Association of the very early rise of human chorionic gonadotropin with adverse outcomes in singleton pregnancies after in vitro fertilization

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Objective: To determine if very early serum hCG, a marker of trophoblast differentiation, is associated with adverse perinatal outcomes in singleton pregnancies.
Design: Retrospective cohort study.
Setting: University fertility program.
Patient(s): A total of 360 singleton IVF live births.
Intervention(s): Serial hCG measurements were used to determine the within-woman slope for hCG (hCG rise).
Main Outcomes Measure(s): Primary outcomes included birth weight and gestational age at delivery. Statistical comparisons used *t* test, chi-square test, and linear and logistic regressions as appropriate.
Result(s): hCG rise was positively associated with birth weight but not gestational age at delivery. Infant sex, gestational age, and type of embryo transfer (fresh vs. frozen/thawed) were significantly associated with birth weight and confounded the associations of interest. hCG rise was slower among subjects delivering an infant with low birth weight (slope 0.386 ± 0.05 vs. 0.407 ± 0.06) or small for gestational age (slope 0.371 ± 0.07 vs. 0.406 ± 0.06). Analysis of hCG rise by quartile showed that, compared with the first quartile (slowest), subjects with a rate of hCG rise in the fourth quartile (fastest) had a significantly decreased risk of delivering an infant of low birth weight. No relationship was noted between hCG rise and hypertensive disorders of pregnancy.
Conclusion(s): Slower very early first-trimester hCG rise is associated with low birth weight but not gestational age at delivery among singleton IVF conceptions. The rate of increase in serum hCG may reflect early trophoblast differentiation and placentation and, possibly, may predict subsequent development. (Fertil Steril® 2016;105:1208–14. ©2016 by American Society for Reproductive Medicine.)
Key Words: Human chorionic gonadotropin, hCG, low birth weight, adverse pregnancy outcomes, in vitro fertilization

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Adverse pregnancy outcomes may result, in part, from an underlying defect in early placentation (1). This period of pregnancy is difficult to study because most women do not routinely present for obstetrical care until later in the first trimester. However, women who conceive after in vitro fertilization (IVF) are monitored frequently and early in pregnancy with the use of serial hormone measurements and thus represent a unique population ideal for study of early placentation events.

Placental trophoblast invasion begins soon after embryo attachment and continues through the first trimester. It is hypothesized that assessment of serial hormone levels, such as of hCG at this early stage of pregnancy

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may be useful in predicting early placental development and possibly perinatal outcome. Serum hCG, a hormone secreted by placental syncytiotrophoblasts and detectable in the serum as early as 6–12 days after ovulation (2), rises rapidly during early pregnancy, peaks around the 10th to 11th week of gestation, and is routinely measured after embryo transfer (ET) in women undergoing IVF.

Although the expected rate of increase in hCG has been defined for an ongoing intrauterine gestation in both assisted reproduction and medically unassisted pregnancy populations (3, 4), the association between rise in serial hCG and pregnancy outcome, particularly adverse outcome at the time of delivery, remains unclear. Studies have shown that low initial serum hCG levels after ET are negatively associated with pregnancy viability (5, 6) and that initial level and rise of hCG may predict live delivery rate (7). However, data demonstrating the association between the rate of early hCG increase and pregnancy outcomes at delivery are lacking.

Therefore, the goal of the present study was to interrogate the association between the rate of increase in hCG in the early first trimester and adverse pregnancy outcomes related to birth weight and gestational age at the time of delivery in a cohort of women who conceived with the use of IVF and subsequently delivered a singleton live-born infant. We hypothesized that the rate of increase in serial hCG levels may serve as a surrogate marker for trophoblast differentiation, and therefore placentation, and that extremes in the rates of increase may identify women at risk for adverse pregnancy outcomes.

MATERIALS AND METHODS

This retrospective cohort study assessed singleton live births conceived with the assistance of IVF from 2005 to 2009 at the Hospital of the University of Pennsylvania (HUP). We chose these years for analysis because during that time period the same laboratory protocols were used for all cases, including culture medium (LifeGlobal) and oxygen tension (95% air/5% CO_2). Included patients had only one gestational sac at the time of a 6-week ultrasound and two or more serial measurements of hCG serum concentrations. Conceptions after both fresh and frozen/thawed ETs were included. Baseline patient demographics and characteristics were obtained from medical records, and serum hCG levels after ET were abstracted from the electronic database. Donor egg cycles and twin and triplet pregnancies were excluded from analysis. The study was approved by the University of Pennsylvania Institutional Review Board (protocol no 813313).

Primary outcomes included birth weight (g) and gestational age (d) at delivery. Secondary pregnancy outcomes included specific adverse events, including delivery of an infant with low birth weight (LBW; <2,500 g), preterm delivery (<37 wk), small for gestational age (SGA; <10th percentile) (8), gestational hypertension, and preeclampsia as defined by internationally accepted diagnostic criteria (9). Infant neonatal intensive care unit (NICU) admission was collected as a surrogate marker of infant health; infant follow-up after hospital discharge was unavailable.

Infant birth weight, date of delivery, and sex were reported by the patient as part of routine post-treatment follow-up for reporting to the Society for Assisted Reproductive Technologies and were confirmed with the use of delivery records when available. The outcomes of gestational hypertension, preeclampsia, and NICU admission were available for a subset of patients who received care and delivered at the primary institution (HUP).

Exposure was defined as the increase in hCG over time, or slope. Our focus was the rise of hCG within the first 6 weeks of gestation, when the natural log-transformed hCG is considered to be linear (4). Values of hCG >10,000 mIU/mL or values obtained from women at a gestational age >6 weeks or >28 days after egg retrieval were excluded.

hCG values were transformed by means of natural log to better meet the assumptions of regression modeling and reduce the influence of large values. For each woman, a slope, or rate of rise in log-transformed hCG levels, was determined with the use of simple linear regression for her data only as well as with the use of linear mixed-effects (LME) regression for the entire sample, which allows for within- and between-subject variation in the rate of hCG rise (10). Both estimates of rise were evaluated as a predictor of adverse pregnancy outcome, and ultimately LME regression estimates were used. Although the two estimates are highly correlated with one another (Pearson correlation coefficient = 0.910; $P<.001$), LME uses within- and between-subject data to enhance precision in slope estimates.

For this analysis, hCG rise is presented as a 1-day change on the natural log scale along with corresponding 2-day percentage increases in hCG (normal scale).

Serum hCG concentrations were measured with the use of either the Abbott AxSYM (Abbott Laboratories) or DPC Immulite (Diagnostic Products Corp.) total immunoassay systems. Both the interassay and intraassay coefficients of variation were <10%. Results are expressed as mIU/mL, using the third international reference hCG standard.

The association between the rate of increase in hCG, or hCG rise, and pregnancy outcomes was assessed with the use of *t* test, chi-square test, and linear and logistic regressions where appropriate. hCG rise was explored as a continuous variable and categorized into quartiles. Multivariable linear or logistic regression was used to explore the effect of potential confounders by means of backwards selection. For each hypothesized confounder, effect modification, or interaction with the primary exposure variable (hCG rise) was first examined and included if significant. Variables with ≥15% change in the regression coefficient were identified as confounders and included in final multivariable modeling.

The statistical software packages SAS 9.2 (SAS Institute) and Stata 11.2 (Statacorp) were used for statistical analysis.

RESULTS

Three-hundred sixty IVF cycles resulting in a singleton live birth met the inclusion criteria. From an original cohort of 687 live births, IVF cycles were excluded for the following reasons: twin (n = 180) or triplet (n = 7) gestations,

donor egg cycles (n = 68), more than one gestational sac seen at 6-week ultrasound (i.e., no "vanishing twins" were included; n = 22), and incomplete or missing serial hCG data (n = 50). Subjects had, on average, 2.44 ± 0.9 (mean ± SD) embryos transferred and 3.1 ± 0.98 serial hCG measurements beginning 15.9 ± 1.7 days after egg retrieval. Sixty-nine (19.2%) of the study population of 360 conceived after frozen ET.

Baseline characteristics for the included study population are presented in Supplemental Table 1 (available online at www.fertstert.org). The majority of patients were non-Hispanic white. The mean initial hCG level was 287 ± 231 mIU/L. The median slope was 0.407, which corresponds to a 2-day increase in hCG of 126%, and the mean ± SD slope was 0.405 ± 0.06. Among the entire study population, 90/360 (25%) contributed two hCG values, 202/360 (56.1%) contributed three hCG values, and 68/360 (18.9%) contributed four or more hCG values.

We first examined the association between hCG rise and the two primary outcomes, birth weight (g) and gestational age (d) at delivery. Unadjusted linear regression demonstrated that hCG rise was significantly positively associated with birth weight (P=.002). For a one-quartile change in slope of hCG rise (or 0.039), birth weight increased by 62.0 g.

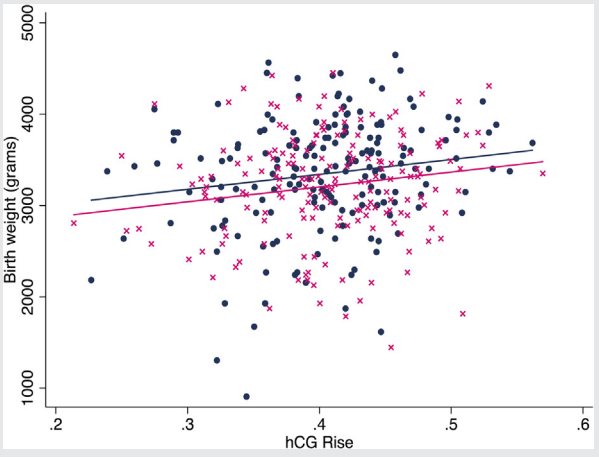
The effects of age, race, ethnicity, parity, type of ET (fresh vs. frozen/thawed), number of embryos transferred, infant sex, number of serial hCG measurements, initial hCG level, and gestational age on this association were assessed with the use of multivariable linear regression. Infant sex, type of ET, gestational age, and race confounded the association between hCG rise and birth weight. Independently, and as expected, gestational age had a significant positive effect on birth weight. For each 1-day increase in gestational age, birth weight increased by 27.5 g (P<.001). Female infants had a significantly lower predicted birth weight (−193.3 g compared to male; P<.001) and infants born after a frozen/thawed ET had a significantly higher predicted birth weight (+150.9 g compared to fresh; P=.012). The association between hCG rise and birth weight, stratified by infant sex and by fresh versus frozen/thawed ET are shown in Figures 1 and 2, respectively. We examined whether the association was different in the fresh versus frozen transfers. Details of this evaluation are found in Supplemental Figure 1 (available online at www.fertstert.org). A statistical test for effect modification due to type of transfer (fresh vs. frozen) did not achieve statistically significance (P=.263).

In a multivariable linear model, the effect of race on this association was no longer significant and was removed from the model. The final model of the association between hCG rise and birth weight included gestational age, ET type (fresh vs. frozen/thawed), and infant sex. After adjusting for infant sex and type of transfer, it was demonstrated that a 1-SD increase in hCG rise resulted in a 50.7-g increase in birth weight (P=.033).

Similarly, the association between the rate of hCG rise and gestational age at delivery was determined. No association was noted between hCG rise and gestational age (P=.178). Analysis of potential confounders did not change this finding.

The mean rate of hCG increase was then compared between subjects with and without specific adverse clinical outcomes (Table 1) with the use of two-sample t tests. Subjects who delivered an LBW infant had a significantly slower hCG rise (P=.035) compared with those who did not. Similarly, subjects delivering an SGA infant also showed a significantly slower hCG rise (P=.038). There was no statistically significant difference in mean hCG rise among subjects with preterm delivery compared with those without, although a trend was noted (P=.096). Among those with delivery records

FIGURE 1



Linear regression of hCG rise versus birth weight in male (*blue dots*) and female (*red x's*) infants. There was a significant positive association between hCG rise and birth weight (P=.002; n = 360).

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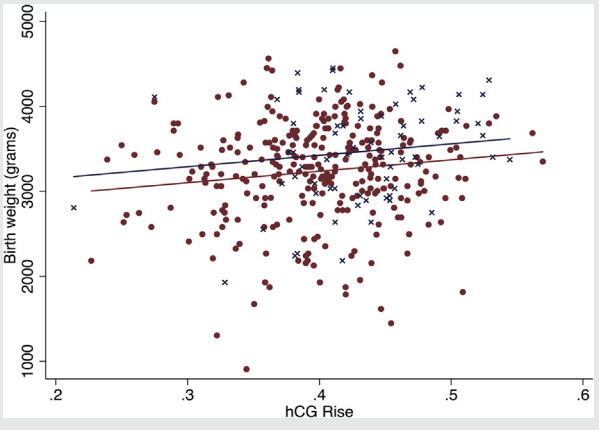
FIGURE 2



Linear regression of hCG rise versus birth weight of singleton pregnancies after fresh embryo transfer cycles (*red dots*) or following frozen/thawed embryo transfer cycles (*blue x's*). There was a significant positive association between hCG rise and birth weight (P=.002; n = 360).

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TABLE 1

Association of hCG rise and adverse perinatal outcomes.

Outcome	n (%)	Rate of hCG rise	2-day increase (%)	*P* value[a]
Low birth weight				
Yes	40 (11.1)	0.386 ± 0.05	116.4	.035
No	319 (88.6)	0.407 ± 0.06	125.7	
Preterm delivery				
Yes	47 (13.1)	0.391 ± 0.06	118.6	.096
No	313 (86.9)	0.407 ± 0.06	125.7	
Small for gestational age				
Yes	13 (3.6)	0.371 ± 0.07	110.0	.038
No	346 (96.4)	0.406 ± 0.06	125.2	
Gestational hypertension				
Yes	11 (6.5)	0.409 ± 0.09	126.6	.908
No	156 (91.8)	0.407 ± 0.06	125.7	
Preeclampsia				
Yes	7 (4.1)	0.411 ± 0.07	127.5	.849
No	160 (94.1)	0.407 ± 0.06	125.7	
Neonatal intensive care unit admission				
Yes	21 (12.4)	0.391 ± 0.07	118.6	.222
No	149 (87.7)	0.409 ± 0.06	126.6	

[a] Two-tail *t* test.

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available for review (n = 170), there was no association between mean hCG rise and gestational hypertension (*P*=.908), preeclampsia (*P*=.849), or infant NICU admission (*P*=.222).

For ease of interpretation, hCG rise was stratified into quartiles. The association with adverse pregnancy outcome is presented in Table 2. The first (slowest) quartile served as the reference quartile. Unadjusted odds ratios (ORs) for adverse outcomes showed that the risk of delivering an LBW infant, compared with the first quartile, decreased as rate of hCG rise increased (*P*=.018 for overall trend). When individual quartiles of hCG rise were assessed, this association between hCG rise and risk of adverse outcome was significantly decreased among individuals in the fourth quartile (OR 0.32, 95% confidence interval [CI] 0.11–0.92). After adjustment for previously identified covariates (gestational age, infant sex, and ET type), the association between the fastest rate of hCG rise (fourth quartile) and a lower risk for LWB persisted (OR 0.13, 95% CI 0.02–0.70).

A similar, though nonsignificant, trend was noted for delivery of an SGA infant and preterm delivery for women in the upper quartiles of hCG rise. We found no association between quartile of hCG rise and hypertensive disorders or NICU admission.

Given reported differences in perinatal outcomes among fresh versus frozen/thawed ETs (11–15), we further investigated the difference in hCG rise between these two groups in our population. We compared the rate of increase in hCG levels between fresh and frozen/thawed ET cycles, assessing curves stratified by absolute hCG value and days from gestation, allowing isolation of the earliest portion of the curve generated by serial hCG values (Supplemental Fig. 2, available online at www.fertstert.org). Rise in hCG after frozen/thawed ET was significantly higher than after fresh ET regardless of absolute hCG value or gestational age.

DISCUSSION

The primary goal of this study was to assess the association between the rate of hCG rise in the early first trimester and adverse perinatal outcomes, hypothesizing that hCG rise may be a marker of trophoblast differentiation and therefore invasion and placentation. We assessed the association of slope of hCG rise and perinatal outcomes in three ways: 1) the correlation of the slope based on the rise of serial hCG serum concentrations with birth weight and gestational age; 2) a comparison of the slope of hCG in those with and without a specific adverse perinatal outcome; and 3) the odds of adverse perinatal outcome depending on the quartile of the hCG slope. The data demonstrated that early first-trimester maternal serum hCG rise is associated with pregnancy outcomes beyond the first trimester. These findings suggest that events occurring in the peri-implantation period may have long-term impact on fetal heath, possibly related to trophoblast differentiation and early placentation.

With the use of linear regression of log-transformed hCG values, we were able to approximate the overall rate of hCG increase for each subject starting ~15–16 days from egg retrieval (or at ~4 weeks gestation). The median rate of 2-day increase in hCG was 126%, consistent with our previous work reporting a 2-day increase of 124% (4). The association between hCG rise and birth weight was confounded by three important factors: infant sex, type of ET (fresh vs. frozen/thawed), and gestational age at delivery. For a given rate of hCG rise, male infants, infants conceived after a frozen ET, and infants who were delivered at a later gestational age had, on average, a greater birth weight. However, even after controlling for these factors we demonstrated a positive association of early hCG rise and birth weight, whereas no association was noted between hCG rise and gestational age (Fig. 1). When comparing the slope of early hCG rise in those who did versus did not have an adverse perinatal outcome, we observed similar findings: The average slope was slower for LBW or SGA infants (Table 1). There was a nonsignificant trend toward a slower slope for infants delivered preterm. Of note, there was no apparent difference in hCG slope for women who developed gestational hypertension or preeclampsia. Although we had limited power to detect differences among these relatively low-prevalence outcomes, this observation may suggest that the second wave of invasion occurring in the late first and early second trimester of pregnancy, a time of different hCG dynamics and not studied in the present investigation, may be responsible for the pathologic placentation associated with gestational hypertensive disorders.

Dividing hCG rise into quartiles allowed us to assess the "dose-response" relationship between exposure and outcome. TheOR for having an LBW infant decreased as the quartile of hCG rise increased, ultimately becoming significantly reduced for subjects in the fourth (fastest) quartile. A test for trend showed that each quartile increase in slope was significantly negatively associated with LBW in unadjusted and adjusted analyses (Table 2). There were nonsignificant trends for greater odds of preterm delivery and an SGA infant, but no association with hCG slope and gestational hypertension or

TABLE 2

Unadjusted and adjusted odds ratios (ORs) for adverse outcomes by quartile of hCG rise.

	OR	aOR	OR	aOR	OR	aOR
hCG rise quartile	**Low birth weight**		**Preterm delivery**		**Small for gestational age**	
1st quartile	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2nd quartile	0.92 (0.40–2.08)	0.87 (0.28–2.64)	1.00 (0.46–2.19)	1.06 (0.48–2.36)	0.13 (0.02–1.11)	0.14 (0.02–1.16)
3rd quartile	0.54 (0.22–1.37)	0.79 (0.23–2.71)	0.49 (0.20–1.23)	0.50 (0.20–1.26)	0.56 (0.16–2.00)	0.62 (0.17–2.26)
4th quartile	0.32 (0.11–0.92)	0.13 (0.02–0.70)	0.55 (0.23–1.33)	0.59 (0.24–1.47)	0.13 (0.02–1.09)	0.15 (0.02–1.30)
Trend (*P* value)	.018	.028	.08	.111	.067	.107
	Gestational hypertension		**Preeclampsia**		**Neonatal intensive care unit admission**	
1st quartile	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2nd quartile	0.50 (0.04–5.74)	0.62 (0.05–7.22)	1.03 (0.14–7.65)	1.14 (0.15–8.74)	0.56 (0.17–1.87)	0.52 (0.10–2.77)
3rd quartile	2.16 (0.37–12.5)	2.54 (0.43–15.0)	NE	NE	0.33 (0.08–1.33)	0.54 (0.09–3.30)
4th quartile	2.05 (0.36–11.8)	2.65 (0.44–15.8)	1.50 (0.24–9.46)	1.97 (0.30–12.7)	0.56 (0.17–1.87)	0.81 (0.16–4.13)
Trend (*P* value)	.230	.153	.881	.667	.244	.774

Note: All outcomes were adjusted for infant sex and embryo transfer type (fresh vs. frozen). Low birth weight and neonatal intensive care unit admission were also adjusted for gestational age at delivery. *P* values presented for trend. aOR = adjusted odds ratio; CI = confidence interval; NE = no event.

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preeclampsia. There was no association with the odds of NICU admission and hCG rise.

Several authors have noted elevated second-trimester hCG levels after frozen ET compared with fresh ET (16–18), but those studies did not specifically assess rates of first-trimester increase. We found that the association of hCG level and type of conception was constant even when we stratified our analysis based on gestational age and absolute hCG concentration, suggesting that the difference in hCG rise is already apparent as early as 15 days after egg retrieval and remains unaltered (Supplemental Fig. 1).

It has been hypothesized that the nonphysiologic maternal environment during a fresh ET may affect early trophoblast differentiation and placentation and help to explain the association of lower perinatal morbidity after frozen ET compared with fresh ET in both single-center and population-based studies (11–15). However, this mechanism may be independent from early hCG rise over time, because we noted an association of LBW and slow hCG rise after both fresh and frozen transfers. The association with obstetrical outcome and hCG rise was in the same direction, with a similar strength of association, when data were stratified by fresh versus frozen conception (data not shown). Moreover, the slope of hCG rise in conceptions after fresh or frozen ET was not different in this cohort (Supplemental Fig. 2).

Currently, there is no definitive explanation for the cellular mechanisms underlying our observations and to explain how early hCG rise correlates with placental health and fetal growth. Nevertheless, it can be hypothesized that variations in trophoblast differentiation toward the invasive/extravillous phenotype versus the hCG-producing/villous phenotype are at the center of these findings (19). This remains to be elucidated.

Our study differs from previous studies that have assessed maternal serum markers and adverse pregnancy outcomes. We captured an earlier period of gestation and assessed a maternal serum marker of placentation as it changes over time. Previous authors assessed maternal serum markers collected as part of aneuploidy screening and correlation with preeclampsia, LBW, stillbirth, and preterm delivery (19–23). However, the use of hCG alone has not been shown to have meaningful clinical utility to predict adverse pregnancy outcomes and is best when used in combination with other screening measures (24, 25). Findings have been inconsistent, including that late first-trimester hCG levels in women who develop preeclampsia or growth restriction are only slightly reduced, if at all, and that in the second trimester, hCG levels may in fact be elevated in those with adverse outcomes (26). This finding may be attributable to a "hypoperfusion-leakage" phenomenon occurring after the failure of an adequate second wave of trophoblast invasion in the late first and early second trimester (27). Although a low hCG level as early as 12 days after cleavage-stage ET has been recently associated with a higher risk of preeclampsia (28), we did not observe such an association. This may be due to the limited number of preeclampsia events in our cohort to allow us to adequately assess the relationship between hCG and preeclampsia. It is plausible that low hCG levels with compensatory faster rise may reflect dysfunctional placentation and be a marker of adverse outcomes in this population later in pregnancy. The assessment of serial hCG in the early first trimester has primarily been used to assess viability, with slower rise associated with miscarriage and faster rise with live birth (6, 7).

Limitations of our study include its retrospective nature. Although we ascertained hCG curves and demographic information on the majority of subjects that met our inclusion criteria, missing data, such as smoking status, body mass index, and history of preterm delivery/LBW were not available. Nevertheless, smoking is low in this patient population, and it is only a theoretic possibility that a history of a poor obstetrical outcome would affect the hCG rise in a subsequent pregnancy. We also did not analyze the impact of the preconception hormonal milieu (i.e., estrogen or progesterone levels). The effect of these potential confounding factors would be an important future direction of this line of research. We attempted to reduce any effect that "vanishing twins" may have had on hCG curves, and on perinatal outcomes, by limiting our study to pregnancies with only one gestational sac at the 6-week ultrasound. However, it was not feasible to limit our analysis to cycles with a single ET owing to the limited number of single ETs (29/360, 8.1%) in our cohort during the period of the study. However we are confident that any confounding based on a potential biochemical vanishing twin would be minimal.

Our study was conducted on a convenience sample specifically chosen to minimize potential confounding based on laboratory techniques and media. A post hoc power calculation determined that given our sample size, we had >90% power to detect a one-half SD difference in the outcome of LBW in this purposeful homogeneous population. Estimating hCG rise for each individual with the use of regression models introduced random error and may have reduced our precision, biasing results toward the null. To address this, we reduced potential modeling error with the use of LME regression to more accurately account for within- and between-subject variation in hCG rise. Future study will be needed to address the effects of different media, oxygen tension or culture conditions.

We think that our study has several strengths. First, we proposed a novel hypothesis: that events very early in pregnancy have an association with ultimate pregnancy outcome. We studied this association with respect to clinically meaningful end points that occur at the time of delivery and did not limit our analysis to first-trimester end points, such as the diagnosis of a viable pregnancy. Furthermore, we restricted our study population to a single gestational sac early in the first trimester resulting in a singleton live births, in an attempt to reduce the effect that multiple pregnancies (even "vanishing twins") have on hCG curves and pregnancy outcomes.

CONCLUSION

We found that among a cohort of women who conceived after IVF and delivered a singleton live-born infant, a faster rate of hCG rise in the first few weeks of early gestation was

associated with a reduced risk of delivering an LBW infant, but not of preterm delivery or hypertensive disorders of pregnancy. This novel finding suggests that events of early pregnancy, such as trophoblast differentiation, implantation, and early placental development, may play a crucial role in the health of the developing embryo and affect infant health. Although our findings are intriguing, much work remains before the cellular mechanism of this clinical observation is elucidated and before this information can be applied clinically.

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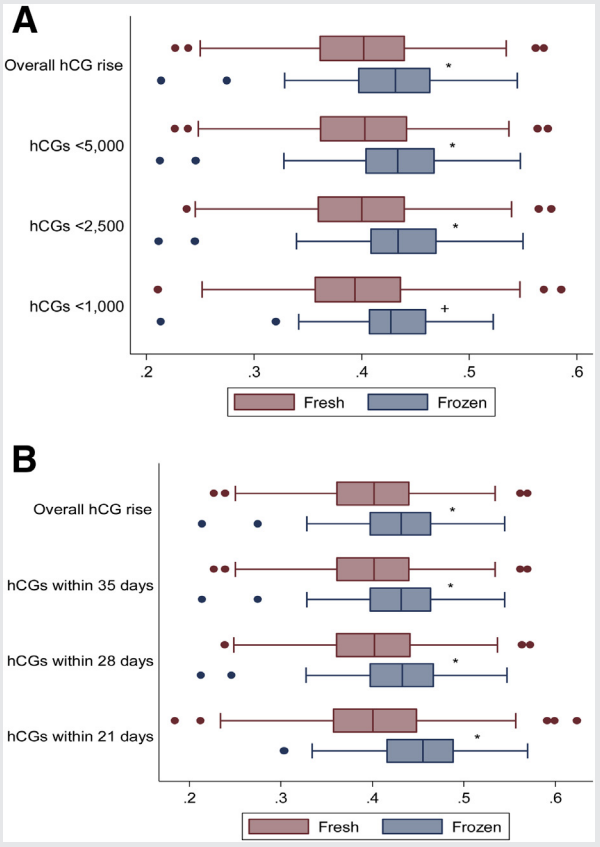
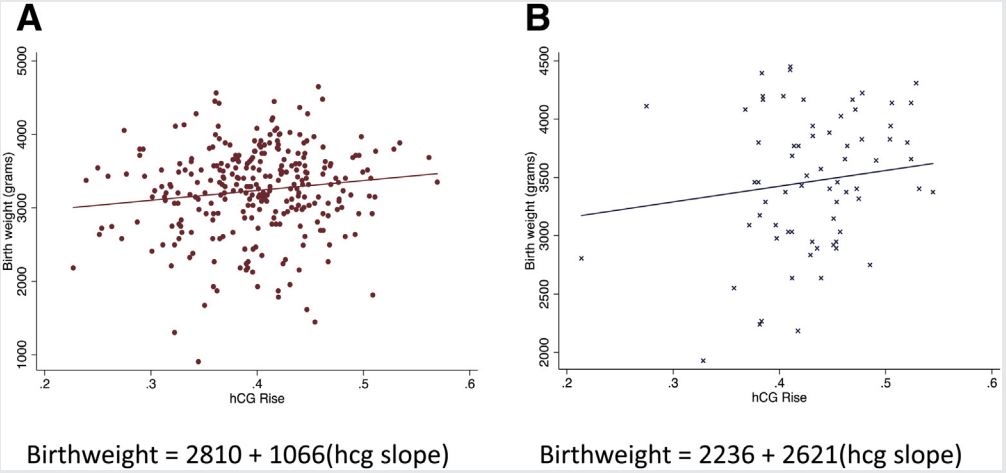
SUPPLEMENTAL FIGURE 1



Linear regressions of hCG rise versus birth weight of singleton pregnancies after (**A**) fresh or (**B**) frozen/thawed embryo transfer cycles. A statistical test for effect modification due to type of transfer (fresh vs. frozen) was not statistically significant (P=.263).

Morse. hCG rise and adverse perinatal outcome. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 2



Box plots of hCG rise after fresh (n = 291) versus frozen/thawed (n = 69) embryo transfer cycles stratified by cutoff points in (**A**) absolute hCG value and (**B**) number of days after egg retrieval. $^{*}P \leq .0001$; $^{+}P \leq .01$.

Morse. hCG rise and adverse perinatal outcome. Fertil Steril 2016.

SUPPLEMENTAL TABLE 1

Patient characteristics (n = 360).

Characteristic	n (%)
Age (y)	
≤30	72 (20)
31–35	148 (41.1)
36–40	126 (35)
>40	14 (3.9)
Race	
White	260 (75.8)
Black	41 (11.4)
Other	42 (11.7)
Missing	17 (4.7)
Ethnicity	
Non-Hispanic	333 (92.5)
Hispanic	8 (2.2)
Missing	19 (5.3)
Gravidity	
Nulliparous	160 (44.4)
≥1 previous pregnancy	200 (55.6)
Initial hCG level (mIU/mL)	
≤250	202 (56.1)
251–500	113 (31.4)
≥500	45 (12.5)
No. of serial hCG measurements	
2	86 (23.9)
3	203 (56.4)
≥4	71 (19.7)
IVF transfer type	
Fresh	291 (80.8)
Frozen	69 (19.2)
No. of embryos transferred	
1 or 2	221 (61.4)
≥3	139 (38.6)

Morse. hCG rise and adverse perinatal outcome. Fertil Steril 2016.