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ORIGINAL ARTICLE ***Infertility***

Live birth and perinatal outcomes following stimulated and unstimulated IVF: analysis of over two decades of a nationwide data

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STUDY QUESTION: Does ovarian stimulation affect perinatal outcomes of preterm birth (PTB) and low birth weight (LBW) following IVF treatment.

SUMMARY ANSWER: Despite no significant differences in the risks of PTB and LBW between stimulated and unstimulated IVF in the present study, the study cannot exclude the effect of ovarian stimulation on the perinatal outcomes following IVF.

WHAT IS ALREADY KNOWN: Pregnancies resulting from assisted reproductive treatments (ART) are associated with a higher risk of pregnancy complications compared to spontaneously conceived pregnancies attributed to the underlying infertility and the *in vitro* fertilization techniques. It is of interest to determine the effect size of ovarian stimulation use in achieving a live birth and whether ovarian stimulation that is routinely used in IVF, affects perinatal outcomes of birth weight and gestational age at delivery compared to unstimulated IVF.

STUDY DESIGN, SIZE, DURATION: Anonymous data were obtained from the Human Fertilisation and Embryology Authority (HFEA), the statutory regulator of ART in the UK. The HFEA has collected data prospectively on all ART performed in the UK since 1991. Data from 1991 to 2011 comprising a total of 591 003 fresh IVF ± ICSI cycles involving 584 835 stimulated IVF cycles and 6168 unstimulated IVF cycles were analyzed.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Data on all women undergoing either stimulated or unstimulated fresh IVF ± ICSI cycles during the period from 1991 to 2011 were analyzed to compare live birth rates, singleton live birth rates, perinatal outcomes of PTB, early PTB (<32 weeks), LBW and very LBW (<1500 grams) among singleton live births. Adjusted logistic regression was performed for each perinatal outcome for confounding factors: female age, period of treatment, cause of infertility, number of previous IVF cycles and previous live birth.

MAIN RESULTS AND THE ROLE OF CHANCE: Analysis of the large nationwide data demonstrated 3.5 times (95% confidence interval (CI): 3.1–3.9) as many unstimulated IVF cycles being required to achieve one live birth compared to stimulated IVF and 2.9 times (95% CI: 2.6–3.2) as many unstimulated IVF cycles being required to achieve one singleton live birth compared to stimulated IVF. There was no significant difference in the unadjusted odds for PTB (odds ratio (OR) 1.27, 95% CI: 0.80–2.00) and LBW (OR 1.48, 95% CI: 0.90–2.42) between stimulated and unstimulated IVF cycles. There was no significant difference in the risk of the adverse perinatal outcomes after adjusting for potential confounders; PTB (adjusted odds ratio (aOR) 1.43, 95% CI: 0.91–2.26) and LBW (aOR 1.58, 95% CI: 0.96–2.58).

LIMITATIONS, REASONS FOR CAUTION: Although the analysis was adjusted for a number of important confounders, the dataset had no information on smoking, body mass index (BMI) and the medical history of women during pregnancy to allow adjustment. Anonymized nature of the dataset did not make it permissible to analyse one cycle per woman. Given the smaller number of perinatal events with unstimulated IVF, a larger study is needed to investigate further.

WIDER IMPLICATIONS OF THE FINDINGS: Analysis of this large dataset demonstrates that ovarian stimulation has a vital role in maximizing efficacy of IVF. Although there were no significant differences for PTB and LBW following stimulated compared to unstimulated IVF, the CIs were wide enough to include possible clinically important effects.

STUDY FUNDING/COMPETING INTEREST(S): No funding was obtained. There are no competing interests to declare.

Key words: stimulated IVF / unstimulated IVF / live birth / preterm birth / low birth weight

Introduction

The introduction of ovarian stimulation into IVF has been a vital clinical milestone to increasing the success rates and currently the majority of IVF cycles involve ovarian stimulation aimed at optimizing the number of oocytes retrieved. The number of oocytes retrieved influence substantially the prognosis for the success of IVF treatment (Sunkara *et al.*, 2011; Steward *et al.*, 2014). The ultimate objective with assisted reproduction treatments (ART) is to efficiently achieve healthy live birth outcomes.

Several studies have shown ART pregnancies to be associated with a higher risk of complications compared to spontaneously conceived pregnancies (Schieve *et al.*, 2007; McDonald *et al.*, 2009, 2010; Pinborg *et al.*, 2013). There is a higher incidence of preterm birth (PTB), low birth weight (LBW) and small for gestational age foetuses following ART. Whilst the underlying subfertility itself could be the cause for the adverse outcomes (Williams *et al.*, 1991; Henriksen *et al.*, 1997), it is suggested that the various processes and procedures associated with ART also carry a risk for the adverse outcomes (Olivennes *et al.*, 1993; Sundström *et al.*, 1997). Whilst the higher incidence of multiple pregnancies following IVF are a major cause for the adverse outcomes of PTB and LBW, singleton pregnancies following IVF are also associated with a higher risk of adverse outcomes (McDonald *et al.*, 2009). The causes for the poor perinatal outcomes following IVF could be multifactorial. There are suggestions relating to epigenetic modifications resulting from ovarian stimulation or embryo culture as possible contributory factors and a higher incidence of 'vanishing twin pregnancies' as a result of multiple embryo transfers that have been shown to influence perinatal risks (Pinborg *et al.*, 2005, 2007; Sunkara *et al.*, 2015).

A recent study demonstrated a higher incidence of PTB and LBW among IVF singleton live births in women with very high number of oocytes (>20) following stimulation compared to women with a normal response (10–15 oocytes) (Sunkara *et al.*, 2015). The study showed no increased risk of the adverse outcomes among women with a suboptimal response (4–9 oocytes) or poor ovarian response (≤3 oocytes). One suggested reason for the adverse perinatal outcomes with very high number of oocytes could be the effect of the resulting high oestradiol levels at the time of embryo implantation (Pereira *et al.*, 2015). However, whether ovarian stimulation itself is associated with a higher risk of the adverse perinatal outcomes is unclear. The main aim of this study was to determine whether ovarian stimulation has an influence on the perinatal outcomes of PTB and LBW following IVF treatment. We also addressed the efficacy of achieving live birth following IVF with and without ovarian stimulation. We used a large national (UK) database involving 584 835 stimulated fresh and 6168 unstimulated fresh IVF cycles between the periods 1991–2011 to address this question.

Materials and Methods

Anonymous data were obtained from the Human Fertilisation and Embryology Authority (HFEA), the statutory regulator of ART in the UK. Information was obtained on all ART cycles carried out in the UK between August 1991 and December 2011. A total of 1 004 487 ART cycles were recorded prospectively during this period. For the purpose of this study only stimulated and unstimulated fresh IVF ± ICSI treatment cycles were analyzed. Data were obtained for the age group of the women (≤34, 35–37, 38–39, 40–42; 43–44; ≥45 years), treatment period (1991–1995, 1996–2000, 2001–2005, 2006–2011), cause of infertility (male factor, tubal disease, ovulatory disorder, endometriosis, unexplained), previous IVF cycles, previous live birth (yes or no), number of oocytes retrieved, number of embryos created, live birth occurrence, singleton live birth, gestational age at delivery and birth weight. A live birth is defined as both singleton and multiple births. Occurrence of a live birth at <37 weeks gestation was defined as a PTB and <32 weeks as an early PTB. Birth weight <2500 grams was defined as LBW and <1500 grams as very LBW. Only singleton live births defined as a singleton live birth event in which the baby is born alive were compared for perinatal outcomes of PTB, early PTB, LBW and very LBW.

Statistical analysis

The characteristics of the cohorts (unstimulated and stimulated fresh IVF ± ICSI cycles) are described using relative frequencies for categorical variables and means or medians with measures of spread for continuous variables. Crude live birth and singleton live birth rates were computed for the individual cohorts. Distributions of the cohorts are described stratified by female age categories, period of treatment, cause of infertility, previous treatment cycles, previous live birth occurrence, number of oocytes collected and number of embryos created. Data on all stimulated and unstimulated fresh IVF cycles were analyzed to compare live birth rates, singleton live birth rates and perinatal outcomes (PTB, early PTB, LBW, very LBW). Multiple births were excluded from the analysis for perinatal outcomes of PTB, early PTB, LBW and very LBW. Adjusted logistic regression was performed for each perinatal outcome for confounding factors: female age category, period of treatment, cause of infertility, number of previous IVF cycles and previous live birth (yes or no). Potential confounders were selected as any factor on which we had information which was determined before the start of each IVF cycle, and which were known or suspected to be related to clinical outcome. A *P*-value <0.05 was considered statistically significant. Data was analyzed using the statistical package Stata, version 12 (StataCorp, College Station, TX).

Results

The data selection process for the study is detailed in Fig. 1. From the initial cohort of 1 004 487 ART cycles, 413 484 cycles were excluded from the analysis for the following reasons: donor insemination cycles, cycles involving frozen embryos, embryo donation, surrogacy, PGD,

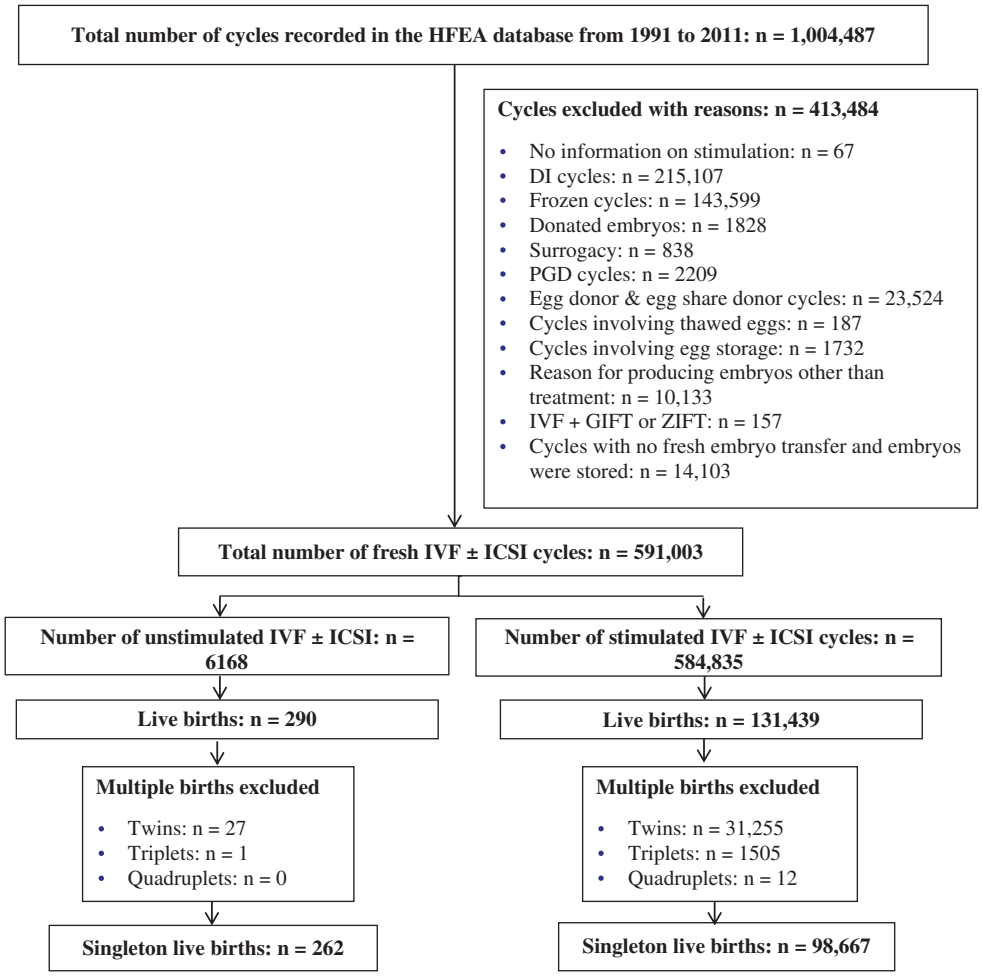

Figure 1 Data selection process for analysis of live births and perinatal outcomes following unstimulated and stimulated IVF. DI, donor insemination; GIFT, gamate intr-fallopian transfer; HFEA, human fertilisation and embryology authority; PGD, preimplantation genetic diagnosis; ZIFT, zygote intra-fallopian transfer.

egg donation or egg sharing, oocyte freezing, gamete intrafallopian transfer or IVF + zygote intrafallopian transfer, cycles where embryos were created for reasons other than infertility treatment, cycles with no fresh embryo transfer and cycles with no information on stimulation use. Overall 6168 unstimulated and 584 835 stimulated fresh IVF ± ICSI cycles were eligible for analysis. There were 290 live births following unstimulated IVF cycles and 131 439 live births following stimulated fresh IVF cycles. There were 28 multiple births with unstimulated IVF and 32 772 multiple births with stimulated IVF. There were therefore 262 and 98 667 singleton live births, respectively, following unstimulated and stimulated fresh IVF ± ICSI cycles.

Characteristics of the cohorts are described in Table I. Of the total cycles, 98.96% had stimulation and 1.04% were unstimulated IVF cycles. Majority of the unstimulated and stimulated cycles were in the younger female age group; 38.7% of unstimulated cycles and 47.7% of stimulated cycles were among women aged ≤34 years, while 27.4% of unstimulated cycles and 14.2% of stimulated cycles were in women aged ≥40 years. The major cause of infertility was male factor in both cohorts.

Of the unstimulated cycles, 44.2% (2726/6168) had no oocytes retrieved compared to 7.1% (41 770/584 835) of stimulated cycles with no oocytes. The median number of oocytes retrieved with unstimulated cycles was 1 (inter-quartile-range [IQR] 0–1) and the median number of oocytes with stimulated cycles was 8 (IQR 5–13) (Fig. 2a). Of the cases, 57.1% (3525/6128) of unstimulated cycles and 11.9% (69 460/584 835) of stimulated cycles had no embryos created. The median number of embryos created with unstimulated cycles was 0 (IQR 0–1) and with stimulated cycles was 5 (IQR 2–8) (Fig. 2b).

Live birth outcomes following unstimulated and stimulated IVF

The overall live birth rates were 4.7% (95% CI: 4.2–5.3%) per cycle following unstimulated fresh IVF versus 22.5% (95% CI: 22.4–22.6%) following stimulated fresh IVF (Fig. 3a). It is estimated that 21.3 (95% CI: 19.0–23.9) unstimulated cycles versus 4.45 (95% C1: 4.43–4.47) stimulated cycles would be needed across all age groups to achieve one live birth event following IVF and fresh embryo transfer. To achieve equivalent live birth events 4.8 times (95% CI: 4.3–5.3) as many unstimulated IVF cycles would be needed compared to stimulated cycles.

Table I Characteristics of the cohorts of unstimulated and stimulated IVF cycles.

Characteristic	Unstimulated IVF *n* = 6168 (1.04%)	Stimulated IVF *n* = 584 835 (98.96%)
Age category		
≤34 years	2384 (38.7%)	279 007 (47.7%)
35–37 years	1295 (21.0%)	141 422 (24.2%)
38–39 years	806 (13.1%)	81 301 (13.9%)
40–42 years	1009 (16.4%)	64 480 (11.0%)
43–44 years	491 (8%)	14 516 (2.5%)
≥45 years	183 (3%)	4109 (0.7%)
Cause of infertility[a]		
Male factor	2903 (47.1%)	300 991 (51.5%)
Tubal disease	2214 (35.9%)	152 013 (26%)
Ovulatory disorder	715 (11.6%)	67 297 (11.5%)
Endometriosis	473 (7.6%)	42 952 (7.3%)
Unexplained	1791 (29.0%)	186 863 (32%)
Number of previous IVF cycles		
0	2217 (35.9%)	301 289 (51.5%)
1	1503 (24.4%)	127 706 (21.8%)
2	900 (14.6%)	68 064 (11.6%)
3 or more	1548 (25.1%)	87 776 (15.0%)
Previous live birth (yes)	402 (6.5%)	37 690 (6.4%)
Oocytes retrieved (Fig. 2a) Median (IQR)	1 (0; 1)	8 (5; 13)
Embryos created (Fig. 2b) Median (IQR)	0 (0; 1)	5 (2; 8)
Treatment cycles in each period		
1991–1995	2692 (43.6%)	79 620 (13.6%)
1996–2000	702 (11.4%)	128 461 (22.0%)
2001–2005	930 (15.1%)	140 288 (24%)
2006–2011	1844 (29.9%)	236 466 (40.4%)

[a]The causes of infertility are not mutually exclusive. IQR, inter-quartile-range.

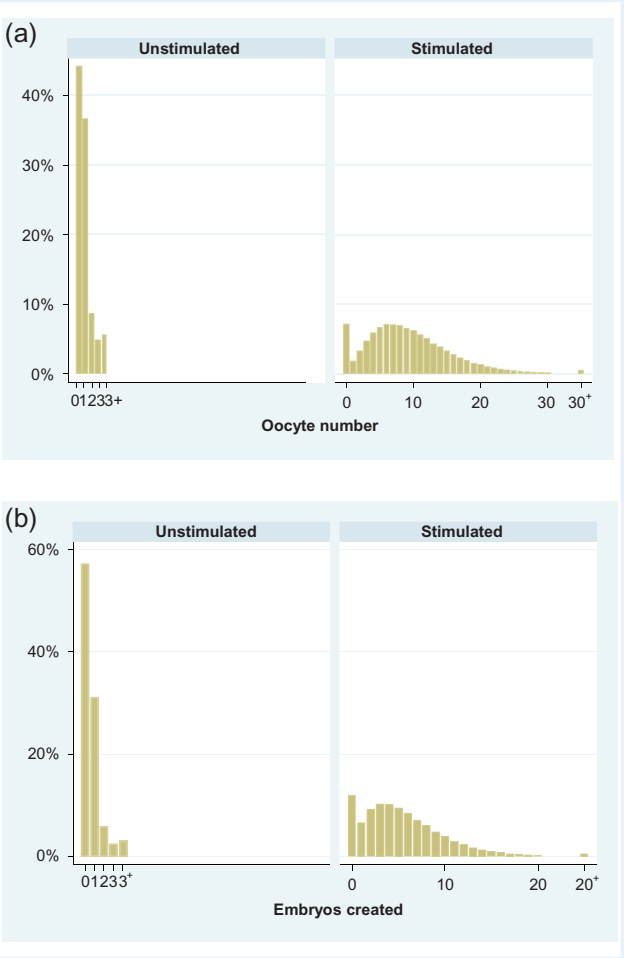

Figure 2 Oocyte number (**a**) and embryos created (**b**) following unstimulated and stimulated IVF cycles.

The singleton live birth rates were 4.2% (95% CI: 3.8–4.9%) per cycle following unstimulated fresh IVF versus 16.9% (95% CI: 16.8–17.0%) following stimulated fresh IVF cycles (Fig. 3b). It is estimated that 23.5 (95% CI: 20.9–26.6) unstimulated IVF cycles versus 5.93 (95% C1: 5.89–5.96) stimulated cycles would be needed across all age groups to achieve one singleton live birth. To achieve equivalent singleton live births 4.0 times (95% CI: 3.5–4.5) as many unstimulated IVF cycles would be needed compared to stimulated IVF cycles.

After adjusting for confounders of female age category, period of treatment, occurrence of previous live birth, number of previous IVF attempts and cause of infertility, the results demonstrate that 3.5 times (95% CI: 3.1–3.9) as many unstimulated cycles would be needed compared to stimulated cycles to achieve one live birth event and 2.9 times (95% CI: 2.6–3.2) as many unstimulated cycles would be needed compared to stimulated IVF to achieve one singleton live birth.

Ovarian stimulation and perinatal outcomes following IVF

Ninety six thousand eight hundred and ten singleton live births with information on gestational age of delivery and 96 386 singleton live births with birth weight information were analyzed for perinatal outcomes. The incidence of PTB was 7.7% (20/260) following unstimulated IVF and 9.6% (9223/96 550) following stimulated IVF. The incidence of early PTB was 0.8% (2/260) following unstimulated IVF and 1.9% (1881/96 550) following stimulated IVF. The incidence of LBW was 6.6% (17/258) following unstimulated IVF and 9.5% (9085/96 128) following stimulated IVF. The incidence of very LBW was 0.4% (1/258) following unstimulated IVF and 1.8% (1771/96 128) following stimulated IVF.

There was no significant difference in the risk of PTB (unadjusted odds ratio—OR 1.27, 95% CI: 0.80–2.00), early PTB (OR 2.56, 95% CI: 0.64–10.31), LBW (OR 1.48, 95% CI: 0.90–2.42) and very LBW (OR 4.82, 95% CI: 0.68–34.39) between stimulated and unstimulated IVF cycles. There was no significant difference in the risk of adverse perinatal outcomes after adjusting for potential confounders of female age category, period of treatment, cause of infertility, number of previous IVF cycles and previous live birth (Table II); PTB (adjusted odds

ratio (aOR) 1.43, 95% CI: 0.91–2.26%), early PTB (aOR 3.0, 95% CI: 0.74–12.08%), LBW (aOR 1.58, 95% CI: 0.96–2.58%) and very LBW (aOR 5.35, 95% CI 0.75–38.16%).

Discussion

The results of the study demonstrate the overall role of ovarian stimulation in maximizing live birth rates following IVF treatment in an unselected group of women. The multiple birth rate was higher following stimulated versus unstimulated IVF. However, the singleton live birth rate was also significantly higher following stimulated IVF. The study results demonstrate a significant proportion of cycles without oocytes and resulting embryos following unstimulated IVF. Previous smaller studies have reported around 40–50% of started cycles not reaching embryo transfer with natural cycle IVF (Aanesen *et al.*, 2010; Kawachiya *et al.*, 2012; Polyzos *et al.*, 2012). Given the high cancellation rate it is important that live birth rates are reported as per cycle started rather than per embryo transfer to make like comparisons between stimulated and unstimulated IVF. To this effect cumulative live births should also be reported per patient and per cycle started to reflect true comparisons. Few studies with such data have reported 3–13% live birth rates per stated cycle in unselected infertile women undergoing natural cycle IVF (Kawachiya *et al.*, 2012; Polyzos *et al.*, 2012; Roesner *et al.*, 2014).

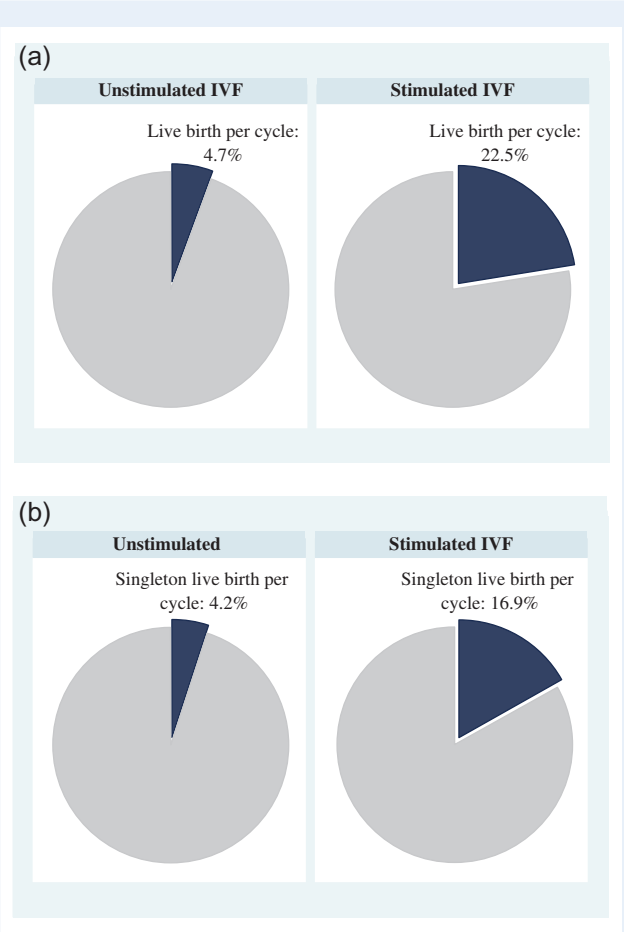

Figure 3 Live births (**a**) and singleton live births (**b**) following unstimulated and stimulated IVF cycles.

This finding of significantly higher live birth rate per cycle following stimulated IVF reiterates previous literature suggesting the number of oocytes as an important prognostic variable for IVF success (Sunkara *et al.*, 2011; Steward *et al.*, 2014). More accurate assessment of ovarian reserve with antral follicle count and anti-mullerian hormone (Broer *et al.*, 2013a,b) along with evolution of drugs used for controlled ovarian stimulation have enabled tailoring stimulation regimens to maximize live birth outcomes whilst avoiding side effects such as ovarian hyperstimulation syndrome (La Marca and Sunkara, 2014).

This present study is the largest study addressing the consequence of ovarian stimulation on perinatal risks of PTB and LBW. Although there were no significant differences for PTB and LBW following stimulated compared to unstimulated IVF, the CIs were wide enough to include possible clinically important effects: including aORs of two or more. Our previous study demonstrated an association between the number of oocytes retrieved following ovarian stimulation and risk of PTB and LBW. Women with >20 oocytes had a significantly higher incidence of PTB and LBW compared to women with 10–15 oocytes, whereas women with ≤3 (poor ovarian response) and 4–9 oocytes did not have an increased risk of the adverse prenatal outcomes (Sunkara *et al.*, 2015). The factors: female age category, occurrence of previous live birth, number of previous IVF attempts and cause of infertility are those well known to influence live birth occurrence and hence have been considered for the adjusted analysis. We did not adjust for potential mediators, such as number of oocytes retrieved, embryos replaced or initial multiple pregnancy leading to singleton live birth; as these are the result of stimulation, and adjusting for them would tend to remove the effect of stimulation.

A recent Cochrane review on natural cycle IVF versus standard IVF found insufficient data leading to imprecise results and called for further studies to address outcomes (Allersma *et al.*, 2013) as was addressed in this study. A very recent study compared perinatal

Table II Perinatal outcomes following unstimulated and stimulated IVF cycles.

Outcome	Unstimulated IVF	Stimulated IVF	OR (95% CI)	aOR (95% CI)
Preterm birth (<37 weeks)	20/260 (7.7%)	9223/96 550 (9.6%)	1.27 (0.80–2.00)	1.43 (0.91–2.26)
Early preterm birth (<32 weeks)	2/ 260 (0.8%)	1881/96 550 (1.9%)	2.56 (0.64–10.31)	3.0 (0.74–12.08)
Low birth weight (<2500 grams)	17/258 (6.6%)	9085/96 128 (9.5%)	1.48 (0.90–2.42)	1.58 (0.96–2.58)
Very low birth weight (<1500 grams)	1/258 (0.4%)	1771/96 128 (1.8%)	4.82 (0.68–34.39)	5.35 (0.75–38.16)

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

outcomes in 174 singleton live births following stimulated IVF versus 190 singleton live births following natural cycle IVF and reported a higher risk of PTB, LBW and very LBW following stimulated IVF (Mak *et al.*, 2016). This study reported exceptionally high rate of PTB in the stimulated and unstimulated groups (42% and 31.5%), respectively which is not consistent with what has been reported in the literature. We consider that very high incidences of PTB in their study are unlikely to be typical as they are derived from a single centre that may have a particularly high-risk population or different clinical practices. Data from large registries on the incidence of PTB in singleton births following ART is reported to be ~9–13% (Schieve *et al.*, 2007; Sunkara *et al.*, 2015). Their unadjusted OR for LBW (we calculate it as 8.9, CI: 2.0–39) is much higher than our study (OR 1.48, 95% CI: 0.90–2.42; aOR 1.58, 95% CI: 0.96–2.58). Considering the CIs the results are clearly inconsistent. Their aOR was reported as 0.07, treating stimulated cycles as the reference group; or we calculate as 14 if stimulation is seen as the intervention, as in our study. A meta-analysis found that singleton pregnancies resulting from IVF/ICSI had increased rates of PTB (1.54, 95% CI: 1.47–1.62) and LBW (Risk ratio 1.65, 95% CI: 1.56–1.75) compared to those resulting from spontaneous conception (Pandey *et al.*, 2012). These results are similar in size to our non-significant results for the differences between stimulated and unstimulated IVF, but without further data, it is impossible to draw clear conclusions.

The strength of the study is the nationwide data from across various centres which allow generalizability of the conclusions. The limitation of the dataset is lack of information on other confounders such as smoking status, BMI, underlying medical history of women during pregnancy. Furthermore, the HFEA data being anonymized did not permit analysis of one cycle per women, the weakness being that individual women could have contributed towards more than one outcome and the true sample size is not known. There were differences in the distribution of the two cohorts in terms of age, time period, previous IVF cycles which were considered as confounders for the adjusted analysis. The very small number of events in the unstimulated group for the perinatal outcomes and resultant wide CIs should be taken into consideration and demonstrate the need for more evidence on these findings.

With cumulative live births following an IVF cycle currently being focussed as the more relevant measure of ART success (Maheshwari *et al.*, 2015); the findings of this study could have important implications in influencing this outcome. Our previous study demonstrated that the chances of having blastocysts cryopreservered was positively associated with the number of oocytes increasing (Hamoda *et al.*, 2010). Although this study demonstrates the efficacy and safety of ovarian stimulation in fresh cycles only, it could be supposed that cumulative live birth rates are likely to be higher with stimulated IVF cycles which could inflate the overall effect size over unstimulated cycles. Considering time to pregnancy (TTP) as an important outcome measure, it could be expected to be shorter with stimulated IVF given the finding of 3.5 times and 2.9 times as many unstimulated cycles being required compared to stimulated IVF to achieve one live birth and singleton live birth, respectively. It is therefore important to validate the findings of this study and assess outcomes of cumulative live births, TTP in large prospective studies in addition to the cost-effectiveness of stimulated versus natural cycle IVF. The findings of this study are of relevance in providing information for clinicians to counsel women in their choices. The findings suggest the effectiveness of ovarian stimulation in IVF whilst its effect on risks of PTB and LBW needs further validation.

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Authors' roles

SKS conceived the hypothesis. SKS directed the data analysis by PTS and drafted the manuscript. PS, LAM, NPP and YK appraised the manuscript and participated in the discussion.

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Conflict of interest

None declared.

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