First trimester pregnancy ultrasound findings as a function of method of conception in an infertile population

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Abstract

Purpose The aim of this study was to determine whether first trimester ultrasound measurements of crown rump length (CRL) and gestational sac diameter (GSD) differ depending on the method of conception among infertile women.

Method Infertile women, ages 21–50 years old, who conceived viable, singleton pregnancies via fresh embryo transfer (ET), frozen ET, non-in vitro fertilization (IVF) fertility treatment, or spontaneously were included in this observational cohort study at an academic fertility practice. Embryonic growth trajectories defined by the CRL and GSD at 6 and 8 weeks' gestation were analyzed and compared among the methods of conception.

Results Crown rump length at 6 weeks' gestation was smaller for conceptions achieved via fresh ET compared with frozen ET in a natural cycle (1.50 vs. 2.50 mm, $p = 0.017$). Crown rump length was smaller at 8 weeks' gestation in conceptions achieved via fresh ET compared to frozen ET in a programmed cycle (16.13 vs. 17.02 mm, $p = 0.039$).

Conclusion Among infertile women, embryo growth may differ between fresh and frozen ET as early as 6 and 8 weeks' gestation.

Keywords First trimester · Crown rump length · Gestational sac diameter · Embryo transfer · Assisted reproduction

Introduction

Pregnancies conceived via assisted reproductive technology (ART) begin in a non-physiologic maternal endocrine milieu,

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The authors consider that the first two authors should be regarded as joint First Authors.

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which is in part due to treatments that result in high numbers of corpora lutea (CL) or the absence of CL [1]. The CL secretes not only estradiol and progesterone but also other products such as relaxin which may influence placentation and pregnancy development. Past studies have demonstrated that ART is associated with an increased risk of certain adverse fetal and maternal outcomes [2–4]. However, relatively few studies have been published regarding fertility treatment and first trimester embryonic growth [5–7], and the available publications have focused mostly on comparing pregnancies conceived by autologous fresh IVF to spontaneous conceptions among fertile women. None have examined first trimester growth parameters specifically as a function of method of conception.

There has been a trend towards increased utilization of frozen-thawed ET after studies have suggested an impact of the unphysiological environment of a fresh ET on pregnancy outcomes [8, 9]. A large meta-analysis showed higher perinatal and maternal morbidity in women who conceived from fresh ET compared to frozen ET [10]. The authors found higher rates of antepartum hemorrhage, preterm birth, small for gestational age, low birth weight, and perinatal mortality in infants among women who received fresh embryos [10]. More recent studies have again shown lower mean birth weights

among those infants conceived from fresh ET [11, 12], but a higher risk of large for gestational age among infants conceived via frozen ET [13–15]. Although studies have been published comparing birth outcomes for fresh and frozen ET, we are unaware of published studies which have examined the possibility of differences in embryonic growth between fresh and frozen ET as early as the first trimester.

We hypothesized that the method of conception may affect embryonic growth early in pregnancy. We also hypothesized that the unphysiologic environment of fresh IVF may impair first trimester growth when compared to frozen ET. Given these hypotheses, the objectives of this study were to determine if first trimester embryonic growth parameters as assessed by ultrasound differed based on the method of conception and to determine if the first trimester growth differed with fresh compared to frozen ET.

Materials and methods

The study was performed at an academic fertility and reproductive health practice and approved by the institution's Institutional Review Board. All women with potentially viable pregnancies were offered participation in the study at the time a potentially viable pregnancy was diagnosed at 6–8 weeks' gestation, and all participants gave informed consent. Participants screened for inclusion in this analysis were the 420 women consented at study launch in October 2011 until data collection for this analysis closed in March 2014. All women had achieved pregnancy either via treatment or spontaneously following a diagnosis of infertility. Infertility was defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.

Inclusion criteria included singleton pregnancies that resulted in live births in which only one gestational sac was present on all ultrasounds from the time of conception. Only participants with available data for the outcome variables crown rump length (CRL) and gestational sac diameter (GSD) were included. Exclusion criteria for this analysis included gestational carrier cycles, pregnancies that resulted in spontaneous abortions, pregnancies that were terminated due to detected fetal anomaly, and the presence of multiple gestational sacs on any ultrasound. Additional exclusion criteria included second pregnancies in women who were already consented for a first pregnancy, cycles in which exact conception dates were unavailable, and women who became pregnant at an outside fertility center. One participant requested to be withdrawn from the study after delivery. After exclusion criteria were applied, out of 420 participants 321 singleton pregnancies were studied, which resulted in measurements from 802 ultrasound examinations (Fig. 1).

The groups for analysis were constructed based on the method of conception and associated CL number at conception because we were specifically interested in the effect of CL number (zero, one, multiple) on early pregnancy development: group 1 with 0 CL ($n = 24$) included IVF autologous egg with programmed frozen ET ($n = 16$), IVF donor egg with fresh ET ($n = 6$), and IVF donor egg with programmed frozen ET ($n = 2$); group 2 with 1 CL ($n = 131$) included spontaneous conception ($n = 72$), intrauterine insemination (IUI) in the context of a natural cycle ($n = 7$), IVF autologous egg with natural cycle frozen ET ($n = 47$), and IVF donor egg with natural cycle frozen ET ($n = 5$); group 3 with multiple CL (non-IVF) ($n = 88$) included ovulation induction only ($n = 11$) and ovulation induction with IUI ($n = 77$); and group 4 ($n = 78$) included only IVF autologous egg with fresh ET. We included a subfertile group with spontaneous conceptions as we were specifically interested in the impact of treatment and not the effect of infertility.

A separate subgroup analysis was performed to compare autologous egg fresh ET ($n = 78$), frozen ET in a natural cycle ($n = 52$), and frozen ET in a frozen programmed cycle ($n = 18$). The decision to perform a frozen ET in a natural or a programmed cycle was made by the treating physician. Transfer in a natural cycle was recommended for women with regular cycles and transfer in a programmed cycle was recommended for women with irregular menstrual cycles or for more precise prediction and control of when the ET was to occur based on the patient's request. Frozen ETs performed in the context of a natural cycle were monitored by serial ultrasound. When adequate endometrial development (to a thickness of 7 mm or greater) and a mature follicle (18 mm or greater) were observed, ovulation was triggered in the evening with human chorionic gonadotropin (HCG) and the ET was performed 7 days later. If the patient had a spontaneous LH surge detected by ovulation predictor kit and confirmed by serum LH, the frozen ET was performed 6 days after the LH surge was first detected. Programmed frozen ETs were performed using oral or transdermal estradiol and vaginal progesterone. A single CL was present in all natural frozen ET cycles, whereas the programmed frozen ET cycles were performed in the absence of a CL as confirmed by ultrasound.

Participant's demographics and history

Electronic medical records were used to obtain each participant's infertility diagnosis, conception data from the index pregnancy (pregnancy for which they were consented), and first trimester obstetric ultrasound dates and measurements. Study participants completed a questionnaire at the time of consent that included maternal and paternal age, race, and ethnicity, as well as the patient's

Fig. 1 Flowchart describing inclusion and exclusion of study participants

past pregnancy history. Maternal age was defined as the age at the time of consent.

Ultrasound scans

The primary outcome variables obtained from the first trimester ultrasounds were CRL and GSD. Most participants underwent two first trimester ultrasounds at approximately 6 and 8 weeks' gestation. However, some participants, particularly those with a history of loss after 8 weeks had more than two ultrasound examinations (up to 7), and approximately 8% had only one ultrasound examination before being transferred to general obstetric prenatal care. All ultrasound examinations were performed at the academic fertility center by reproductive endocrinologists who each has greater than 15 years of experience performing first trimester ultrasound.

Transvaginal ultrasound was performed utilizing the GE Voluson S6 in the obstetric mode or using the GE Logiq P5 in the obstetric mode. The gestational sac was measured in three dimensions and the mean sac diameter was reported for use in this analysis. The CRL length was measured in the longest dimension.

Calculation of gestational age

Gestational age at the time of each ultrasound was calculated based on conception data and the ultrasound date (Supplemental Table). For IVF and IUI cycles, the date of ET and IUI were used to calculate precise gestational age. For timed intercourse cycles, the date of conception was estimated from the date of ovulation based on LH surge or hCG shot. Spontaneous conceptions were dated based on ovulation date defined as the day after the LH surge from home ovulation predictor kits.

Statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at the institution [16]. The patient baseline characteristics were summarized and compared between CL groups using nonparametric Kruskal-Wallis test for continuous variables and percentages, and assessed by Fisher's exact test for categorical variables. LOWESS (locally weighted scatterplot smoothing) regression was applied to characterize the growth trajectories for the CRL and GSD by using 20% of the data near the time neighborhood. The linear mixed model with interaction term of CL group and gestational age was used to predict the two variables at 42 days (6 weeks) and 56 days (8 weeks). Kenward-Roger method was used to approximate the degree of freedom when comparing the fixed effects at 42/56 days and Tukey-Kramer adjustment accounted for the multiple comparison at an overall 0.05 significance level. All analyses were done in R 3.2.3 and SAS 9.4.

Results

Demographics

Patient and partner demographics are presented in Table 1, demonstrating similarity between the groups with one exception. Participant age was higher for the 0 CL group compared with the other three CL groups ($p = 0.007$). Partner age, participant and partner race/ethnicity, and mean parity were comparable between the groups. Participants and partners were predominantly of Asian or White race.

Table 1 Baseline characteristics of study participants and their partners at time of consent

	No CL	1 CL	Multiple CL/non-IVF	Fresh IVF
Number	24	131	88	78
Participant age at first ultrasound (mean $\pm$ SD)	38.4 $\pm$ 5.6	35.4 $\pm$ 4.2	34.7 $\pm$ 3.7	36.5 $\pm$ 3.9
Infertility diagnosis (%)				
Age	12.5	1.5	1.1	5.1
Diminished ovarian reserve (DOR)	25.0	7.6	8.0	24.4
Male	16.7	16.8	12.5	30.8
Polycystic ovarian syndrome (PCOS)	8.3	7.6	28.4	6.4
Ovulatory disorder (non-PCOS)	4.2	3.1	2.3	6.4
Tubal	4.2	8.4	1.1	15.4
Uterine	12.5	0.8	3.4	2.6
Endometriosis	0	9.2	1.1	9.0
Recurrent pregnancy loss (RPL)	4.2	34.4	12.5	9.0
Single-gene disorder	8.3	3.8	0	0
Sex selection	0	2.3	0	3.8
Single female (no partner)	4.2	0.8	1.1	1.3
Lesbian female	4.2	0	0	1.3
Unexplained	12.5	18.3	36.4	16.7
Other	8.3	4.6	2.3	2.6
Participant race (%)				
Asian	62.5	45.0	56.8	56.4
African American	0	1.5	0	0
Native Hawaiian or other Pacific Islander	0	0.8	1.1	1.3
White	33.3	43.5	33.0	38.5
Other	4.2	9.9	11.4	3.8
Unknown	0	0.8	0	0
Participant ethnicity (%)				
Hispanic or Latino	8.3	4.6	6.8	5.1
Non-Hispanic or non-Latino	91.7	95.4	90.9	94.9
Other	0	0	2.3	0
Partner age at first ultrasound (mean $\pm$ SD)	40.3 $\pm$ 6.7	37.2 $\pm$ 5.8	37.1 $\pm$ 5.1	38.3 $\pm$ 5.4
Partner race (%)				
American Indian or Alaska Native	0	0	1.1	0
Asian	45.8	39.7	48.9	48.7
African American	0	0.8	0	0
Native Hawaiian or other Pacific Islander	0	0	1.1	1.3
White	41.7	47.3	38.6	43.6
Other	0	6.9	2.3	2.6
Unknown	0	4.6	5.7	1.3
None of the above	0	0.8	0	0
Partner ethnicity (%)				
Hispanic or Latino	4.2	4.6	2.3	3.8
Non-Hispanic or non-Latino	83.3	86.3	83.0	85.9
Other	4.2	7.6	11.4	5.1
Parity (mean $\pm$ SD)	0.29 $\pm$ 0.46	0.41 $\pm$ 0.59	0.42 $\pm$ 0.60	0.37 $\pm$ 0.67
Prior pregnancy outcomes (%)				
Live birth	29.2	36.6	38.6	26.9
Fetal demise	4.2	2.3	1.1	1.3
Spontaneous abortion	45.8	51.1	27.3	33.3
Therapeutic abortion	16.7	18.3	8.0	11.5

Table 1 (continued)

	No CL	1 CL	Multiple CL/non-IVF	Fresh IVF
Ectopic	4.2	10.7	4.5	10.3
Biochemical	8.3	16.8	14.8	16.7
Sperm source (%)				
Partner	87.5	99.2	92.0	91.0
Donor	8.3	0.8	6.8	5.1
Partner and donor	0	0	0.0	1.3
Egg source (%)				
Autologous	75	96.2	100	100
Donor	25	3.8	0	0

Data are presented as percentage of the group, except when otherwise indicated as a mean

Method of conception analysis

LOWESS regression growth trajectories defined by CRL were plotted to compare the four groups (Fig. 2). Point estimates of CRL from linear mixed model were determined at 6 and 8 weeks' gestation (Table 2). At both 6 and 8 weeks' gestation, no statistically significant difference was observed between method of conception and mean CRL. Although there was a trend for the 1 CL group to be larger than the fresh IVF group at 6 and 8 weeks' gestation, statistical significance was not reached ($p = 0.105$ and $p = 0.060$, respectively). Growth trajectories using CRL measurements followed expected upward trends (Supplemental Fig. 1).

LOWESS regression growth trajectories defined by GSD were plotted to compare the four groups (Fig. 2). Point estimates of GSD were determined at 6 and 8 weeks' gestation (Table 2). Gestational sac diameter was comparable among

the four groups. Individual growth trajectories using GSD measurements followed expected upward trends (Supplemental Fig. 2).

IVF subgroup analysis

LOWESS regression growth trajectories defined by CRL and GSD were plotted to compare the three IVF groups (Fig. 3). The fresh IVF group had a significantly smaller mean CRL at 6 weeks compared with the frozen natural IVF group ($p = 0.017$). There was a trend for the CRL to be smaller in the fresh IVF group compared to frozen natural IVF at 8 weeks, but the difference was not statistically significant ($p = 0.08$). Crown rump length was significantly smaller at 8 weeks' gestation in the fresh IVF group compared to the frozen programmed IVF ($p = 0.039$). All adjusted p values for GSD were greater than 0.05 indicating no significant difference in GSD with any comparison (Table 3).

Fig. 2 LOWESS curves for CRL (mm) vs. gestational age (days) and GSD (mm) vs. gestational age (days) for CL groups. CRL crown rump length, GSD gestational sac diameter, CL corpus luteum or corpora lutea, IVF in vitro fertilization

Table 2 Least squares mean of CRL and GSD at 6 weeks (42 days) and 8 weeks (56 days) gestation based on the linear mixed model including the CL group, gestational age, and their interaction as predictors

	Mean, 95% CI 0 CL (<i>n</i> = 24)	1 CL (<i>n</i> = 131)	Multiple CL/ non-IVF (<i>n</i> = 88)	Fresh IVF (<i>n</i> = 78)
CRL-42 days	2.07 (1.11, 3.03)	2.32 (1.91, 2.73)	1.94 (1.41, 2.47)	1.52 (0.97, 2.07)
CRL-56 days	17.03 (16.29, 17.77)	16.86 (16.55, 17.17)	16.75 (16.34, 17.16)	16.18 (15.77, 16.59)
GSD-42 days	14.90 (12.88, 16.92)	14.50 (13.68, 15.32)	14.37 (13.29, 15.45)	13.71 (12.59, 14.83)
GSD-56 days	29.97 (28.30, 31.64)	30.12 (29.39, 30.85)	29.15 (28.17, 30.13)	29.40 (28.44, 30.36)

CRL crown rump length, GSD gestational sac diameter, CL corpus luteum or corpora lutea, IVF in vitro fertilization

Discussion

To the best of our knowledge, this is the first study to report early pregnancy growth differences between fresh and frozen ETs. In this analysis, among conceptions achieved via IVF, CRL was smaller at 6 and 8 weeks' gestation for fresh ETs compared to frozen ETs. Although these differences in first trimester CRL are not large, it is notable that there are differences detectable so early in pregnancy.

Studies of first trimester CRL growth in IVF pregnancies have not led to consistent findings to date, possibly due to differences in study design or patient population. Eindhoven et al. found similar first trimester growth trajectories between pregnancies conceived via IVF and spontaneously conceived pregnancies in fertile women [6]. Conway also noted no significant difference in CRL at 9–12 weeks' gestation among women who conceived via IVF (*n* = 63), non-IVF treatment (*n* = 64), or spontaneous conceptions among fertile women (*n* = 1535) [17]. In contrast, Bonne et al. reported larger first trimester CRL measurements with IVF treatment, including both fresh and frozen

ETs, compared to spontaneous pregnancies among fertile women [7]. Cooper and colleagues found that first trimester CRL measurements were smaller in infertile women compared to fertile women, suggesting that infertility and not the specific medical treatment for infertility might be the most significant factor when considering first trimester embryonic growth [5]. In comparison to spontaneously conceived pregnancies among fertile women, they found smaller first trimester CRL among infertile women who conceived spontaneously and via IUI, but no difference with IVF, with only fresh ET cycles included [5]. The heterogeneity among studies of ART pregnancy outcomes in the first trimester makes it difficult to draw any clear conclusions at this time. Based on our analysis in the context of the literature to date, we suggest that it is important that future studies of first trimester growth include separate analysis for fresh and frozen ETs, and include comparator groups with spontaneous conceptions in fertile and infertile populations whenever possible.

In our study, GSD in the first trimester was comparable among all groups. Supplemental Figs. 1 and 2 demonstrate

Fig. 3 LOWESS curves for CRL (mm) vs. gestational age (days) and GSD (mm) vs. gestational age (days) for IVF groups. CRL crown rump length, GSD gestational sac diameter, IVF in vitro fertilization

Table 3 Subgroup analysis of patients who underwent IVF. Least squares mean of CRL and GSD at 6 weeks (42 days) and 8 weeks (56 days) of gestation based on the linear mixed model including the CL group, gestational age, and their interaction as predictors

	Mean, 95% CI IVF fresh (<i>n</i> = 78)	IVF frozen natural (<i>n</i> = 52)	IVF frozen programmed (<i>n</i> = 18)
CRL-42 days ^a	1.50 (1.05, 1.95)	2.50 (1.95, 3.05)	1.88 (0.98, 2.78)
CRL-56 days ^b	16.13 (15.81, 16.44)	16.71 (16.30, 17.12)	17.02 (16.39, 17.65)
GSD-42 days	13.70 (12.68, 14.72)	13.72 (12.47, 14.97)	14.97 (12.89, 17.05)
GSD-56 days	29.41 (28.53, 30.29)	29.96 (28.82, 31.10)	29.61 (27.90, 31.32)

CRL crown rump length, GSD gestational sac diameter, IVF in vitro fertilization

^a CRL: IVF fresh vs. IVF frozen natural at 42 days, $p = 0.017$

^b CRL: IVF fresh vs. IVF frozen natural at 56 days, $p = 0.080$

^c CRL: IVF fresh vs. IVF frozen programmed at 56 days, $p = 0.039$

the large variability in individual GSD, which may have limited our ability to detect differences between groups.

One strength of our study is the inclusion of multiple methods of conception among infertile women and detail available regarding IVF conceptions. In addition, this study is the first to compare first trimester growth between conceptions with a single CL, multiple CL, or absence of the CL. Another strength of this study is exclusion of vanishing twins. Pregnancies were only included if precise dates of conception were known. Recall bias about history is unlikely because participants completed the demographics questionnaire before the outcome of their pregnancy was known.

This study has several limitations. Our study focused on CRL at 6–8 weeks' gestation, and did not include CRL measurements from the late first trimester. The study included only infertile women, and our focus was on the method and associated CL number at conception. Although the age was slightly higher in programmed cycles with 0 CL, a study by Bottomley et al. also found that maternal age (40 years compared with 20 years old) was associated with a smaller CRL in early gestation, but a larger CRL by 12 weeks' gestation [18]. It is difficult to compare our study with theirs given that our study has a narrower range of age with ultrasound findings limited to 6–8 weeks' gestation. Although the total number of participants was relatively large in our study compared with other studies in an infertile population, some of the subgroups were small and it is possible that a larger study could demonstrate statistically significant differences in first trimester growth based on CL number.

One could ask whether the CRL for fresh ETs could be considered “too small” or whether the CRL for frozen ETs is “too big.” After the original first trimester growth curves were established by Robinson and Fleming in 1973, Hadlock published data that are widely used in algorithms to date pregnancy based on CRL measurements [19, 20]. As noted in their publication, CRL is expected to be 3 mm at 5.9 weeks, 4 mm at 6.1 weeks, and 16 mm at 8.0 weeks of gestation [20]. All of these values are close to the values calculated in our model, but it is not possible to draw any

definite conclusions by comparing the data from these authors with the findings in this manuscript.

Although the potential physiological significance of the larger CRL we found for the frozen compared with fresh ET cycles is not certain, several studies have observed a positive correlation between CRL at more advanced gestational age (greater than 10 weeks) and birth weight [21–23]. A large study comparing fresh versus frozen IVF pregnancies using sibling pairs found an increased risk of large for gestational age infants in pregnancies conceived by frozen ET [13], and groups have reported an increased risk of large for gestational age and macrosomia in frozen ET cycles [13–15]. In contrast, fresh IVF cycles have been associated with an increased risk of small for gestational age and low birth weight [4]. Given these observations, future larger studies of fresh versus frozen ET should consider the potential correlation of first trimester growth and risk of low birth weight and macrosomia.

It is interesting to speculate why embryonic growth differences were seen as early as the first trimester. It is possible that cryopreservation and thaw of the embryos affects early embryo growth. It is also possible that differences in early growth may be due to the differences in the maternal endocrine milieu between fresh and frozen embryo transfers. In conclusion, when comparing fresh ET with frozen ET, this study suggests that small but statistically significant differences in CRL are detectable as early as the first trimester. Further study is warranted to better understand what may be leading to these observed differences, as well as to the lower incidence of low birth weight and higher incidence of macrosomia with frozen ET.

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Compliance with ethical standards All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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