Continuous variables are represented as mean ± standard deviation. Categorical variables are represented as frequency

Also of note, the neonatal measurements at birth did not vary significantly by mode of conception. Head circumference (13.2 versus 12.3 in., $p = 0.29$), birth length (20.2 versus 19.9 in., $p = 0.98$), and 5-min Apgar scores (8.6 for both spontaneous and infertility $p = 0.93$) were not different among spontaneous and infertility conceptions, as well as in subgroup analysis of spontaneous, NIFT, and IVF conceptions.

Assessment of placental characteristics at delivery revealed no difference in findings of preeclampsia, chorioamnionitis, or in placenta shapes in spontaneous versus infertility conceptions. Placenta accreta, however, was higher in infertility conceptions; specifically IVF conceptions as there were no placenta accreta diagnosed in the NIFT subgroup [spontaneous $n = 16$ (1.2%) versus NIFT 0 versus IVF 4 (5%)] (Table 5). Adjusting for placenta accreta diagnosis and gestational age, or placenta accreta diagnosis alone, also found no difference between groups for BW, PW, and BW/PW ratios.

Discussion

Our data demonstrate that mode of conception does not affect fetal growth, growth patterns, placental size, and ratios of fetal growth-to-placental weight in both early gestation and delivered cohorts of spontaneous, NIFT, and IVF conceived gestations. Further, neonatal measurements at birth such as head circumference, birth length, and 5-min Apgar score do not vary significantly by mode of conception. Placenta accreta, however, is more common in fertility treatment-assisted conceptions than in spontaneous conceptions.

In our study population, infertility patients were older and, in the early gestation cohort, more likely to be hypertensive. As infertility increases with age, this is not a surprising finding. The older age of spontaneous mothers in the early gestation cohort is consistent with women seeking CVS procedures for the common indication of advanced maternal age.

Table 4 Delivered cohort outcomes

	Spontaneous <i>N</i> = 1333	Infertility (NIFT + IVF) <i>N</i> = 110	<i>p</i> value
Delivery type, <i>n</i> (%)			0.005
Cesarean	602 (45.2%)	65 (59.0%)	
Vaginal	718 (53.9%)	44 (40%)	
Gestational age at delivery, weeks	38.5 ± 2.7	38.1 ± 3.4	0.26
Birth weight (BW), g	3104.2 ± 677.9	3090.4 ± 795.8	0.61
Placental weight (PW), g	456.7 ± 118.3	460.6 ± 456.7	0.61
Birth weight/placental weight (BW/PW) ratio	7.0 ± 1.4	6.8 ± 1.3	0.36
Head circumference, in.	13.2 ± 3.7	13.3 ± 2.3	0.29
Birth length, in.	20.2 ± 4.3	19.9 ± 3.7	0.98
5-min Apgar	8.6 ± 1.0	8.6 ± 1.2	0.93

Importantly, however, regardless of maternal age, or gestational age at CVS assessment and delivery, women receiving fertility treatments are not at increased risk for altered fetal growth-to-placenta size ratios or neonatal measurements at birth.

We did not see a significant difference in BW of infertility or IVF conceptions compared to spontaneous as has been seen in earlier studies [7, 9]. Though ART pregnancies have been found to have statistically significant lower BW, the actual

difference is only a few hundred grams and is overall likely to be clinically insignificant. While prior studies have found significant differences in preterm birth and low birth weight, and consider these factors to be the most important determinants of neonatal morbidity [34, 35], the mean gestational age at delivery in our delivered cohort was 38 weeks and BW 3100 g, well within the range of weight appropriate for gestational age for either fetal gender [36]. Our findings support the

Fig. 3 Birth weight (BW) to placenta weight (PW) ratios by **a** spontaneous conception versus patients receiving fertility treatment and **b** subgroup analysis by type of fertility treatment

Fig. 4 Growth patterns according to gestational age of **a** placenta weight and **b** birth weight

Table 5 Placental characteristics of delivered cohort

	Spontaneous <i>N</i> = 1333	Infertility (NIFT + IVF) <i>N</i> = 110	<i>p</i> value
Preeclampsia findings, <i>n</i> (%)	111 (8.3%)	9 (8.2%)	0.96
Chorioamnionitis, <i>n</i> (%)	392 (29.4%)	35 (31.8%)	0.59
Accreta, <i>n</i> (%)	16 (1.2%)	4 (3.6%)	0.036*
Placental shape, <i>n</i> (%)			0.23
Discoid	737 (55.3%)	58 (52.7%)	
Ellipsoid	202 (15.2%)	15 (13.6%)	
Ovoid	200 (15%)	14 (12.7%)	
Circular/round	63 (4.7%)	5 (4.5%)	
Other	50 (3.8%)	9 (8.2%)	

* Statistically significant, $p < 0.05$

largely similar values for BW between IVF and spontaneous conceptions.

Balanced growth of the fetus and the placenta are important for appropriate development. BW/PW ratios have long been used as a marker of fetal nutrition and uteroplacental function [37], but studies highlighting the importance of the ratios of fetal-to-placental weight, rather than focusing on individual parameters, are becoming increasingly common. A recent study found that BW/PW ratios are significantly lower in stillbirths than in live births [38]. Studies in twin gestations with selective intrauterine growth restriction (IUGR) have found that the BW/PW ratio of the IUGR twin is significantly higher than that of the normally grown twin [39]. Another study looking at IUGR twins found that overall placental weight is lower in both monochorionic and dichorionic twins compared to non-IUGR twins, but that there is no difference in the BW/PW ratios [40]. This is consistent with the fact that the placenta plays a critical role in regulating the growth of the fetus. The maternal environment also plays an important role, as BW/PW ratios are higher in diabetic versus non-diabetic mothers [41]. These findings are in line with the fact that perturbations of the balance of fetal-to-placental growth may lead to disrupted BW/PW ratios and this has been associated with perinatal mortality and morbidity, as well as with mortality associated with cardiovascular disease in adult life [42, 43].

That being said, there have also been associations with fetal growth in the first trimester and risk of prematurity, small for gestational age, and cardiovascular disease in childhood [44]. While placental volume in the late first trimester is not affected by mode of conception [23, 24], it is worth noting that reduced placental volume in this gestational period has been significantly associated with adverse pregnancy outcomes such as preeclampsia, IUGR, small for gestational age, and placental abruption [28]. Thus, as demonstrated by prior studies, if an ART pregnancy has diminished placental volume, regardless of how the pregnancy was conceived, the risk for abnormal

fetal growth, IUGR, or small for gestational age is higher as compared to a pregnancy with appropriate placental volume [21, 34, 35].

Our results are consistent with prior studies demonstrating an increased incidence of placenta accreta in patients receiving fertility treatment [45–49]. This suggests that inappropriate trophoblast migration and invasion into the myometrium and spiral arteries during placentation may also be a factor involved in adverse outcomes. In our study, there was an overall low number of placenta accreta, but the presence of this diagnosis did not appear to affect BW/PW ratios. The degree to which abnormal trophoblast invasion occurs may have other implications beyond simply a placenta accreta diagnosis, and may contribute to adverse outcomes that arise in pregnancies conceived with fertility treatments, but further studies are needed.

A major strength of our study is that we assessed a large number of patients and were able to focus on a cohort in early gestation, also a cohort that had delivered an infant. We were also able to study subgroups of IVF and NIFT conceptions compared to spontaneous conceptions. A single examiner calculated the EPV, minimizing the variance in placental size estimates in the early gestation. Histopathology analysis of placentae was also performed at our single center allowing for consistency of pathologic diagnoses.

Limitations of our study include its retrospective nature. The early gestation and delivered cohorts were distinct and did not have adequate overlap to draw conclusions about the same patients in both cohorts. As is the case with any retrospective study, there were pieces of individual data missing, but utilizing standardized histopathology reports allowed for the majority of data to be captured. Our assessment of placenta accreta by specific mode of conception was limited due to the absence of placenta accreta diagnoses in the NIFT population.

In conclusion, while a single animal study found that increased placental weight and reduced fetal-to-placental weight ratios were observed in ART mice [22], this is the first study to evaluate fetal to placenta growth ratios by mode of conception in humans. Although an animal study identified a difference in fetal-to-placental weight ratios by mode of conception, based on our study findings, this does not hold true for human pregnancies. The lack of difference in fetal-to-placental weight ratios and growth parameters, both in the first trimester and at delivery, suggests an alternative mechanism by which adverse outcomes arise in pregnancies conceived with fertility treatments. Given the increase in placenta accreta in IVF pregnancies, potentially the degree to which trophoblasts invade into the myometrium may play a role. Differences in patient population and environmental influence throughout pregnancy may lead to abnormal outcomes, but these are not detected with fetal growth-to-placenta growth ratios in either early gestation or at delivery. The lack of difference detected in terms of fetal growth and neonatal birth parameters is overall

reassuring as more children are born with the assistance of fertility treatments.

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Compliance with ethical standards

The Institutional Review Board of Cedars-Sinai Medical Center in Los Angeles approved the study.

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