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ASSISTED REPRODUCTION TECHNOLOGIES

Impact of elevated peak serum estradiol levels during controlled ovarian hyperstimulation on the birth weight of term singletons from fresh IVF-ET cycles

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Abstract
Purpose To investigate the impact of elevated serum estradiol (E_2) levels on the day of hCG trigger on the birth weight of term singletons after fresh In Vitro Fertilization (IVF)-Embryo Transfer (ET) cycles.
Methods Retrospective cohort study of all patients initiating fresh IVF-ET cycles resulting in live births between January 2004 and February 2013. The incidence of low birthweight (LBW) term singletons in patients with E_2 levels on day of hCG trigger above or below the 95 % cutoff for E_2 values in our clinic (3,069.2 pg/mL) was estimated. Multiple gestations and vanishing twin pregnancies were excluded.
Results Two thousand nine hundred thirty-nine singleton live births were identified for inclusion. One hundred forty seven (5 %) and 2792 (95 %) live singleton births occurred in patients with peak E_2 levels above and below 3,069.2 pg/mL, respectively. The overall incidence of term LBW was 5.4 % in the >3,069.2 pg/mL group compared to 2.4 % in the ≤3,069.2 pg/mL group (P=.038). An E_2 level >3,069.2 pg/mL on the day of hCG administration was associated with increased odds of LBW term singletons (OR=2.29; 95 % CI=1.03–5.11). The increased odds remained unchanged when adjusting for maternal age (aOR=2.29; 95 % CI=1.02–5.14; P=.037), gestational age at delivery (aOR=2.04; 95 % CI=1.22–3.98; P=.025), and day 3 versus blastocyst transfer (aOR=2.5; 95 % CI=1.11–5.64; P=.023).
Conclusions Peak E_2 level >3,069.2 pg/mL is associated with increased odds of LBW term singletons after fresh IVF-ET cycles. Conservative stimulation protocols aiming not to exceed an E_2 level of 3,000 pg/mL may be advantageous for placentation and fetal growth if a fresh transfer is planned.

Keywords Estradiol level · Birth weight · Small for gestational age · IVF · Controlled ovarian hyperstimulation

Capsule Peak estradiol levels and birth weight

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Introduction

The use of Assisted Reproductive Technology (ART) to overcome the problem of infertility continues to increase steadily [1]. Overall, ART contributed to 1.5 % of all live U.S. births in 2012 [2]. In recent years, there has been concern about the safety of ART, particularly IVF [3–5]. The majority of singleton births after IVF are uncomplicated; however, studies have suggested that IVF pregnancies may be independently associated with increased risks for low birthweight (LBW) [6–8], preterm birth [9], and perinatal mortality [7, 8] compared with spontaneous singleton conceptions. Although the pathogenesis of LBW in IVF singletons still remains unknown, recent data have suggested that the supraphysiologic hormonal milieu during ovarian hyperstimulation (COH) may be a possible mediator of LBW in IVF singletons [10, 11]. To address this hypothesis, we set out to investigate the impact of elevated E_2 levels on the day of hCG administration on the birth weight of term singletons after fresh IVF-ET cycles at our center.

Materials and methods

Cycle inclusion criteria

The institutional review board at Weill Cornell Medical College approved our study protocol. All patients initiating fresh IVF-ET cycles at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine resulting in live births between January 2004 and February 2013 were analyzed for potential inclusion. Cycles that resulted in multiple births, selective reduction, vanishing twins, or had incomplete records were excluded. Preterm birth was defined as any live birth ≤37 weeks of gestational age. Preterm birth <34 weeks of gestation was defined as early preterm birth, while preterm between >34 and ≤37 weeks of gestation was defined as late preterm birth [12]. LBW was defined as birth weight <2,500 g irrespective of gestational age [13]. Very low birth weight (VLBW) was defined as birth weight <1,500 g irrespective of gestational age [9, 13]. E_2 levels of cycles resulting in singleton live births were analyzed for E_2 level, and the 95th percentile was defined as elevated E_2.

Clinical and laboratory protocols

COH, hCG trigger, oocyte retrieval, embryo culture, and ET were carried out per our standard protocols [14–16]. Some patients were down regulated using a GnRH agonist (Lupron; Abbott Pharmaceuticals) followed by stimulation with gonadotropins (Follistim [Merck]; Gonal-F [EMD-Serono]; and/or Menopur [Ferring]). Flare protocols were used as clinically indicated. Alternatively, patients were stimulated with gonadotropins followed by pituitary suppression with a GnRH antagonist (Ganirelix Acetate, 0.25 mg [Organon]; or Cetrotide, 0.25 mg [EMD-Serono]). Patients who required pretreatment for follicular synchronization were started on oral contraceptive (OC) pills (Ortho-Novum, Janssen Pharmaceuticals), or 0.1 mg E_2 patches (Climara, Bayer Healthcare Pharmaceuticals) with or without Ganirelix. For GnRH antagonist cycles, patients were started on 0.25 mg of Ganirelix or Cetrotide based on a flexible protocol as previously described [15]. Ovarian stimulation was carried out to maximize follicular response while minimizing risk of ovarian hyperstimulation syndrome (OHSS). Selection of the initial gonadotropin dose was based on multiple factors such as patient age, weight, antral follicle count, day 3 FSH/E2, antimüllerian hormone (subsequent to 2010), and previous response to stimulation.

Oocyte maturation was triggered via hCG (Profasi [EMDSerono]; Novarel [Ferring Pharmaceuticals]; or Pregnyl [Schering-Plough]), according to a dosing scheme ranging from 10,000 to 3,300 IU based on serum E_2 levels [14–16]. In general, the hCG trigger was administered when the two lead follicles attained a mean diameter ≥17 mm. For GnRH antagonist cycles considered to be at high risk for OHSS, an ovulatory trigger of 2 mg leuprolide acetate in conjunction with 1,500 IU hCG was administered, with appropriate E_2 and progesterone (P) luteal support [17]. In all other cases, luteal support was begun the day after retrieval with 50 mg of intramuscular P. Oocyte retrieval was performed with transvaginal ultrasound guidance under conscious sedation 35–37 h after hCG administration. Fertilization was performed using conventional insemination or intracytoplasmic sperm injection according to the couple's history and male partner's semen analysis. Embryos were incubated in sequential in-house culture media. Most patients underwent ET on day 3; however, patients with several good-quality embryos on day 3 were eligible for and underwent blastocyst transfer on day 5. All embryo transfers were performed with Wallace catheters (Marlow/Cooper Surgical).

Study variables

Demographic characteristics extracted from patient charts included age, parity, body mass index (kg/m^2), infertility diagnosis, number of previous IVF attempts, basal follicle stimulating hormone (FSH) level (mIU/mL), COH protocol during

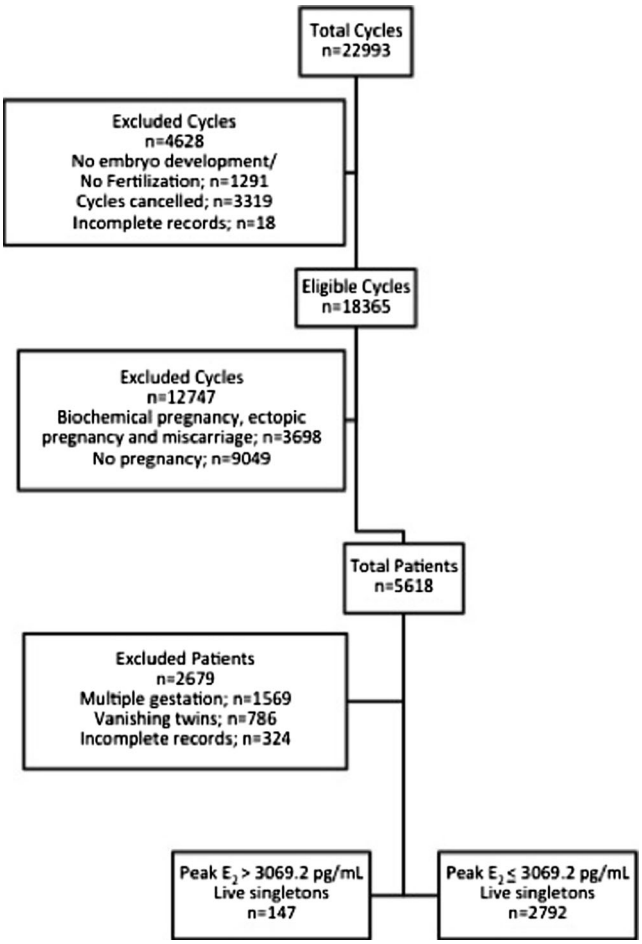

Fig. 1 Study cohort selection

current IVF cycle, endometrial stripe thickness (mm) on day of hCG administration, total days of stimulation, total dosage of gonadotropins administered (IU), number of embryos transferred, and day of ET. Birth outcomes analyzed included birth weight, mode of delivery, incidence of preterm birth, and incidence of term LBW.

Statistical analysis

All statistical analyses were performed using STATA version 13 (College Station, TX: StataCorp LP). Continuous variables were expressed as mean±standard deviation (SD), and categorical variables were expressed as number of cases (n) and percentage of occurrence (%). Wilcoxon rank sum test and student's *t*-test were utilized for continuous variables. Chi-square ($\chi 2$) with Mantzel-Hansel correction and Fisher's exact test were used for categorical variables. Odds ratios (OR) with 95 % confidence intervals (CI) for the incidence of term LBW were calculated. Adjusted odds ratios (aOR) were estimated using logistic regression controlling for maternal age, gestational age at delivery, hCG trigger dose, and day of ET. Statistical significance was set at $P<.05$.

Results

Figure 1 summarizes the selection of the study cohort. A total of 5618 patients underwent fresh IVF-ET cycles resulting in live birth during the study period. Of these, 1569 (27.9 %) patients were excluded due to multiple gestation, 786 (14 %) patients were excluded due to vanishing twins and 324 (5.8 %) patients were excluded for incomplete records. The remaining (52.3 %) patients accounted for 2939 live singleton births. The mean E_2 level±SD and the 95th percentile±SD on the day of hCG administration for the study cohort was 1675.6± 748.1 pg/mL and 3069.2±748.1 pg/mL, respectively. There were 147 live singleton births in the E2>3069.2 pg/mL group and 2792 live singleton births in the $E_2 \leq 3069.2$ pg/mL group.

Table 1 compares the demographic characteristics of patients with peak E_2 levels above and below 3,069.2 pg/mL. Overall, there were no differences in mean age, parity, body mass index, number of previous IVF attempts, basal FSH levels, peak endometrial stripe, total days of stimulation, or mean embryos transferred between the two groups. There was also no difference in distribution of infertility diagnoses and COH protocols within each group. However, the total dosage of gonadotropins administered in the >3069.2 pg/mL group

Table 1 Baseline characteristics of study cohort (n=2939)

Parameter	Peak E_2>3069.2 pg/mL (n=147)	Peak $E_2 \leq 3069.2$ pg/mL (n=2792)	P
Age (years)	34.8 (±4.6)	35.2 (±4.5)	.29
Parity	.27 (±.58)	.33 (±.59)	.22
BMI (kg/m^2)	22.5 (±4.5)	22.9 (±6.4)	.45
Infertility diagnoses			.99
Ovulatory	30 (20.4)	579 (20.7)	
Tubal	10 (6.8)	169 (6.1)	
Endometriosis	5 (3.4)	119 (4.3)	
Male factor	36 (24.5)	628 (22.5)	
Idiopathic	11 (7.5)	227 (8.1)	
Other	55 (37.4)	1070 (38.3)	
Previous IVF attempts	1.58 (±1.60)	1.63 (±1.93)	.77
Basal FSH (mIU/mL)	4.23 (±2.03)	4.46 (±2.74)	.19
COH Protocol			.65
Follicular phase GnRH-ant	46 (31.3)	947 (33.9)	
Follicular phase GnRH-a	44 (30)	929 (33.3)	
Luteal phase GnRH-a	29 (19.7)	453 (16.2)	
Other	28 (19)	463 (16.6)	
Peak endometrial stripe (mm)	11.5 (±2.6)	11.4 (±6.8)	.86
Total stimulation days	9.6 (±1.7)	9.6 (±1.9)	1
Total gonadotropins administered (IU)	1923.1 (±1007.1)	2977.2 (±1772.1)	**<.0001**
Total number of oocytes	17.3 (±6.9)	11.4 (±5.7)	**<.0001**
Embryos transferred	2.6 (±1.3)	2.7 (±1.1)	.29
Blastocyst transfer	46 (31.3)	391 (14)	**.003**

Data are presented as mean± standard deviation and n (%)

BMI Body Mass Index

IVF In Vitro Fertilization

FSH Follicle Stimulating Hormone

COH Controlled Ovarian Hyperstimulation

GnRH-ant Gonadotropin Releasing Hormone-Antagonist

GnRH-a Gonadotropin Releasing Hormone-Agonist

Bolded numbers indicate significance

was significantly lower than the ≤3069.2 pg/mL group ($P<.0001$). The mean number of oocytes±SD retrieved in the E_2>3069.2 pg/mL group (17.3±6.9) was higher compared to the E_2≤3069.2 pg/mL group (11.4±5.7). A significantly higher number of blastocyst transfers occurred in the E_2> 3069.2 pg/mL group ($P=.003$). Patients in the E_2> 3069.2 pg/mL group exhibited a robust response to gonadotropins, as evident from the number of oocytes retrieved in this group compared to the E_2≤3069.2 pg/mL group. Due to this response, patients required comparatively lower doses of gonadotropins. In order to prevent OHSS in this group of patients, transfer was more often deferred until day 5, so as to observe patients for signs of early OHSS; thus, a higher number of blastocyst transfers occurred in the E_2>3069.2 pg/mL group.

Birth outcomes were available for all 2939 births. Table 2 compares the birth outcomes between the two E_2 groups; rates of vaginal and cesarean deliveries were comparable. Furthermore, no differences in the rates of term births (88.4 % vs. 90 %), late preterm births (9.5 % vs. 7.7 %), or early preterm birth (2.1 % vs. 2.3 %) were found between the two groups. There was also no difference in the mean overall birth weight (range 3261.6–3268.0 g) and mean term birth weight (range 3335.8–3354.0 g) when comparing the two groups. A significant difference was found in the incidence of term LBW singletons (5.4 % in the >3069.2 pg/mL group versus 2.4 % in the ≤3069.2 pg/mL group ($P=.038$). Patients with E_2 levels >3,069.2 pg/mL on the day of hCG administration had more than twice the risk of giving birth to a LBW term infant as compared to patients with lower E2 levels (OR=2.29; 95 % CI=1.03–5.11). The increased odds remained unchanged when adjusting for maternal age (aOR=2.29; 95 % CI= 1.02–5.14; $P=.037$), gestational age at delivery (aOR=2.04; 95 % CI=1.22–3.98; $P=.025$), hCG trigger dose (aOR=1.99; 95 % CI=1.08–3.99; $P=.036$), as well as adjusting for the day of embryo transfer (aOR=2.5; 95 % CI=1.11–5.64; $P=.023$). There were no term VLBW births in either group.

Table 2 Birth outcomes of study cohort ($n=2939$)

Parameter	Peak E_2>3069.2 pg/mL ($n=147$)	Peak E_2≤3069.2 pg/mL ($n=2792$)	*P*
Mode of Delivery			.20
Vaginal	68 (46.3)	1122 (40.2)	
Cesarean	76 (51.7)	1558 (43.8)	
Unknown	3 (2.0)	112 (4.0)	
Term Birth	130 (88.4)	2514 (90)	.26
Preterm Birth			.30
Late preterm	14 (9.5)	214 (7.7)	
Early preterm	3 (2.1)	64 (2.3)	
Overall Birth Weight (g)	3261.6 (±547.0)	3268.0 (±555.2)	.99
Term LBW	7 (5.4)	61 (2.4)	**.038**
Term VLBW	0	0	–

Data are presented as mean±standard deviation and n (%)

Term: >37 weeks gestational age

Preterm: ≤37 weeks gestational age

Late preterm: >34 and ≤37 weeks gestational age

Early preterm: ≤34 weeks gestational age

LBW Low Birth Weight i.e., birth weight <2500 g irrespective of gestational age

VLBW Very Low Birth Weight i.e., birth weight <1500 g irrespective of gestational age

Bolded numbers indicate significance

Discussion

Our study adds to the growing body of literature suggesting an association between supraphysiologic E_2 levels during COH and altered placental dynamics in IVF singletons. Our data showed increased odds of term LBW at a lower E_2 threshold than previously reported i.e., 3,069.2 pg/mL versus 3,450 pg/mL [11].

In 2002, Schieve et al. highlighted the potential association between IVF and LBW [6]. In that study, the authors found that the overall odds of LBW in IVF singletons were 1.8 times higher than spontaneous singletons. Since then, several studies have corroborated these findings [7, 8]. Latest data indicate that infants conceived with ART comprise 5.6 % of all LBW infants in the United States, though much of this morbidity is due to multiple gestations [1]. Putative mechanisms ranging from the intrinsic characteristics of the infertile couple to the hormonal milieu during COH for IVF have been suggested to explain the association between LBW in singletons and IVF, however the exact mechanisms still remain unknown [4, 5, 10, 11].

Studies reporting the association between supraphysiologic E_2 levels during COH and LBW have begun to emerge [10, 11]. Kalra et al. [10] highlighted this potential association in the their analysis of birth weights in 56,792 singletons. The authors reported a 1.73 times higher odds of LBW at term in singletons from fresh autologous IVF as compared to frozen-thawed cycles. In another retrospective study of 292 IVF singletons, Imudia et al. [11] reported 9.4 times higher odds of delivering LBW singletons in patients with E_2 levels >3, 450 pg/mL on the day of hCG administration. Consistent with these findings, our data show twice the odds of term LBW singletons in patients with E_2 levels >3,069.2 pg/mL on the day of hCG administration compared to patients with E_2 levels below this cutoff.

The supraphysiologic hyperestrogenic milieu during COH may contribute to the pathogenesis of LBW, at least in animal models, by creating a poorer environment for implantation [4, 18]. For example, supraphysiologic E_2 levels have been shown to have a toxic effect on the developing embryo in

mice, leading to impairment in embryonic adhesion and implantation potential [19–21]. Elevated estrogen levels also impair the expression of implantation-associated genes in mice, leading to aberrant placentation [22]. Altered implantation physiology has been demonstrated in a baboon model, where elevated E_2 levels are associated with attenuation of spiral artery invasion [23]. Consistent with these animal models, supraphysiologic E_2 levels can modulate endometrial gene expression profiles in humans, thereby potentially affecting implantation and placentation [24–28]. Resulting modifications to trophoblastic invasion may lead to placental dysfunction and contribute to the pathogenesis of LBW and preeclampsia in IVF singletons [22].

The odds of delivering LBW singletons (2 times higher in our study cohort), was lower than the 9 times higher odds in the Imudia et al. study possibly because of the much larger size of our cohort. Although the overall rate of preterm birth (10 %) in our study cohort was higher than that reported by Imudia et al. (6.85 %), we found no difference in rates of preterm birth in patients with peak E_2 levels above and below 3,069.2 pg/mL; moreover, this rate of preterm birth is consistent with overall rates of preterm birth (12–13 %) in spontaneously conceived pregnancies in the U.S. [29]. Similarly, Kalra et al. found no difference in the rate of preterm birth in their cohort. Although our findings remain unchanged even when adjusting for age and day of embryo transfer, we recognize that the confidence intervals remain relatively wide. Therefore, larger prospective studies to confirm these findings are encouraged. Of course, while several studies have implicated an endometrial effect underlying the observations delineated above, a primary adverse effect on gametes from vigorous stimulation remains to be further interrogated. It is also possible an elevated E_2 level may merely be a surrogate for some other uncharacterized molecular marker [30]. Even if E_2 levels are implicated in the pathogenesis of LBW in IVF singletons, the supraphysiologic threshold for such an effect still remains unknown [30].

The impact of the hyperestrogenic milieu during COH on implantation and placentation is an area of active investigation. Although maximizing follicular response during COH is important, it is more important to minimize the risks of OHSS and LBW associated with supraphysiologic E_2 levels, especially given the correlation between LBW and adult cardiovascular disease, diabetes, and dyslipidemia [31–33]. While there has been a recent shift towards frozen embryo transfer cycles in the name of improved endometrial physiology, it is plausible that conservative stimulation protocols with autologous, fresh transfer offer the same benefits, provided serum E_2 levels are carefully monitored.

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

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