Elevated progesterone and its impact on birth weight after fresh embryo transfers

Yetunde Ibrahim^{1,2} · Miriam J. Haviland¹ · Michele R. Hacker¹ · Alan S. Penzias^{1,3} · Kim L. Thornton^{1,3} · Denny Sakkas³

Received: 30 January 2017 / Accepted: 4 April 2017 / Published online: 17 April 2017
© Springer Science+Business Media New York 2017

Abstract

Purpose The purpose of the study was to examine the association between serum progesterone levels on the day of hCG administration and birth weight among singleton live births after fresh embryo transfer.

Methods This study was conducted as a retrospective cohort database analysis on patients who underwent IVF treatment cycles from January 2004 to April 2012. The study was performed at a University affiliated private infertility practice. All cycles that had achieved a singleton live birth after fresh embryo transfer and for which progesterone was measured on the day of hCG administration were examined. Generalized linear models were used to calculate mean birth weight and z-scores. **Results** We analyzed 817 fresh IVF embryo transfers in which birth weight, gestational age, and progesterone (ng/mL) level on day of hCG administration were documented. While there was a decrease in birth weight as progesterone quartile [≤ 0.54 ; >0.54 to ≤ 0.81 ; >0.81 to ≤ 1.17 ; >1.17 ng/mL] increased, the difference in mean birth weights among the four quartiles was not statistically significant ($p = 0.11$) after adjusting for maternal age and peak estradiol levels. When dichotomizing based on a serum progesterone considered clinically elevated,

cycles with progesterone >2.0 ng/mL had a significantly lower mean singleton birth weight (2860 g (95% CI 2642 g, 3079 g)) compared to cycles with progesterone ≤ 2.0 ng/mL (3167 g (95% CI 3122 g, 3211 g) $p = 0.007$) after adjusting for maternal age and estradiol.

Conclusion We demonstrated that caution should be exercised when performing fresh embryo transfers with elevated progesterone levels and in particular with levels (>2.0 ng/mL) as this may lead to lower birth weight.

Keywords Live birth weight · IVF · Progesterone · Fresh embryo transfer

Introduction

National databases and multiple studies have indicated that infants born after assisted reproductive technology (ART) are smaller than those born from natural conception [1–4]. Aside from the impact multiple births has had on birth weight, subfertility itself is believed to be a risk factor for low birth weight (LBW) as it has been demonstrated that spontaneous conception after a diagnosis of infertility increases the risk of adverse birth outcomes [5–7].

The most conclusive evidence linking ART procedures to LBW has arisen from a study by Shih et al. [8] who demonstrated that singletons from frozen embryo transfer procedures have higher mean birth weight and are less likely to be LBW than those from fresh embryo transfers. Several other studies [9, 10] have also demonstrated this finding including our own [11], which has important implications on the potential etiology of LBW in ART cycles.

A key important physiological difference between frozen and fresh embryo cycles is that during frozen cycles, the embryo is not exposed to the supraphysiologic hormonal milieu

Electronic supplementary material The online version of this article (doi:10.1007/s10815-017-0920-8) contains supplementary material, which is available to authorized users.

✉ Denny Sakkas
dsakkas@bostonivf.com

¹ Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, 330 Brookline Ave. KS 3, Boston, MA 02215, USA

² Present address: Utah Center for Reproductive Medicine, 675 Arapleen Drive, Suite 205, Salt Lake City, UT 84108, USA

³ Boston IVF, 130 Second Ave, Waltham, MA 02451, USA

that is characteristic of controlled ovarian hyperstimulation (COH) during fresh IVF cycles. In addition, Kalra et al. [12] specifically showed that when comparing frozen embryo transfer cycles and fresh transfer cycles in oocyte donor recipients, who do not undergo any ovarian stimulation, no difference in LBW was demonstrated. One of the major factors believed to impact pregnancy in fresh embryo transfers is elevated progesterone. In a meta-analysis of over 60,000 cycles, Venetis et al. [13] concluded that elevated progesterone on the day of hCG administration is associated with a decreased probability of pregnancy in fresh IVF cycles in women undergoing COH using GnRH analogues and gonadotrophins.

To our knowledge, there are no published studies investigating whether there is an association between elevated progesterone levels on the day of hCG administration and live birth weight. During COH, elevation of serum progesterone is generally prevented by suppressing luteinizing hormone secretion with a gonadotropin releasing hormone agonist or antagonist. Despite these medications, subtle increases in serum progesterone are still observed, with elevated progesterone on the day of hCG administration in as many as 35% of cycles [14–16]. This phenomenon has been referred to as premature luteinization, progesterone elevation, and/or premature progesterone rise [17, 18] and, as stated above, has been shown to negatively impact clinical and live birth rates [13, 19, 20].

Although the pathogenesis of LBW in IVF singletons is not known, we hypothesize that elevated progesterone levels on the day of hCG administration may not only negatively impact pregnancy and live birth rates, there may be an impact on placental function resulting in lower birth weight in pregnancies achieved in a high progesterone environment. To address this hypothesis, we investigated the effect of elevated progesterone on the day of hCG administration on the birth weight of live born term singletons after fresh embryo transfer IVF cycles at our center.

Materials and methods

Study population and design

We performed a retrospective study of all fresh IVF cycles from January 2004 to April 2012 that resulted in a singleton live birth and for which progesterone was measured on the day of hCG administration. We included only the first eligible cycle for each woman, and cycles with missing data on birth weight, gestational age at delivery, or progesterone were excluded.

We collected baseline demographic characteristics, cycle characteristics, laboratory values, and cycle outcomes from medical records. The primary outcome was birth weight. Infants who weighed less than 2500 g at birth were considered LBW. Sex-specific birth weight for gestational age (*z*-scores) was calculated using Fenton growth curves [21]. Infants with

z-scores below the 10th percentile were considered small for gestational age (SGA). The institutional review board at Beth Israel Deaconess Medical Center approved this study.

Stimulation protocol

Patients underwent treatment protocols for ovarian stimulation, monitoring, and oocyte retrieval as previously described [22]. Briefly, cycles were monitored with daily serum E2 levels and transvaginal ultrasound examinations beginning on treatment days 6 to 8. When at least three follicles measured 15 to 20 mm, either 250 µg recombinant hCG (Ovidrel; EMD Serono) or 10,000 U of urinary hCG (Novarel; Ferring Pharmaceuticals) was administered subcutaneously. More recently, a GnRH agonist trigger (leuprolide acetate) has been used to mitigate risk of OHSS, however during the period of 2004–2012 less than 3% of cycles used a GnRH agonist trigger. Embryos were transferred into the uterus either 3 or 5 days after oocyte retrieval. Patients received luteal phase support until 8 weeks of gestation. Intracytoplasmic sperm injection and assisted hatching were performed when indicated.

Hormone measurements

Whole blood was collected between 6:30 and 9 a.m. on the day of hCG administration. Progesterone and estradiol levels were measured using the Immulite 2000 Immunoassay System (Siemens Healthcare Global), which has a sensitivity of 0.1 ng/mL for progesterone and 15 pg/mL for estradiol. This assay was used for the duration of the study. Although a consensus is not available on what is a high progesterone value [13, 23], we chose >2.0 ng/mL as a clinically relevant high progesterone level which would impact live birth rates in a fresh IVF cycle.

Patients were also divided into quartiles according to serum progesterone on the day of hCG administration. Patients were assigned to groups as follows: quartile 1, ≤0.54 ng/mL; quartile 2, >0.54 to ≤0.81 ng/mL; quartile 3, >0.81 to ≤1.17 ng/mL; and quartile 4, >1.17 ng/mL.

To investigate the role of estradiol, patients were also divided into quartiles according to their peak estradiol levels on the day of hCG trigger. They were assigned as follows: quartile 1, ≤1396 pg/mL; quartile 2, >1396 to ≤2193 pg/mL; quartile 3, >2193 to ≤3326 pg/mL; and quartile 4, >3326 pg/mL.

Statistical analysis

Descriptive data are presented as median (interquartile range) or count and proportion. Fisher's exact and chi-square tests were used to compare categorical variables among the progesterone quartiles. Continuous variables were compared using the Kruskal-Wallis test. Generalized linear models were used to calculate mean birth weight and *z*-scores for each

progesterone and estradiol quartile. As we did not observe a linear relationship between progesterone and estradiol quartiles and birth weight, we modeled both progesterone and estradiol as categorical variables. The progesterone models were adjusted for maternal age at cycle start and peak estradiol level, while the peak estradiol models were adjusted for maternal age at cycle start and progesterone level. Generalized linear models were also used to calculate and compare mean birth weight and z-scores between women with progesterone levels >2.0 ng/mL and those with levels ≤ 2.0 ng/mL. These models were also adjusted for maternal age at cycle start and peak estradiol level. The proportions of LBW (<2500.0 g) and small for gestational age (<10 th percentile) infants were compared between cycles with progesterone levels >2.0 and those with levels ≤ 2.0 . p values <0.05 were considered statistically significant.

Results

Participant characteristics

There were 6223 fresh IVF cycles performed during the study period resulting in 1451 live births. After excluding multiple gestations ($n = 370$) and cycles with missing data on birth weight, gestational age, and progesterone level on day of hCG administration ($n = 264$), 817 cycles were included in the final analysis. Participant characteristics stratified by progesterone quartile are presented in Table 1. Women in each quartile were similar with regard to maternal age, partner age, gravidity, parity, and body mass index. The numbers of embryos transferred, as well as number of embryos frozen, also were similar. Peak estradiol levels and the numbers of oocytes retrieved increased with increasing progesterone levels across

Table 1 Baseline characteristics for all cycles and cycles broken down into quartiles of progesterone values on the day of hCG trigger for patients receiving embryo transfers and achieving a singleton live birth

	All	Quartile 1 ≤ 0.54 ng/mL	Quartile 2 $>0.54\text{--}\leq 0.81$ ng/mL	Quartile 3 $> 0.81\text{--}\leq 1.17$ ng/mL	Quartile 4 >1.17 ng/mL
Singleton deliveries	$n = 817$	$n = 206$	$n = 206$	$n = 203$	$n = 202$
Age at cycle start (years)	35.0 (32.0–38.0)	34.0 (32.0–37.0)	35.0 (31.0–38.0)	35.0 (31.0–38.0)	35.0 (31.0–37.0)
Partner age (years)	36.4 (32.9–40.5)	36.4 (33.5–40.4)	36.3 (32.5–40.1)	37.2 (34.1–41.3)	36.1 (32.5–39.9)
Body mass index	24.0 (21.5–27.1)	24.6 (21.8–28.9)	24.3 (22.1–27.1)	23.4 (21.0–26.9)	23.5 (21.6–26.6)
Gestational age at delivery	37.1 (35.7–38.6)	37.1 (35.9–38.4)	37.1 (35.6–38.6)	37.6(35.9–38.6)	37.0 (35.6–38.7)
Gravidity					
0	364 (44.5)	97 (47.1)	89 (43.2)	88 (43.4)	90 (44.6)
1	230 (28.2)	59 (28.6)	67 (32.5)	52 (25.6)	52 (24.4)
≥ 2	223 (27.3)	50 (24.3)	50 (24.3)	63 (31.0)	60 (29.7)
Parity					
0	583 (71.4)	144 (69.9)	150 (72.8)	140 (69.0)	149 (73.8)
1	192 (23.5)	53 (25.7)	51 (24.8)	48 (23.7)	40 (19.8)
≥ 2	42 (5.1)	9 (4.4)	5 (2.4)	15 (7.4)	13 (6.4)
Infant sex*					
Male	362 (46.1)	98 (49.3)	87 (43.9)	87 (44.4)	90 (46.9)
Female	423 (53.9)	101 (50.8)	111 (56.1)	109 (55.6)	102 (53.1)
Fetal sac number					
1	602 (73.7)	157 (76.2)	147 (71.4)	156 (76.9)	142 (70.3)
≥ 2	215 (26.3)	49 (23.8)	59 (28.6)	47 (23.2)	60 (29.7)
Preterm delivery	356 (43.6)	90 (43.7)	95 (46.1)	75 (37.0)	96 (47.5)
Number of embryos transferred	2.0 (2.0–3.0)	2.0 (2.0–2.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)
Peak estradiol (pg/mL)	2201.0 (1401.0–3330.0)	1613.5 (1050.0–2287.0)	2152.5 (1414.0–3326.0)	2352.0 (1472.0–3401.0)	2955.0 (1997.0–4907.0)
Number of oocytes retrieved	11.0 (7.0–17.0)	8.5 (6.0–12.0)	11.0 (7.0–17.0)	11.0 (8.0–16.0)	15.0 (9.0–20.0)
Number oocytes fertilized	11.0 (7.0–16.0)	8.0 (6.0–12.0)	11.0 (7.0–16.0)	11.0 (8.0–16.0)	14.0 (9.0–19.0)
Number of embryos frozen	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)
Cycles that used ICSI	366 (44.8)	87 (42.2)	91 (44.2)	97 (47.8)	91 (45.1)

Data presented as median (interquartile range) or n (%) * infant sex not reported in 32 cases

Table 2 Mean birth weight and z-score stratified by quartiles of progesterone on the day of hCG trigger

	Birth weight						z-score					
	Crude			Adjusted ^a			Crude			Adjusted ^a		
	Mean	95% CI	<i>p</i>	Mean	95% CI	<i>p</i>	Mean	95% CI	<i>p</i>	Mean	95% CI	<i>p</i>
Progesterone quartile (ng/mL)	0.07			0.11			0.08			0.06		
≤0.54	3245	3158, 3333		3242	3152, 3332		0.46	0.34, 0.57		0.47	0.35, 0.59	
>0.54–≤0.81	3117	3029, 3204		3116	3029, 3204		0.28	0.16, 0.39		0.28	0.16, 0.39	
>0.81–≤1.17	3167	3079, 3255		3164	3076, 3253		0.34	0.22, 0.45		0.34	0.22, 0.45	
>1.17	3087	2999, 3175		3093	3002, 3183		0.26	0.14, 0.38		0.25	0.13, 0.37	

^a Progesterone models are adjusted for maternal age and peak estradiol levels

quartiles. The incidence of preterm delivery was 43.7, 46.1, 37.0, and 47.5% with increasing progesterone quartile, respectively.

Birth weight

Table 2 shows the association between serum progesterone quartiles on the day of hCG administration and birth weight. While the mean birth weight was 150 g lower in the highest progesterone quartile compared to the lowest quartile, the overall difference in mean birth weight among the four quartiles was not statistically significant ($p = 0.11$), after adjusting for maternal age at cycle start and peak estradiol levels. There was also no significant difference in mean gestational age adjusted z-score among the four quartiles, after controlling for maternal age and peak estradiol ($p = 0.06$).

When stratifying by the clinically relevant progesterone level, we found a significant difference in mean birth weight even after adjusting for maternal age and peak estradiol (Table 3; $p = 0.007$). There was, however, no significant difference in mean z-score between cycles with serum progesterone >2.0 and ≤2.0 ng/mL ($p = 0.07$). The median gestational age for participants with a progesterone >2.0 ng/mL was 36.9 weeks (34.0–38.0) while it was 37.3 weeks (35.7–38.6) for those with progesterone ≤2.0 ng/mL. The incidence of LBW was significantly higher in cycles with serum progesterone >2.0 ng/mL (27.3%) compared to those ≤2.0 ng/mL

(14.3%; $p = 0.04$). There was, however, no significant difference in the incidence of small for gestational age infants between cycles with serum progesterone >2.0 (3.0%) compared to those ≤2.0 (3.8%); $p = 1.0$).

There was no difference in mean birth weight or z-score across the estradiol quartiles after adjusting for maternal age and progesterone levels on the day of hCG administration (Supplemental Table 1; $p = 0.18$ and 0.29, respectively).

Discussion

The clinical recommendation of delaying transfer in a fresh IVF cycle when progesterone levels are elevated has recently been proposed as a way of maintaining higher pregnancy rates [24, 25]. The practice has, however, come under some scrutiny [26–28], even though a large meta-analysis of over 60,000 cycles indicated that higher progesterone levels are detrimental to pregnancy rates [13]. This meta-analysis indicated that even using a threshold ≥0.8 ng/mL, there was a significant association with a decreased probability of pregnancy in fresh IVF cycles. The elevated progesterone threshold levels used by clinics are, however, very dependent on individual clinic thresholds and are not conclusive [13]. We therefore used a cutoff of 2.0 ng/mL as a clinically relevant high level for our analysis. Our study indicates that in addition to the recommendation of delaying transfer when progesterone is elevated, there

Table 3 Mean birth weight and z-score stratified by clinically relevant progesterone level on the day of hCG trigger

	Birth weight						z-score					
	Crude			Adjusted ^a			Crude			Adjusted ^a		
	Mean	95% CI	<i>p</i>	Mean	95% CI	<i>p</i>	Mean	95% CI	<i>p</i>	Mean	95% CI	<i>p</i>
Progesterone	0.006			0.007			0.07			0.07		
P4 ≤2.0 ng/mL	3167	3122, 3212		3167	3122, 3211		0.34	0.28, 0.40		0.34	0.29, 0.40	
P4 >2.0 ng/mL	2854	2636, 3072		2860	2642, 3079		0.07	−0.21, 0.36		0.07	−0.22, 0.36	

^a Progesterone models are adjusted for maternal age and peak estradiol levels

may be a higher progesterone level where the impact may be on fetal development itself and translate to lower birth weights. In this case of extremely high progesterone on the day of hCG administration, it may be prudent to delay transfer.

The exact mechanism of LBW in IVF pregnancies has not been clearly elucidated. Factors intrinsic to the subfertile couple, as well as the supraphysiological hormone levels, have been suggested as possible mechanisms. We know that estradiol plays a key role in the morphology and functional differentiation of syncytiotrophoblasts, as well as modulation of uteroplacental blood flow critical for optimal fetal growth in primates [29–31]. It also appears that low levels of estradiol as seen in early pregnancies are required to permit the normal placental invasion of uterine spiral arteries [32]. There is evidence that not only is an elevated estradiol level toxic to implantation in mice [33–35], but it also results in aberrant placentation [32, 33]. While our study does not demonstrate an association between elevated estradiol on the day of hCG administration and LBW, several studies have demonstrated this association [12, 36–38].

On the other hand, elevated progesterone on the day of hCG administration is associated with differential vascular endothelial growth factor expression in the endometrium and this is thought to alter endometrial receptivity resulting in decreased implantation [39]. We therefore hypothesized that elevated progesterone may be associated with adverse perinatal outcomes. We grouped our cycles into quartiles according to progesterone levels on the day of hCG administration. We chose those particular quartiles because using similar quartile cutoffs, we previously have shown a negative association with live birth [23].

Our results from 817 cycles demonstrated a decreasing live birth weight with increasing progesterone levels, in particular at higher levels. We also found that cycles with progesterone >2.0 ng/mL had lower mean birth weights than cycles with lower levels of progesterone.

In contrast to fresh embryo transfers, several studies have suggested better outcomes among frozen embryo transfer cycles that utilized an embryo obtained from a cycle with elevated progesterone on the day of hCG administration [20, 25]. As more data emerges regarding the improved perinatal outcomes with frozen as opposed to fresh embryo transfer cycles, including a lower incidence of preterm delivery and small for gestational age neonates, there may be fewer reasons to proceed with a fresh embryo transfer if cryopreservation is an option [10, 24] when progesterone levels are elevated on the day of hCG administration.

One limitation of our study is a lack of access to all obstetric records of the cycles included in our analysis. For example, we cannot comment on the rates of preeclampsia based on progesterone quartiles. In addition, we recognize that the biggest limitation of our study is the small sample size, which prevents us from making definitive conclusions. However, we

are unaware of other published reports on this association. In addition, the utilization of z-scores assumes that they are representative of an IVF population. That is not necessarily the case as the distribution of IVF patients would be older than the control population used to establish the z-scores. We therefore conclude that based on these findings and the many studies analyzed by Venetis et al. [40], it seems prudent to exercise caution when performing fresh embryo transfers when progesterone levels are elevated on the day of hCG administration. We await further studies to critically evaluate the association observed in this study.

Compliance with ethical standards

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

References

1. Doyle P, Beral V, Maconochie N. Preterm delivery, low birthweight and small-for-gestational-age in liveborn singleton babies resulting from in-vitro fertilization. *Hum Reprod*. 1992;7:425–8.
2. Wang YA, Sullivan EA, Black D, Dean J, Bryant J, Chapman M. Preterm birth and low birth weight after assisted reproductive technology-related pregnancy in Australia between 1996 and 2000. *Fertil Steril*. 2005;83:1650–8.
3. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. *N Engl J Med*. 2002;346:731–7.
4. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ*. 2004;328:261.
5. Ghazi HA, Spielberger C, Kallen B. Delivery outcome after infertility—a registry study. *Fertil Steril*. 1991;55:726–32.
6. Olivennes F, Rufat P, Andre B, Pourade A, Quiros MC, Frydman R. The increased risk of complication observed in singleton pregnancies resulting from in-vitro fertilization (IVF) does not seem to be related to the IVF method itself. *Hum Reprod*. 1993;8:1297–300.
7. Bergh T, Ericson A, Hillensjö T, Nygren KG, Wennerholm UB. Deliveries and children born after in-vitro fertilisation in Sweden 1982–95: a retrospective cohort study. *Lancet*. 1999;354:1579–85.
8. Shih W, Rushford DD, Bourne H, Garrett C, McBain JC, Healy DL, et al. Factors affecting low birthweight after assisted reproduction technology: difference between transfer of fresh and cryopreserved embryos suggests an adverse effect of oocyte collection. *Hum Reprod*. 2008;23:1644–53.
9. Belva F, Henriot S, Van den Abbeel E, Camus M, Devroey P, Van der Elst J, et al. Neonatal outcome of 937 children born after transfer of cryopreserved embryos obtained by ICSI and IVF and comparison with outcome data of fresh ICSI and IVF cycles. *Hum Reprod*. 2008;23:2227–38.
10. Maheshwari A, Pandey S, Shetty A, Hamilton M, Bhattacharya S. Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis. *Fertil Steril*. 2012;98:368–77.
11. Maas K, Galkina E, Thornton K, Penzias AS, Sakkas D. No change in live birthweight of IVF singleton deliveries over an 18-year period despite significant clinical and laboratory changes. *Hum Reprod*. 2016;31:1987–96.

12. Kalra SK, Ratcliffe SJ, Coutifaris C, Molinaro T, Barnhart KT. Ovarian stimulation and low birth weight in newborns conceived through in vitro fertilization. *Obstet Gynecol*. 2011;118:863–71.
13. Venetis CA, Kolibianakis EM, Bosdou JK, Tarlatzis BC. Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60 000 cycles. *Hum Reprod Update*. 2013;19:433–57.
14. Edelstein MC, Seltman HJ, Cox BJ, Robinson SM, Shaw RA, Muasher SJ. Progesterone levels on the day of human chorionic gonadotropin administration in cycles with gonadotropin-releasing hormone agonist suppression are not predictive of pregnancy outcome. *Fertil Steril*. 1990;54:853–7.
15. Silverberg KM, Burns WN, Olive DL, Riehl RM, Schenken RS. Serum progesterone levels predict success of in vitro fertilization/embryo transfer in patients stimulated with leuprolide acetate and human menopausal gonadotropins. *J Clin Endocrinol Metab*. 1991;73:797–803.
16. Ubaldi F, Bourgain C, Tournaye H, Smits J, Van SA, Devroey P. Endometrial evaluation by aspiration biopsy on the day of oocyte retrieval in the embryo transfer cycles in patients with serum progesterone rise during the follicular phase. *Fertil Steril*. 1997;67:521–6.
17. Hamori M, Stuckensen JA, Rumpf D, Kniewald T, Kniewald A, Kurz CS. Premature luteinization of follicles during ovarian stimulation for in-vitro fertilization. *Hum Reprod*. 1987;2:639–43.
18. Schoolcraft W, Sinton E, Schlenker T, Huynh D, Hamilton F, Meldrum DR. Lower pregnancy rate with premature luteinization during pituitary suppression with leuprolide acetate. *Fertil Steril*. 1991;55:563–6.
19. Bosch E, Labarta E, Crespo J, Simon C, Remohi J, Jenkins J, et al. Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. *Hum Reprod*. 2010;25:2092–100.
20. Xu B, Li Z, Zhang H, Jin L, Li Y, Ai J, et al. Serum progesterone level effects on the outcome of in vitro fertilization in patients with different ovarian response: an analysis of more than 10,000 cycles. *Fertil Steril*. 2012;97:1321–7.
21. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13:59.
22. The Boston IVF handbook of infertility: a practical guide for practitioners who care for infertile couples. 3rd ed. CRC Press, 2011.
23. Humm KC, Ibrahim Y, Dodge LE, Hacker MR, Thornton KL, Penzias AS, et al. Does elevated serum progesterone on the day of human chorionic gonadotropin administration decrease live birth rates? *J Reprod Health Medicine*. 2016; 2 (Suppl. 2):S15–8.
24. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Clinical rationale for cryopreservation of entire embryo cohorts in lieu of fresh transfer. *Fertil Steril*. 2014;102:3–9.
25. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Embryo cryopreservation rescues cycles with premature luteinization. *Fertil Steril*. 2010;93:636–41.
26. Vanni VS, Vigano P, Quaranta L, Pagliardini L, Giardina P, Molgora M, et al. Are extremely high progesterone levels still an issue in IVF? *J Endocrinol Invest*. 2017;40:69–75.
27. Bhattacharya S. Maternal and perinatal outcomes after fresh versus frozen embryo transfer-what is the risk-benefit ratio? *Fertil Steril*. 2016;106:241–3.
28. Isikoglu M. Is it too early for a major change? A critical objection to the freeze all policy. *Arch Gynecol Obstet*. 2016;293:1359–60.
29. Albrecht ED, Pepe GJ. Central integrative role of oestrogen in modulating the communication between the placenta and fetus that results in primate fetal-placental development. *Placenta*. 1999;20:129–39.
30. Babishkin JS, Burleigh DW, Mayhew TM, Pepe GJ, Albrecht ED. Developmental regulation of morphological differentiation of placental villous trophoblast in the baboon. *Placenta*. 2001;22:276–83.
31. Pepe GJ, Albrecht ED. Actions of placental and fetal adrenal steroid hormones in primate pregnancy. *Endocr Rev*. 1995;16:608–48.
32. Albrecht ED, Bonagura TW, Burleigh DW, Enders AC, Aberdeen GW, Pepe GJ. Suppression of extravillous trophoblast invasion of uterine spiral arteries by estrogen during early baboon pregnancy. *Placenta*. 2006;27:483–90.
33. Valbuena D, Martin J, de Pablo JL, Remohi J, Pellicer A, Simon C. Increasing levels of estradiol are deleterious to embryonic implantation because they directly affect the embryo. *Fertil Steril*. 2001;76:962–8.
34. Bittner AK, Horsthemke B, Winterhager E, Grummer R. Hormone-induced delayed ovulation affects early embryonic development. *Fertil Steril*. 2011;95:2390–4.
35. Ertzeid G, Storeng R. The impact of ovarian stimulation on implantation and fetal development in mice. *Hum Reprod*. 2001;16:221–5.
36. Imudia AN, Awonuga AO, Doyle JO, Kaimal AJ, Wright DL, Toth TL, et al. Peak serum estradiol level during controlled ovarian hyperstimulation is associated with increased risk of small for gestational age and preeclampsia in singleton pregnancies after in vitro fertilization. *Fertil Steril*. 2012;97:1374–9.
37. Pereira N, Reichman DE, Goldschlag DE, Lekovich JP, Rosenwaks Z. Impact of elevated peak serum estradiol levels during controlled ovarian hyperstimulation on the birth weight of term singletons from fresh IVF-ET cycles. *J Assist Reprod Genet*. 2015;32:527–32.
38. Sunkara SK, La Marca A, Seed PT, Khalaf Y. Increased risk of preterm birth and low birthweight with very high number of oocytes following IVF: an analysis of 65 868 singleton live birth outcomes. *Hum Reprod*. 2015;30:1473–80.
39. Chen X, Jin X, Liu L, Man CW, Huang J, Wang CC, et al. Differential expression of vascular endothelial growth factor angiogenic factors in different endometrial compartments in women who have an elevated progesterone level before oocyte retrieval, during in vitro fertilization-embryo transfer treatment. *Fertil Steril*. 2015;104:1030–6.
40. Venetis CA, Kolibianakis EM, Papanikolaou E, Bontis J, Devroey P, Tarlatzis BC. Is progesterone elevation on the day of human chorionic gonadotropin administration associated with the probability of pregnancy in in vitro fertilization? A systematic review and meta-analysis. *Hum Reprod Update*. 2007;13:343–55.