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Antenatal fetal growth patterns in uncomplicated pregnancies according to mode of conception and placental location

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ABSTRACT

Newborns resulting from in-vitro fertilisation (IVF) had a significantly (P= 0.002) higher birthweight centile than those resulting from spontaneous conception (SC) but no significant changes were found in ultrasound estimated fetal weight (EFW) centile between 20-22 and 32–34 weeks between the IVF and SC groups. When stratified for the IVF methods used, significant (P = 0.02) fastest in-utero fetal growth (mean increase in centile of 5 between 2nd to 3rd trimester) was observed in the frozen embryo transfer (FET) subgroup compared to SC, and to IVF pregnancies resulting from fresh blastocyst transfer (FBT) or from oocyte donation (OD). Low placentation was significantly (P < 0.001) more common in the IVF group than in the SC group but was not associated with a change in growth pattern suggesting that fetal growth in-utero is independent of placental location but may be influenced by embryo freezing.

1. Introduction

In-vitro fertilisation (IVF) has been associated with an increased incidence of small-for-gestational age (SGA) and low-birth weight (LBW) newborns [1,2]. Abnormally slow fetal growth has been reported to be more common in singleton compared to multiple IVF pregnancies [2]. Different IVF techniques have been shown to have a different impact on the risk of pregnancy complications and oocyte donation (OD) is associated with 4–5 times higher risk of pre-eclampsia than spontaneous conception (SC) [3,4]. Patients with a thinner endometrium are also more at risk of placental malperfusion resulting in fetal growth restriction (FGR) [5]. IVF is associated with a higher risk of low placentation i.e., low-lying/placenta previa [6] and placental development inside the low uterine segment (LUS) has been associated with a higher risk of SGA [7,8].

Prenatal fetal growth patterns and birthweight are influenced by many factors, however, most epidemiologic and cohort studies on the perinatal outcomes of IVF pregnancies do not adjust their data for confounding factors mainly maternal parity, exposure to tobacco smoke, body mass index (BMI) and ethnicity. In addition, most cohort studies provided little data on pre-existing maternal condition such as chronic hypertension glucose intolerance or thrombophilia, which are also, known factors affecting fetal growth and none provide longitudinal data on antenatal growth. The aim of the present study was to further evaluate the possible impact of conception mode and placental location on fetal growth patterns during the second half of pregnancy.

2. Methods

We conducted a single–centre, retrospective case control study of 203 uncomplicated singleton pregnancies that resulted in live births between 37 and 41 weeks of gestation over a 5 year-period ending in June 2022, at the Portland Hospital, London, UK. The study group included 116 couples with unexplained infertility with IVF pregnancies, resulting from autologous fresh emryo/blastoyst transfer (FBT) (n = 50), autologous frozen embryo transfer (FET) (n = 49) or (OD) (n = 17). All patients were managed using a standardised protocol which included, progesterone (400 mg pessary twice daily), low molecular weight heparin (20 mg SC daily) and aspirin (20 mg PO daily) supplements during the first trimester. The control group included 87 uncomplicated pregnancies resulting from SC managed during the same period by the same obstetric team. Cases and controls were matched for parity and ethnicity. Exclusion criteria included multiple pregnancies, maternal exposure to active or passive smoking, preconception maternal medical conditions, medical complications during pregnancy, fetal congenital defect, and premature delivery. Ethical committee approval (HCA

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Healthcare UK R&D/22/008) was obtained prior to the start of this study.

Pregnancies were dated according to the last menstrual period (LMP) and confirmed by the fetal crown-rump length (CRL) at 11–14 weeks. Standardised ultrasound fetal biometry measurements were obtained at 20–22 and 32–34 weeks. The estimated fetal weight (EFW) and the corresponding percentiles and birthweight (BW) percentiles were calculated using the growth curves of the Fetal Medicine Foundation (https://fetalmedicine.org/).

The placental location was recorded as anterior, posterior, or fundal when in the upper segment of the uterus, or as low-lying (when the placental edge was 0.5–2 cm from the internal os) or previa (when the placenta was < 0.5 cm from the internal os or covering it) at any gestational age after 16 weeks [9]. All examination were performed by the same operator (EJ) using a GE Voluson E10, GE Medical System, Zipf, Austria.

Stata/IC version 15.0 (StataCorp LLC, TX, USA) was used for analysis. Categorical variables were compared using the Pearson's chi-square test and continuous variables using a *t*-test. Changes in fetal weight centile between the second and third trimester were analysed using Analysis of Covariance (ANCOVA). A P value < 0.05 was considered significant.

3. Results

Patients in the IVF group were significantly older (35.8 (SD 4.2) vs 34.3 (SD 3.9) years of age, $P = 0.03$) and the corresponding newborns had a significantly higher BW centile (56.0 (22.9) vs 48.9 (23.2), $P = 0.002$) than those in the SC group. There was no significant difference for the other parameters (BMI, maternal age and fetal gender) between the groups. There was no significant difference between the IVF group as a whole and the SC control group in terms of changes in EFW centile from 2nd to 3rd trimester (Table 1). FET was associated with the fastest in-utero fetal growth (Fig. 1), with a mean increase in centile of 5, compared to controls and to FBT and OD ($P = 0.02$). There was no difference in growth patterns between fetuses conceived by FBT or OD. IVF was associated with a significantly ($P < 0.001$) higher incidence of low placentation compared to SC (42.2% vs 11.49%). No difference in changes in fetal growth pattern was found according to the placental location (IVF vs. controls, $P = 0.82$; IVF subgroups $P = 0.95$).

4. Discussion

Systematic reviews have reported a higher incidence SGA, preterm birth, congenital malformation and perinatal mortality in IVF pregnancies compared to SC controls [1] but the authors did not stratify the data for placental-related pregnancy complications nor for other confounding factors that can influence fetal growth. Similarly, studies on fetal growth and placental location did not exclude patients with pre-existing medical disorders such as thrombophilia and those who were active smokers [7,8].

A recent study using a novel unified prenatal-postnatal modelling in IVF pregnancies found a higher EFW and birthweight Z-scores in FET than in FBT [10]. The data of our study, confirm the lower risks of SGA at birth in FET pregnancies compared to other IVF methods [10–12] and shows for the first time that the faster fetal growth in FET pregnancies starts from mid-gestation. The trophoblastic cells in IVF-FET present a different expression in imprinted genes PEG10 mRNA and protein compared to IVF-ET controls [13] suggesting that the effect of embryo freezing on fetal growth may be due to difference in placental development.

The main strength of the present study is the homogeneity of our cohort of uncomplicated IVF pregnancies, stratified for different IVF techniques and to include the main factors influencing fetal growth in the analysis. The primary limitation of our cohort study is its retrospective design. However, all ultrasound measurements were performed by the same operator using the same ultrasound equipment and a standardised protocol limiting the ascertainment bias of larger cohorts and epidemiologic studies.

Table 1
Comparison of birthweight centile between study groups for change from 2nd to 3rd trimester.

Comparison/group	n	2nd trimester Mean (SD)	3rd trimester Mean (SD)	Change Mean (SD)	*P*-value (*)
All IVF vs. control					0.85
Control	87	52 (17)	53 (20)	0 (22)	
All IVF	116	56 (16)	56 (18)	0 (19)	
IVF subgroups					0.07 (#)
FBT	50	53 (13)	49 (16)	−4 (14)	
FET	49	59 (18)	64 (18)	5 (24)	
OD	17	56 (14)	53 (17)	−3 (16)	
IVF subgroups vs. control					
Control	87	52 (17)	53 (20)	0 (22)	
FBT	50	53 (13)	49 (16)	−4 (14)	0.62 (+)
FET	49	59 (18)	64 (18)	5 (24)	**0.02** (+)
OD	17	56 (14)	53 (17)	−3 (16)	1.00 (+)

(*) *P*-values for change in fetal weight between 2nd and 3rd trimester between groups. Differences adjusted for weight at 2nd trimester.
(#) *P*-value for overall comparison between three IVF subgroups.
(+) *P*-values given a Bonferroni adjustment to allow for multiple comparisons to the control group.
FBT = fresh blastocyst transfer; FET = frozen embryo transfer; OD = oocyte donation.

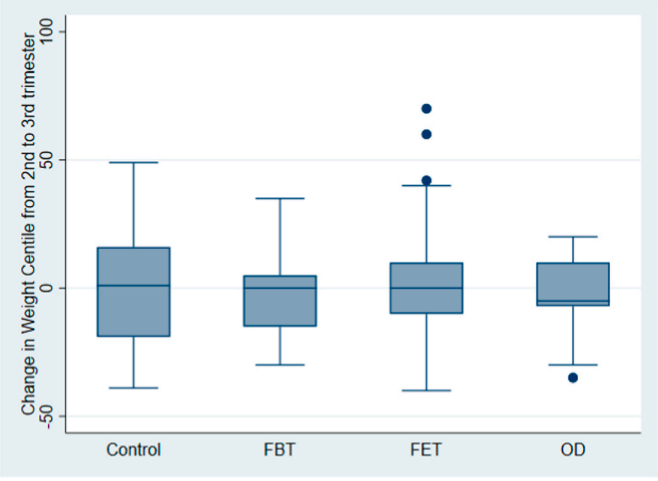

Fig. 1. Box of changes in EFW centile between 2nd and 3rd trimester in the control group vs fresh blastocyst transfer (FBT), frozen embryo transfer (FET) and oocyte donation (OD).

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Declaration of competing interest

The authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2023.11.016.

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