Supraphysiological estradiol levels on the hCG trigger day are associated with SGA for singletons born from fresh embryo transfer

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Abstract

The effects of supraphysiological estradiol (E2) on neonatal outcomes and the significance of specific E2 concentrations remain unclear. The purpose of this study was investigate whether supraphysiological E2 levels on the hCG trigger day are associated with small size for gestational age (SGA) in singletons born from fresh embryo transfer (ET) cycles. Patients with singleton pregnancies with delivered after transfer of fresh embryos, during the period of July 2012 to December 2017 at our center were included. We excluded cycles involving a vanishing twin, maternal age >35 years, basal FSH ≥10 mIU/ml, AMH ≤1 ng/ml or incomplete records. We then divided all cycles into 5 groups by E2 level on the day of hCG trigger: group A, <2000 pg/ml (reference group); group B, 2000 pg/ml≤E2<2999 pg/ml; group C, 3000 pg/ml≤E2<3999 pg/ml; group D, 4000 pg/ml≤E2<4999 pg/ml; and group E, ≥5000 pg/ml. The prevalence of SGA among singletons from fresh ET was the primary outcome. The SGA rate significantly increased when the E2 level was ≥4000 pg/ml, as observed by comparing groups D (odds ratio [OR]: 1.79, 95% confidence interval [CI]: 1.16–2.76, P=0.01) and E (OR: 1.68, 95% CI: 1.10–2.56, P=0.02) with the reference group. Multivariate logistic regression indicated that a serum E2 level of at least 4000 pg/ml on the hCG trigger day was associated with increased SGA and with significant differences for groups D (adjusted OR [AOR]: 1.65, 95% CI: 1.05–2.59, P=0.03) and E (AOR: 1.60, 95% CI: 1.03–2.53, P=0.04) relative to the reference group. In conclusion，for fresh ET cycles, supraphysiological E2 ≥4000 pg/ml on the hCG trigger day increases the risk of singleton SGA.

Background

The use of assisted reproductive technology (ART) to treat infertility is steadily increasing, and the number of frozen embryo transfer (FET) cycles has dramatically risen over the past decade[1]. In a recent European survey, FET cycles accounted for 32.4% of all in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles, representing a significant increase from previously reported data[2]. Based on observational studies and randomized controlled trials, the following reasons may explain this phenomenon. First, vitrification, a newer technology, has significantly increased embryo cryosurvival rates relative to slow freezing, leading to improved clinical outcomes for FET cycles[3]. Second, to minimize the occurrence of multiple pregnancies, single embryo transfer (ET) has become the dominant strategy. Moreover, the development of preimplantation genetic diagnoses (PGD) and preimplantation screening (PGS) has resulted in additional extra embryos for cryopreservation. Finally, perinatal and neonatal safety has always been of profound importance. We previously reported that based on data from 2053 FET cycles and 2059 ET cycles, FET was associated with a reduced risk of small size for gestational age (SGA) and low birth weight (LBW) for singleton births[4]. Several other studies have reported similar findings[5–7], which have important implications for the potential physiological mechanisms of SGA and LBW in ART cycles.

The most notable difference between fresh ET and FET cycles is that fresh ET cycles expose embryos to the supraphysiological estradiol (E_2) milieu that is characteristic of controlled ovarian hyperstimulation (COH). In an oocyte donor study involving 56,792 identified infants from oocyte donor recipients who underwent no ovarian hormonal stimulation, including 38,626 infants and 18,166 infants conceived following the transfer of fresh and frozen embryos, respectively, the risk of LBW did not differ between fresh ET and FET cycles[8]. Whether supraphysiological E_2 impacts neonatal birthweight remains uncertain. Imudia et al.[9] reported that high peak serum E_2 (> 3450 pg/ml) during COH was associated with increased risks of SGA and preeclampsia for singleton pregnancies after IVF. In a subsequent study, these researchers confirmed that elective cryopreservation of all embryos in patients with elevated peak serum E_2 may reduce the risk of SGA for singleton births[10]. Additionally, Pereira et al.[11] reported that a peak E_2 level > 3069.2 pg/ml during fresh ET cycles was associated with increased odds of full-term LBW for singleton births. Liu et al. [12] reported that high E_2 levels after COH were correlated with lower birth weight and SGA. Moreover, Pereira et al.[13] found that supraphysiological E_2 (≥ 2500 pg/ml) was an independent predictor of LBW for full-term singletons born

after fresh ET. However, Wang et al.[14] reported that high serum E_2 (> 3757 pg/ml) associated with COH did not increase the risks of LBW, preterm birth (PTB) or neonatal malformation. In addition, Dunne et al.[15] suggested that high serum E_2 (≥ 13035 pmol/l) was unassociated with adverse maternal or neonatal outcomes, including PBT and SGA, among others. Therefore, the effects of supraphysiological E_2 on neonatal outcomes and the significance of specific E_2 concentrations remain unclear. Thus, this study assessed the impact of supraphysiological E_2 levels on the day of human chorionic gonadotropin (hCG) trigger following COH on SGA, LBW, PTB and full-term LBW for singleton births.

Materials And Methods

Population

The review board of the Third Affiliated Hospital of Zhengzhou University approved this retrospective cohort study. All patients who underwent fresh IVF/ICSI-ET cycles that resulted in singleton live births at the Reproductive Center of the Third Affiliated Hospital of Zhengzhou University between July 2012 and December 2017 were analyzed for potential inclusion. Cycles with pregnancy-related complications, including pregnancy-induced hypertension, gestational diabetes mellitus, placenta previa, placental abruption and premature membrane rupture, were excluded. We further excluded cycles involving a vanishing twin, maternal age > 35 years, basal follicle-stimulating hormone (FSH) ≥ 10 mIU/ml, anti-Müllerian hormone (AMH) ≤ 1 ng/ml, neonatal malformation or incomplete records.

We then divided all cycles into 5 groups by E_2 level on the day of hCG trigger: group A, < 2000 pg/ml (reference group); group B, 2000 pg/ml ≤ E_2 < 2999 pg/ml; group C, 3000 pg/ml ≤ E_2 < 3999 pg/ml; group D, 4000 pg/ml ≤ E_2 < 4999 pg/ml; and group E, ≥ 5000 pg/ml.

Clinical and laboratory protocols

All women underwent a standardized ovarian stimulation regimen using a gonadotrophin-releasing hormone agonist (GnRH-a) (Diphereline, Ipsen, France) and recombinant follicle-stimulating hormone (Gonal-f, Merck Serono, Germany). The follicle-stimulating hormone dose depended on maternal age, weight, and AMH and was adjusted based on ovarian response monitoring via three-dimensional (3D) ultrasonography and testing of serum sex steroids. Recombinant human chorionic gonadotropin (hCG; Merck, Darmstadt, Germany) at a dose of 5000 to 10000 IU was injected to induce oocyte maturation when at least 60% of the follicles measured 18 mm or more. On the trigger day, we routinely measured serum E_2, progesterone, FSH and LH levels, using the Roche cobas immunoassay (Roche Diagnostics). The preparation, set up, dilutions, adjustment, assay and quality control procedures were performed per the manufacturer's instructions. Intra- and interassay coefficients of variation were less than 10% for all measurements. Vaginal ultrasound-guided oocyte retrieval was performed 36 to 38 hours later. Based on sperm quality, routine IVF or ICSI was performed approximately 4 to 6 hours after follicular aspiration. Luteal-phase support was provided by injecting 60 mg of progesterone (Xianju, Zhejiang, China) or intravaginally administering 90 mg of a sustained-release progesterone vaginal gel (Merck Serono, Germany), beginning on the day of oocyte retrieval. Based on the recommendations of the American Society for Reproductive Medicine, up to two 2-day embryos or one 5-day blastocyst was selected and transferred. Beta hCG serum levels were measured 14 days after transfer. For women with a positive hCG test, luteal-phase support was continued until 10 weeks of pregnancy. All data regarding maternal and neonatal outcomes were obtained via reviewing our center's medical records.

Outcome measures

Our primary concern was whether the risk of SGA was associated with the E_2 level on the day of hCG trigger of the fresh ET. SGA was defined as a neonatal birthweight below the 10th percentile for gestational age[16]. Prespecified secondary efficacy outcomes included LBW (birthweight < 2,500 g), very low birth weight (VLBW, birthweight < 1,500 g), PTB (gestational weeks < 37) and full-term LBW (gestational weeks ≥ 37 and birthweight < 2,500 g).

Statistical analysis

For continuous data, the one-sample Kolmogorov-Smirnov test was used to check for normality. The Wilcoxon rank-sum test was performed to assess differences in continuous variables with abnormal distributions, and these variables were represented by medians and interquartile ranges. Categorical variables were expressed as the number of cases (n) and the corresponding percentage (%); differences in measurements were assessed using chi-square analyses. For SGA, LBW, and full-term LBW, multivariate logistic regression was used to adjust for effects of the study site and baseline characteristics. Unadjusted odds ratios (ORs) and their 95% confidence intervals (CIs) as well as adjusted odds ratios (AORs) and their 95% CIs were calculated. All statistical management and analyses were performed using SPSS software, version 22.0. A two-sided P value < 0.05 was considered statistically significant.

Results

Study population

From July 2012 through December 2017, a total of 12547 fresh ET cycles were performed, and 3033 cycles satisfied the eligibility criteria. There were 9514 cycles excluded for the following reasons: nonpregnancy (n = 6133), miscarriage (n = 951), multiple gestation (n = 750), a vanishing twin (n = 204), repeated patients (n = 56), maternal age > 35 years, basal FSH ≥ 10 mIU/ml or AMH ≤ 1 ng/ml (n = 1093), pregnancy complications (including pregnancy-induced hypertension, gestational diabetes mellitus, placenta previa, placental abruption and premature membrane rupture), neonatal malformation (n = 117), history of PTB (n = 68) or incomplete records (n = 142). Based on the E_2 level on the hCG trigger day, the 3033 included cycles were divided into five groups: group A (n = 551), group B (n = 748), group C (n = 649), group D (n = 500) and group E (n = 585) (Fig. 1).

Characteristics of the study groups

Table 1 lists the study groups' fundamental maternal and cycle characteristics. No significant between-group differences were observed in maternal age, infertility duration type, infertility, parity, ovarian stimulation duration, ART method, number of embryos transferred, gestational weeks, delivery mode or neonatal sex. However, maternal body mass index (BMI) (P = 0.00) and infertility diagnoses (P = 0.01) differed between groups. Between-group differences were found in basal FSH (0.01), AMH (P = 0.00), antral follicle count (P = 0.00), gonadotropin dosage (P = 0.00), endometrial thickness on the hCG trigger day (P = 0.03), number of embryos retrieved (P = 0.00) and embryo stage (P = 0.00). Multivariate logistic regression was used to adjust for baseline characteristics.

Table 1
Material and cycle characteristics between A-E groups

	Group A	Group B	Group C	Group D	Group E	P value
No. of cases	551	748	649	500	585	
Age(years)	29(27–32)	29(27–31)	28(26–32)	28(26–31)	28(27–31)	0.08
Body mass index (kg/m^2)	23.3(21.1–25.6)	22.8(20.7–25.0)	22.2(20.3–24.3)	21.6(20.0-23.5)	21.5(19.9–23.2)	0.00
Duration of Infertility (years)	3(2–5)	3(2–4)	3(2–5)	3(2–4)	3(2–4)	0.12
Type of infertility						0.10
Primary infertility (%)	54.4	58.7	60.9	62.2	58.6	
Secondary infertility (%)	45.6	41.3	39.1	37.8	41.4	
Infertility diagnosis						0.01
Tubal factor (%)	53.9	50.5	48.4	50.6	56.6	
Male factor (%)	21.4	26.5	27.3	26.0	26.0	
Others (%)	24.7	23.0	24.3	17.4	17.4	
Parity						0.46
0 (%)	79.1	78.7	81.2	81.6	82.1	
≥ 1 (%)	20.9	21.3	18.8	18.4	17.9	
Basal FSH(mIU/ml)	6.6(5.2-8.0)	6.4(5.3–7.6)	6.3(5.2–7.6)	6.3(5.1–7.4)	6.3(5.1–7.6)	0.01
AMH(ng/ml)	4.5(2.9–6.8)	4.5(3.1-7.0)	4.8(3.4–7.3)	4.8(3.5–6.9)	4.8(3.6–6.9)	0.00
No. of antral follicle count	11(8–15)	12(9–18)	12(9–18)	13(10–18)	12(10–18)	0.00
Dosage of gonadotropins (IU)	2550.0(2145.0-3782.0)	2450.0(1821.0-3310.0)	2550.0(1937.0-3250.0)	2450.0(1750.0-3300.0)	2450.0(1765.0-3078.5)	0.00
Duration of ovarian stimulation (days)	15(13–16)	15(13–16)	14(13–16)	15(13–16)	15(13–16)	0.52
Endometrial thickness on the day of hCG trigger (mm)	11.0(9.2–12.5)	11.0(10.0-12.5)	11.0(10.0-12.8)	11.0(9.5–12.3)	11.0(9.8–12.7)	0.03

	Group A	Group B	Group C	Group D	Group E	P value
No. of embryos retrieved	6(4–8)	10(7–13)	12(9–15)	13(10–16)	14(12–17)	0.00
Method of ART						0.09
IVF (%)	73.7	68.4	66.6	67.6	68.7	
ICSI (%)	26.3	31.6	33.4	32.4	31.3	
Embryo stage						0.00
D3 (%)	96.2	89.4	82.3	79.6	72.6	
D5 (%)	3.8	10.6	17.7	20.4	27.4	
No. of embryos transferred	2(2–2)	2(2–2)	2(2–2)	2(2–2)	2(2–2)	0.52
Gestational weeks	39(38–40)	39(38–40)	39(38–40)	39(38–40)	39(38–40)	0.25
Mode of delivery						0.31
Vaginal (%)	22.7	22.1	24.5	25.6	26.5	
Cesarean (%)	77.3	77.9	75.5	74.4	73.5	
Gender						0.54
Male (%)	50.3	52.7	53.5	55.2	54.4	
Female (%)	49.7	47.3	46.5	44.8	45.6	
Birthweight (grams)	3400(3000–3700)	3400(3000–3700)	3300(3000–3600)	3300(3000–3600)	3300(3000–3650)	0.00
Note: Data are expressed as median (interquartile range) or percentage. FSH: follicle-stimulation hormone; AMH: anti-Mullerian hormone.						

SGA and secondary outcomes

Differences in serum E_2 levels on the hCG trigger day were associated with significant differences in SGA, LBW, and full-term LBW (Table 2). When serum E_2 levels were at least 4000 pg/ml, the risk of SGA was significantly increased, with an OR of 1.79 (95% CI: 1.16–2.76, P = 0.01) for group D compared with that of group A. SGA incidence was significantly higher in group E than in the reference group, with an associated OR of 1.68 (95% CI: 1.10–2.56, P = 0.02).

Table 2
Odds ratio of SGA, LBW, VLBW, PTB, full-term LBW with increasing E2 levels

	Group A	Group B	Group C	Group D	Group E
SGA					
n(%)	37(6.7)	36(4.8)	54(8.3)	57(11.4)	63(10.8)
OR(95%CI)	1	0.70(0.44–1.13)	1.26(0.82–1.95)	1.79(1.16–2.76)	1.68(1.10–2.56)
P value		0.14	0.30	0.01	0.02
LBW					
n(%)	30(5.4)	35(4.7)	45(6.9)	50(10.0)	61(10.4)
OR(95%CI)	1	0.85(0.52–1.41)	1.29(0.80–2.08)	1.93(1.21–3.09)	2.02(1.28–3.18)
P value		0.53	0.29	0.01	0.00
VLBW					
n(%)	3(0.5)	2(0.3)	6(0.9)	0(0)	2(0.3)
OR(95%CI)	1	0.49(0.08–2.94)	1.71(0.42–6.85)	0.00	0.63(0.10–3.76)
P value		0.44	0.45	0.99	0.61
PTB					
n(%)	36(6.2)	45(6.0)	48(7.4)	36(7.2)	38(6.5)
OR(95%CI)	1	0.97(0.62–1.54)	1.21(0.77–1.91)	1.18(0.73–1.92)	1.06(0.66–1.70)
P value		0.91	0.40	0.50	0.82
Full-term LBW					
n(%)	16(2.9)	11(1.5)	17(2.6)	34(6.8)	42(7.2)
OR(95%CI)	1	0.50(0.23–1.08)	0.90(0.45–1.80)	2.44(1.33–4.48)	2.59 (1.44–4.66)
P value		0.08	0.76	0.00	0.00

Note: OR: odds ratio; CI: confidence interval; E_2: estradiol; SGA: small-for-gestational age; LBW: low birthweight; VLBW: very low birthweight; PT: preterm birth.

The LBW rate was significantly higher in groups D and E than in the reference group, with ORs of 1.93 (95% CI: 1.21–3.09, P = 0.01) and 2.02 (95% CI: 1.28–3.18, P = 0.00), respectively. Moreover, the frequency of full-term LBW was greater in groups D (OR: 2.44, 95% CI: 1.33–4.48, P = 0.00) and E (OR: 2.59, 95% CI: 1.44–4.66, P = 0.00) than in the reference group. However, VLBW and PTB did not significantly differ between the five groups.

Variables independently associated with SGA, LBW and full-term LBW: multivariate logistic regression analysis

Multivariate logistic regression analysis was performed to adjust for confounding factors (Table 3). The model included maternal age (< 30 years vs. ≥30 years), BMI, parity (0 vs. ≥1), infertility type (primary vs. secondary), infertility diagnosis (tubal/male/other), gonadotropin dosage (< 2500 IU vs. ≥2500 IU), endometrial thickness on the hCG trigger day, ART method (IVF vs. ICSI), embryo stage (D3 vs. D5), number of embryos transferred (1 vs. 2), mode of delivery

(vaginal vs. cesarean), neonatal sex (male vs. female) and E_2 level on the hCG trigger day (divided into the five aforementioned groups).

Table 3
Multiple logistic regression analysis to account for confounding variables of SGA、LBW and full-term LBW

	SGA		LBW		Full-term LBW	
	AOR(95%CI)	P value	AOR(95%CI)	P value	AOR(95%CI)	P value
Age(＜30/≥30)	0.80(0.58–1.10)	0.17	0.99(0.72–1.37)	0.97	0.92(0.59–1.42)	0.70
Body mass index (kg/m^2)	0.87(0.82–0.91)	0.00	0.94(0.89–0.99)	0.02	0.89(0.82–0.96)	0.00
Parity(0/≥1)	0.78(0.50–1.22)	0.28	0.69(0.44–1.07)	0.10	0.65(0.34–1.24)	0.19
Type of infertility (Primary/ Secondary)	1.04(0.74–1.48)	0.82	1.31(0.92–1.86)	0.13	1.08(0.67–1.75)	0.74
Infertility diagnosis (Tubal/ Male/ Others)	0.97(0.81–1.17)	0.78	1.08(0.90–1.30)	0.42	1.05(0.81–1.35)	0.73
Dosage of gonadotropins (< 2500/ ≥2500 IU)	1.24 (0.92–1.67)	0.17	1.23(0.90–1.69)	0.20	1.27(0.86–1.93)	0.22
Endometrial thickness on the day of hCG trigger (mm)	0.95(0.89–1.01)	0.13	0.99(0.94–1.07)	0.89	0.98(0.89–1.07)	0.58
Serum E_2 on the day of hCG trigger(ng/l)						
< 2000	1		1		1	
2000–2999	0.70(0.43–1.13)	0.15	0.84(0.51–1.40)	0.51	0.49(0.23–1.08)	0.08
3000–3999	1.21(0.77–1.89)	0.42	1.25(0.77–2.03)	0.37	0.84(0.42–1.70)	0.63
4000–4999	1.65(1.05–2.59)	0.03	1.87 (1.15–3.03)	0.01	2.27(1.22–4.25)	0.01
≥ 5000	1.60(1.03–2.53)	0.04	1.97(1.23–3.16)	0.01	2.42(1.31–4.49)	0.01
Method of ART (IVF/ICSI)	1.14(0.85–1.53)	0.38	0.99(0.73–1.36)	0.98	1.10 (0.73–1.66)	0.66
Embryo stage (D3/D5)	0.58(0.26–1.12)	0.08	0.92(0.40–2.12)	0.84	0.53(0.17–1.68)	0.28
No. of embryos transferred (1/≥2)	0.80(0.43–1.47)	0.47	1.59(0.74–3.45)	0.24	1.27(0.46–3.52)	0.64
Mode of delivery (vaginal/ cesarean)	1.21(0.88–1.66)	0.24	1.14(0.82–1.59)	0.44	0.98(0.64–1.49)	0.91
Gender (male/female)	1.04(0.80–1.35)	0.79	0.87(0.66–1.16)	0.34	0.86(0.59–1.25)	0.44
Note: AOR: adjusted odds ratios						

The variables that significantly affected SGA were maternal BMI (AOR: 0.87, 95% CI: 0.82–0.91, P = 0.00), serum E_2 level on the hCG trigger day, and being in groups D (AOR: 1.65, 95% CI: 1.05–2.59, P = 0.03) or E (AOR: 1.60, 95% CI: 1.03–2.53, P = 0.04).

LBW was significantly increased in groups D (AOR: 1.87, 95% CI: 1.15–3.03, P = 0.01) and E (AOR: 1.97, 95% CI: 1.23–3.16, P = 0.01) compared with that in the reference group. In addition, maternal BMI significantly affected the LBW rate (AOR: 0.94, 95% CI: 0.89–0.99, P = 0.02).

The factors that significantly affected full-term LBW were maternal BMI (AOR: 0.89, 95% CI: 0.82–0.96, P = 0.00), serum E_2 level on the hCG trigger day, and being in groups D (AOR: 2.27, 95% CI: 1.22–4.25, P = 0.01) or E (AOR: 2.42, 95% CI: 1.31–4.49, P = 0.01).

Discussion

In our study of women with infertility and normal ovarian reserves who underwent IVF/ICSI, those with supraphysiological E_2 levels on the day of hCG trigger had significantly higher rates of SGA, LBW and full-term LBW than did women with lower E_2 levels. Multivariate analysis revealed associations between E_2 levels of more than 4000 pg/ml on the trigger day and SGA, LBW and full-term LBW.

Moreover, we found that lower BMI was an independent risk factor for the SGA, LBW and full-term LBW rates.

Comparisons with other reports

Singleton births via ART are associated with significantly increased risks of SGA, LBW, PTB, perinatal mortality, and maternal complications [17–23] compared with spontaneous singleton births. Biological traits that may be associated with this phenomenon include intrinsic characteristics of the infertile couple, in vitro culture methods/media, the supraphysiological hormonal environment associated with COH, or a combination of these factors; however, the exact mechanisms leading to increased risks of these conditions remain unknown. In recent years, observational studies have demonstrated that singletons from FET have a reduced risk of LBW[4, 5, 24]. The most important physiological difference between FET and fresh ET is that FET involves a hormonal milieu closer to that of the physiological environment. Therefore, studies regarding how supraphysiological E_2 levels during COH are associated with LBW or SGA have begun to emerge[9, 11–14]. However, no unified standard definition exists for E_2 levels. Supraphysiological serum E_2 levels have been defined in various ways, such as in terms of the 50th[14, 25], 75th[26], 90th[15], and 95th[11] percentiles. Therefore, no universal standard exists for E_2 levels for different populations, ovulation protocols or laboratory standards. Many studies have suggested that a supraphysiological hormonal milieu may contribute to LBW, albeit with variable confounding factors. Recently, Pereira et al.[13], using ROC analysis and multivariable logistic regression analysis to account for potential confounding factors, highlighted that supraphysiological E_2, defined as $E_2 \geq 2500$ pg/ml, independently predicted LBW for full-term singletons born from fresh ET, with an AOR of 10.8 (95% CI: 9.2–12.5). However, this study included cycles with pregnancy complications, which are also associated with neonatal outcomes, including LBW, SGA, macrosomia and large size for gestational age (LGA). For example, Yen et al. [27] found that preeclampsia increased the risk of VLBW. Additionally, a population-based study showed that chronic hypertension increased the probability of SGA after adjusting for important confounders. Therefore, the effects of high E_2 levels on SGA occurrence, accounting for neonatal sex and gestational weeks, should be further explored. SGA is an important cause of neonatal death; it affects physical and mental development during childhood and adolescence and is associated with significantly increased arterial stiffness and metabolic dysfunction during adulthood[28].

Plausible biological mechanisms

The results of our study suggest that supraphysiological E_2 levels on the day of hCG trigger may contribute to SGA pathogenesis; however, the exact biological mechanism underlying this phenomenon remains unknown. The main mechanisms addressed in the research are as follows. First, Valbuena et al.[29] reported that high E_2 levels were deleterious to embryo adhesion in vitro, mainly because they exert direct toxic effects on embryos. Moreover, Ertzeid G et al.[30] performed a study using an embryo donation model in mice and concluded that ovarian stimulation appeared to impair embryo quality and uterine milieu. Additionally, Bittner et al.[31] analyzed the effects of ovulation on embryonic development in mice and showed that a supraphysiological hormonal milieu had toxic effects on fertility and embryonic development during ART treatment. Second, at least in animal models, elevated E_2 levels also affect normal trophoblastic vascular invasion. Albrecht et al.[32] reported that E_2 during early baboon pregnancy suppressed the extravillous trophoblast invasion of uterine spiral arteries. In addition, Bonagura et al.[33] found that prematurely elevating E_2 during the early stages of baboon pregnancies diminished uterine artery remodeling and affected the expression of extravillous placental vascular endothelial growth factors, thereby potentially contributing to neonatal SGA and LBW pathogeneses. Consistent with these animal model studies, human research has shown that elevated E_2 levels can affect endometrial receptivity[34] by altering endometrial gene expression profiles[35, 36], leading to abnormal implantation and placentation. Ng et al.[37] used 3D ultrasound examination to reconfirm that ovarian stimulated cycles were associated with lower endometrial and subendometrial blood flow than natural cycles. Kolibianakis et al.[38], using aspirational endometrial biopsies, observed more advanced endometrial maturation in fresh embryo cycles. Given this evidence from both humans and animals, supraphysiological levels of E_2 after COH expose embryos to an abnormal uterine and endometrial environment, which negatively affects embryo quality, extravillous trophoblast invasion, endometrial receptivity and placental development, thus disrupting fetal growth.

Regarding maternal weight, we found that lower BMI was associated with higher risks of SGA, LBW and full-term LBW, although our study did not explore specific values. Consistent with the findings from a prior prospective multicenter cohort study, low maternal birth weight was an independent risk factor for SGA[39]. Spada et al.[40] reported that maternal height and BMI should be considered when evaluating birth weight. In further research, we will explore the effects of maternal BMI on offspring birth weights to provide suggestions for clinics to reduce the occurrence of adverse pregnancy outcomes. Such research will require a large prospective data sample for the examined population.

Strengths and limitations

The strengths of this study include its large dataset (n = 3131). To our knowledge, our study, for which selection and statistical bias were minimized, is the largest investigation (n = 3131) to explore the effect of serum E_2 levels on the day of hCG trigger on SGA for fresh ET cycles. Moreover, to reduce potential bias, our study accounted for variables that could potentially impact neonatal birthweight, including maternal age, BMI, parity, infertility type, infertility diagnosis, gonadotropin dosage, endometrial thickness on the hCG trigger day, ART method, embryo stage, number of embryos transferred, delivery mode, neonatal sex and E_2 levels on the day of hCG trigger. Another strength of our study is that our findings are applicable to clinical practice: when $E_2 \geq 4000$ pg/ml, embryos should be frozen and ET performed later in the subsequent cycle.

Our study was limited by its retrospective design; therefore, a prospective cohort study is needed. Furthermore, between-group differences were found in certain baseline characteristics, including BMI (P = 0.00), infertility diagnosis (P = 0.01), basal FSH (P = 0.01), AMH (P = 0.00), antral follicle count (P = 0.00), gonadotropin dosage (P = 0.00), number of embryos retrieved (P = 0.00), endometrial thickness on the hCG trigger day (P = 0.03) and embryo stage (P = 0.00); however, multivariable regression analysis was performed to minimize sources of bias.

Conclusion

In conclusion, our results indicated that for fresh ET cycles, supraphysiological E_2 (≥4000 pg/ml) on the day of hCG trigger increases the risks of singleton SGA, LBW and full-term LBW, further confirming the adverse effects of a supraphysiological hormonal environment on offspring safety. Additionally, our study demonstrated that lower maternal BMI is an independent risk factor for SGA, LBW and full-term LBW; however, the exact mechanism is unclear.

Abbreviations

ART
assisted reproductive technology
FET
frozen embryo transfer
IVF
in vitro fertilization
ICSI
intracytoplasmic sperm injection
ET
embryo transfer
PGD
preimplantation genetic diagnoses
PGS
preimplantation screening
E2
estradiol
hCG
human chorionic gonadotropin
COH
controlled ovarian hyperstimulation
SGA
small size for gestational age
LBW
low birth weight
PTB
preterm birth
OR
odds ratio
CI
confidence interval

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of The Third Affiliated Hospital of Zhengzhou University.

Consent for publication

Not applicable.

Availability of data and material

All data are included in this article and its additional files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SLJ and ZJW designed the study and selected the population to be included and excluded. LZ, WLL and WYL were involved in the data extraction and analysis. HJJ and WYX reviewed the data. ZJW and DMZ were involved in drafting this article. All authors have approved the final version of the manuscript. ZJW and DMZ contributed equally to this article.

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Figures

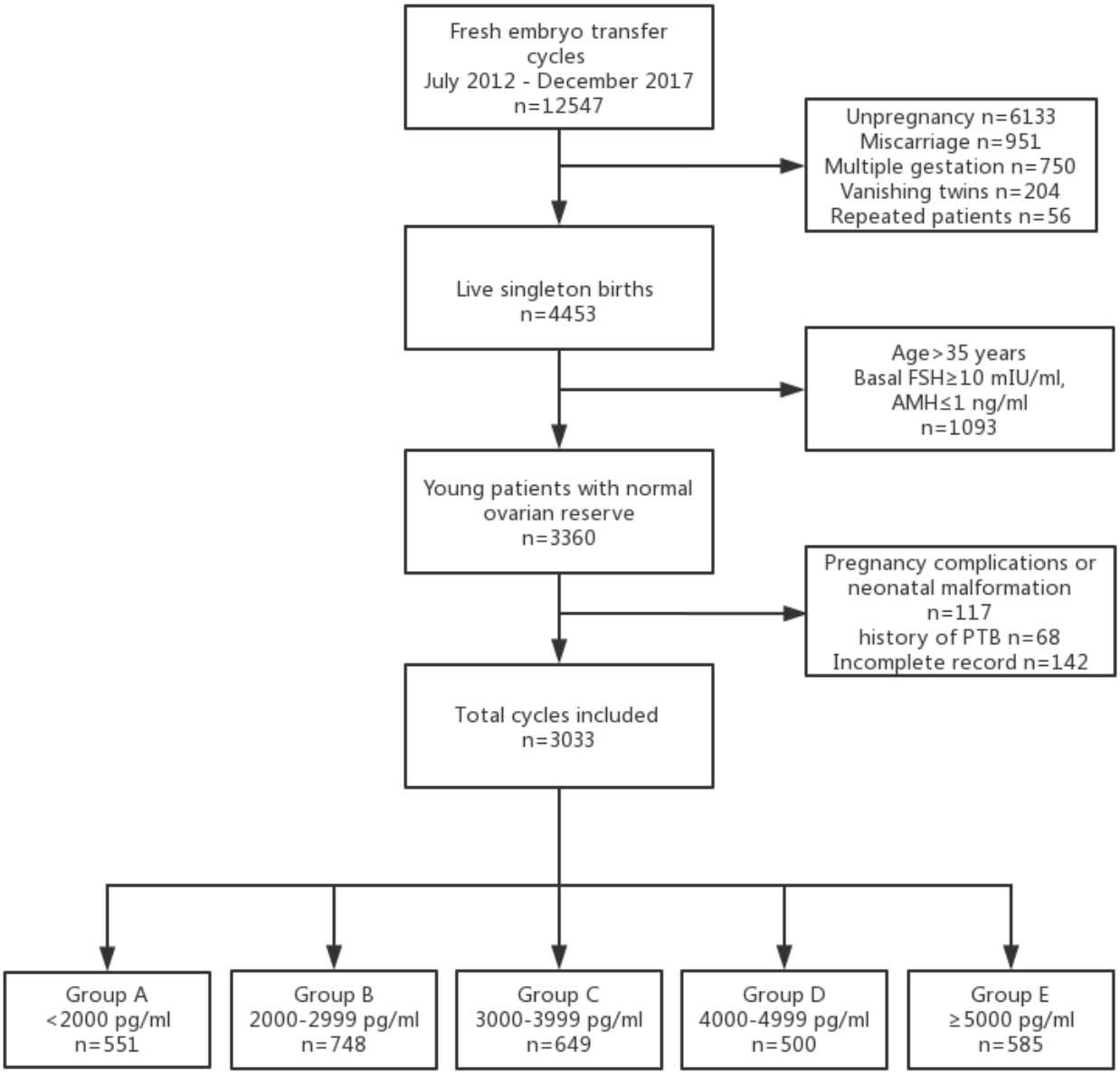

Figure 1

Overview of the inclusion and exclusion criteria