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ORIGINAL ARTICLE ***Reproductive epidemiology***

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

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STUDY QUESTION: Is there a relation between the number of oocytes retrieved following ovarian stimulation and obstetric outcomes of preterm birth (PTB) and low birthweight (LBW) following IVF treatment?

SUMMARY ANSWER: There is an increased risk of PTB (<37 weeks gestation) and LBW (<2500 g) following IVF in women with a high number (>20) of oocytes retrieved.

WHAT IS KNOWN ALREADY: Pregnancies resulting from assisted reproductive treatments (ART) are associated with a higher risk of pregnancy complications compared with spontaneously conceived pregnancies. Whether ovarian ageing in women with poor ovarian response is associated with an increased risk of adverse obstetric outcomes is debated. It is also unclear if an excessive response and high egg numbers following ovarian stimulation have an association with adverse obstetric outcomes.

STUDY DESIGN, SIZE, DURATION: Observational study using anonymized data on all IVF cycles performed in the UK from August 1991 to June 2008. Data from 402 185 IVF cycles and 65 868 singleton live birth outcomes were analysed.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Data on all women undergoing a stimulated fresh IVF cycle with at least one oocyte retrieved between 1991 and June 2008 were analysed for birth outcomes. Logistic regression analysis of the association between ovarian response (quantified as number of oocytes retrieved) and outcomes of PTB and LBW was performed.

MAIN RESULTS AND THE ROLE OF CHANCE: There was a significantly higher risk of adverse obstetric outcomes of PTB and LBW among women with an excessive response (>20 oocytes) compared with women with a normal response (10–15 oocytes): adjusted odds ratio (OR) 1.15, 95% confidence interval (CI) 1.03–1.28 for PTB, adjusted OR 1.17, 95% CI 1.05–1.30 for LBW, respectively. There was no increased risk of the adverse outcomes among women with a poor ovarian response (≤3 oocytes) compared with women with a normal response: adjusted OR 0.88, 95% CI 0.76–1.01 for PTB, adjusted OR 0.92, 95% CI 0.79–1.06 for LBW, respectively.

LIMITATIONS, REASONS FOR CAUTION: Although the analysis was adjusted for a number of potential confounders, the dataset had no information on other important confounders such as smoking, BMI and the medical history of women during pregnancy. Furthermore, the dataset did not allow specific identification of women with PCOS and its anonymized nature did not make it permissible to analyse one cycle per woman.

WIDER IMPLICATIONS OF THE FINDINGS: Analysis of this large dataset suggests that a high oocyte number (>20) following IVF is associated with a higher risk of PTB and LBW. These findings lead to speculation whether ovarian dysfunction and/or an altered endometrial milieu resulting from supraphysiological steroid levels underlie the unfavourable outcomes and warrant further research. Ovarian stimulation regimens should optimize the number of oocytes retrieved to avoid the risk of adverse outcomes associated with very high numbers of oocytes.

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

Key words: IVF / oocytes retrieved / preterm birth / low birthweight

Introduction

Pregnancies following assisted reproductive treatments (ART) are associated with a significantly higher risk of adverse obstetric outcomes such as preterm birth (PTB) and low birthweight (LBW) compared with spontaneous pregnancies (Schieve *et al.*, 2007; McDonald *et al.*, 2009, 2010). The possible reason for adverse obstetric outcomes following ART has been attributed to the underlying infertility itself and embryo specific epigenetic modifications due to the IVF techniques (Pinborg *et al.*, 2013). Studies have also reported higher rates of PTB and LBW among women of advanced maternal age (Ludford *et al.*, 2012; Phadungkiatwattana *et al.*, 2014) and this is thought to be the result of vascular ageing and vascular endothelial dysfunction (Pell *et al.*, 2004; Bonamy *et al.*, 2011; Hastie *et al.*, 2011). Vascular endothelial dysfunction associated with advanced female age is in turn attributed to sex steroid depletion, which is a consequence of ovarian ageing (Herrington *et al.*, 2001; Vita and Keaney, 2001). It is therefore a matter of interest whether women with poor response to ovarian stimulation, which is a manifestation of early ovarian ageing, are at increased risk of these adverse obstetric outcomes following IVF treatment.

There have been few studies addressing the association between response to ovarian stimulation and obstetric outcomes following IVF treatment. A matched controlled study comparing pregnancy outcomes following IVF in 150 women with a poor ovarian response ($\leq$3 oocytes retrieved) and 150 women with a normal response (8–12 oocytes retrieved) found no significant difference in the incidences of pregnancy-related hypertensive disorders, gestational age at delivery and birthweight (van Disseldorp *et al.*, 2010). Women with a poor, normal or excessive response to ovarian stimulation have different prognoses following IVF treatment. Women with poor ovarian response have a poor prognosis with lower live birth rates (Ulug *et al.*, 2003) and higher miscarriage rates (Sunkara *et al.*, 2014). Studies analysing the association between the number of oocytes and IVF outcomes demonstrated optimal live birth rates with 15 oocytes, with higher numbers being associated with an increased risk of ovarian hyperstimulation syndrome (OHSS) and no increase, or in fact a negative impact, on live birth rates (Sunkara *et al.*, 2011; Steward *et al.*, 2014).

It is uncertain whether the response to ovarian stimulation has an influence on the obstetric outcomes following IVF treatment. Theoretically, the obstetric outcomes could be influenced by ovarian and vascular ageing in poor responders, and could also be influenced by the ovarian dysfunction and probable detrimental effect of very high steroid levels on the endometrium among women with an excessive response following ovarian stimulation. We therefore explored whether there was an association between ovarian response to stimulation and obstetric outcomes. The aim of the study was to determine the relation between ovarian response, quantified as number of oocytes retrieved following stimulation, and the obstetric outcomes of PTB and LBW following IVF treatment. We used a large national (UK) database involving 402 185 stimulated fresh IVF cycles and 65 868 singleton live births to address this question.

Materials and Methods

Anonymous data were obtained from the Human Fertilization 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 June 2008. A total of 787 030 ART cycles were recorded prospectively during this period. For the purpose of this study only stimulated fresh IVF $\pm$ ICSI treatment cycles which had one or more oocytes retrieved were analysed. Data were obtained for the age group of the women (18–34, 35–37, 38–39, 40 years and over), treatment period (1991–2008), type of infertility (female primary or secondary), cause of infertility (tubal disease, ovulatory disorder, endometriosis, male factor, unexplained), number of oocytes retrieved following stimulation, live birth occurrence, gestational age at delivery, birthweight and multiplicity of births. A singleton live birth is defined as a singleton live birth event in which the baby is born alive. Occurrence of a live birth at $<$37 weeks gestation was defined as a PTB and $<$32 weeks as an early PTB. Birthweight $<$2500 g was defined as LBW and $<$1500 g as very LBW.

Statistical analysis

The characteristics of the cohort are described using absolute and relative frequencies with confidence intervals (CIs). To study the association between the number of oocytes and adverse obstetric outcomes, a maximum likelihood logistic regression model was fitted with the obstetric outcomes (PTB, early PTB, LBW and very LBW) as the dependent variables and number of oocytes as the main exposure of interest. Adjusted logistic regression was performed for each of the outcomes of PTB, early PTB, LBW, and very LBW for confounding factors which were female age category (18–34, 35–37, 38–39, 40 years and over), treatment period (1991–1995, 1996–2000, 2001–2005, 2006–2008), type of infertility (female primary or secondary), cause of infertility (tubal disease, ovulatory disorder, endometriosis, male factor, unexplained), number of embryos transferred (1 versus $\geq$2) and initial singleton or multiple pregnancies that led to singleton live births. Analyses were performed using oocyte number as a categorical variable; $\leq$3, 4–9, 10–15, 16–20 and $>$20 oocytes retrieved. Finally, tables were created for association between the IVF risk factors and each of the outcomes of PTB and LBW. A *P*-value of $<$0.05 was considered statistically significant. Data were analysed using the statistical package Stata, version 13.1 (StataCorp, College Station, TX, USA).

Results

The process of data selection was as previously described. Briefly, from the initial cohort of 787 030 ART cycles, 384 845 cycles were excluded from the analysis for the following reasons: cycles with missing data, cycles with no stimulation or where there was no information regarding the use of stimulation, cycles involving embryo donation, surrogacy, PGD, oocyte donation or oocyte sharing, frozen embryos, oocyte freezing, gamete intrafallopian transfer or IVF + zygote intrafallopian transfer, cycles where embryos were created for reasons other than infertility treatment, and cycles with no oocytes retrieved and/or no fresh embryo transfer (Sunkara *et al.*, 2014).

Overall 402 185 fresh stimulated IVF $\pm$ ICSI cycles were eligible for analysis of which 91 839 cycles resulted in a live birth, giving an overall live birth rate of 22.8% (95% CI: 22.5–22.9%) for the entire cohort. Of these, 1845 live births had missing information on either birthweight or gestational age of delivery; there were 22 765 twin births, 1350 triplets and 11 quadruplets, which were excluded from the analysis. Therefore, 65 868 singleton live births following IVF $\pm$ ICSI, with outcomes of birthweight and gestational age at delivery were analysed (Fig. 1). The incidence of term (59 803), PTB (6065) and early PTB (1064) was 90.8% (CI: 90.6–91.1%), 9.2% (CI: 9.0–9.4%) and 1.6% (CI: 1.5–1.7%), respectively. The incidence of LBW (6114) and very LBW (1087) neonates was 9.3% (CI: 9.0–9.5%) and 1.7% (CI: 1.5–1.8%), respectively. Characteristics of the cohort are detailed in Table I.

PTB and LBW stratified by age

The rates of PTB, early PTB and very LBW remained stable across all age groups; $P = 0.53$, 0.26 and 0.50, respectively. LBW was slightly more common in women aged 18–34 and ≥40 years (both 9.6%) than in women aged 35–37 and 38–39 years (8.8 and 8.6%, respectively); $P = 0.0061$ (Fig. 2a, Table I).

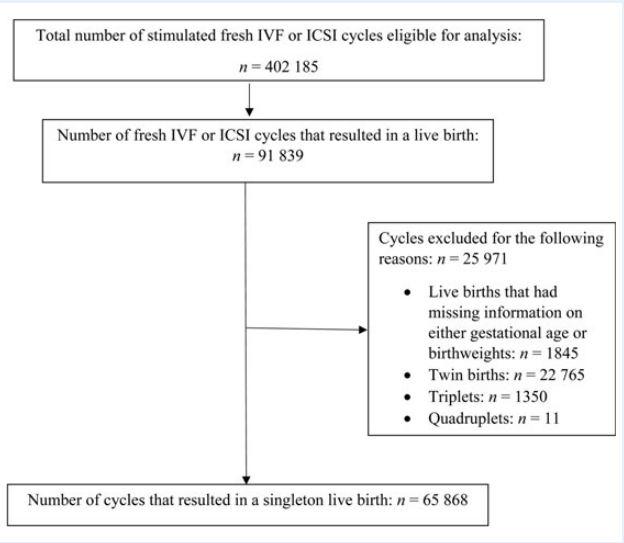

Figure 1 Data selection process for analysis of the association between ovarian response and adverse obstetric outcomes of preterm birth and low birthweight.

PTB and LBW by time period

There was a reduction in the incidence of PTB and LBW between the time period 1991–1995 and the subsequent periods (1996–2000; 2001–2005; 2006–2008); $P = 0.0000$ for PTB and $P = 0.0003$ for LBW (Fig. 2b, Table I). Hence, data from the period 1996–2008 were used to derive the rates of PTB and LBW in relation to risk factors.

Relationship between number of oocytes and adverse obstetric outcomes

Relating the number of oocytes retrieved to the rate of adverse obstetric outcomes, analysis of the dataset demonstrated an association between oocyte number and the outcomes of PTB, early PTB, LBW and very LBW. There was a general increase in the event rates with higher numbers of oocytes, particularly above 20 oocytes (Fig. 3) and these effects remained after adjusting for major predictors. The unadjusted odds of PTB (odds ratio (OR) 1.17, CI 1.06–1.30), early PTB (OR 1.35, CI 1.08–1.69) and LBW (OR 1.20, CI 1.08–1.33) were significantly higher with >20 oocytes compared with women with 10–15 oocytes. For very LBW the result was not statistically significant (OR 1.24, CI 0.99–1.56). The higher risk of the adverse outcomes with >20 oocytes was maintained after adjusting for the major predictors, female age category, treatment period, type of infertility, cause of

Table I Characteristics of the cohort of 65 868 singleton live births following assisted reproductive treatment.

	Term birth *n* (%)	Preterm birth *n* (%)	Early preterm birth *n* (%)	Birthweight >2500 g *n* (%)	Low birthweight *n* (%)	Very low birthweight *n* (%)
Overall	59 803 (90.8)	6065 (9.2)	1064 (1.6)	59 754 (90.7)	6114 (9.3)	1087 (1.7)
Age in years						
18–34	34 232 (90.7)	3510 (9.3)	623 (1.7)	34 126 (90.4)	3616 (9.6)	620 (1.6)
35–37	15 327 (91.0)	1524 (9.0)	266 (1.6)	15 362 (91.2)	1489 (8.8)	265 (1.6)
38–39	6664 (91.1)	653 (8.9)	102 (1.4)	6687 (91.4)	630 (8.6)	127 (1.7)
≥40	3580 (90.5)	378 (9.6)	73 (1.8)	3579 (90.4)	379 (9.6)	75 (1.9)
Female primary infertility	34 583 (91.4)	3264 (8.6)	562 (1.5)	34 384 (90.8)	3463 (9.2)	579 (1.5)
Cause of infertility*						
Male factor	32 858 (91.1)	3226 (8.9)	520 (1.4)	32 807 (90.9)	3277 (9.1)	554 (1.5)
Tubal disease	15 058 (89.3)	1810 (10.7)	307 (1.8)	15 166 (89.9)	1702 (10.1)	314 (1.9)
Ovulatory disorder	7079 (89.6)	823 (10.4)	178 (2.3)	7069 (89.5)	833 (10.5)	179 (2.3)
Endometriosis	4258 (90.4)	454 (9.6)	77 (1.6)	4278 (90.8)	434 (9.2)	83 (1.8)
Unexplained	19 183 (91.5)	1791 (8.5)	318 (1.5)	19 104 (91.1)	1870 (8.9)	321 (1.5)
Treatment period						
1991–1995	7287 (88.5)	946 (11.5)	160 (1.9)	7367 (89.5)	866 (10.5)	154 (1.9)
1996–2000	15 964 (90.8)	1625 (9.2)	293 (1.7)	15 986 (89.9)	1646 (9.4)	319 (1.8)
2001–2005	21 403 (91.3)	2041 (8.7)	341 (1.5)	21 365 (90.3)	2128 (9.1)	344 (1.5)
2006–2008	15 149 (91.3)	1453 (8.8)	270 (1.6)	15 165 (90.6)	1474 (8.9)	270 (1.6)

*The causes of infertility are not mutually exclusive.

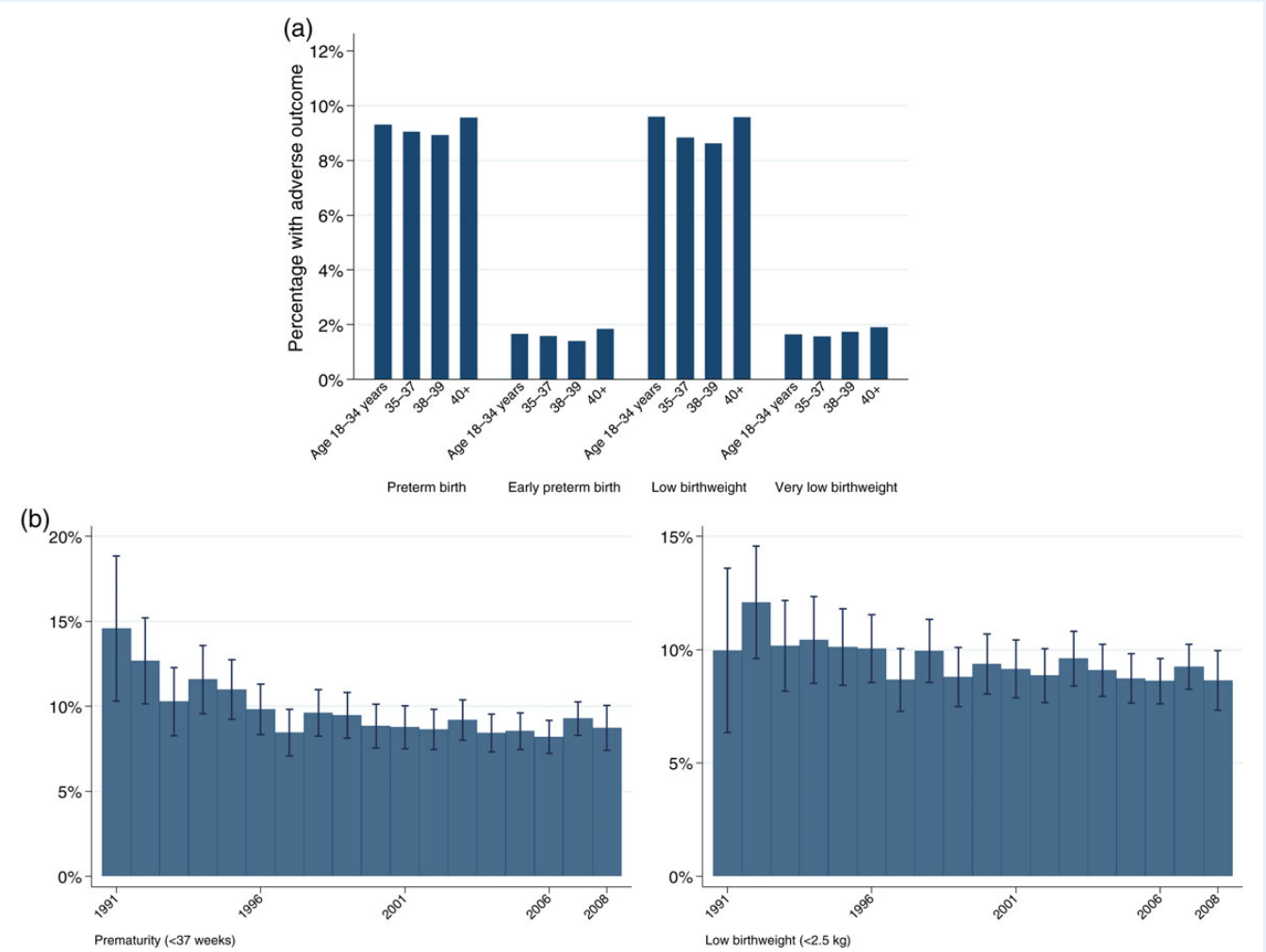

Figure 2 (**a**) Preterm birth, early preterm birth, low birthweight and very low birthweight stratified by age. (**b**) Preterm birth and low birthweight stratified by time period.

infertility, number of embryos transferred and initial singleton or multiple pregnancies progressing to a singleton live birth: adjusted OR for PTB 1.15, CI 1.03–1.28; adjusted OR for early PTB 1.30, CI 1.03–1.64, adjusted OR for LBW 1.17, CI 1.05–1.30 and adjusted OR for very LBW 1.23, CI 0.97–1.55.

Women with poor ovarian response (≤3 oocytes) did not have an increased risk of the adverse outcomes compared with women with 10–15 oocytes; with unadjusted odds for PTB (OR 0.90, CI 0.79–1.04), early PTB (OR 1.05, CI 0.78–1.40), LBW (OR 0.91, CI 0.81–1.04), very LBW (OR 0.91, CI 0.67–1.22) and the adjusted odds for PTB (adjusted OR 0.88, CI 0.76–1.01), early PTB (adjusted OR 1.11, CI 0.82–1.53), LBW (adjusted OR 0.92, CI 0.79–1.06), very LBW (adjusted OR 0.98, CI 0.71–1.35).

Association between risk factors and adverse obstetric outcomes

Data from 1996 to 2008 including 57 635 singleton live births, 5119 PTB and 5248 LBW were used to derive the rates of PTB and LBW in relation to risk factors. The principal risk factors for PTB were >20 oocytes retrieved, female causes of infertility (ovulatory disorder and tubal disease), female secondary infertility and initial multiple pregnancies leading to singleton live births. The principal risk factors for LBW were >20 oocytes retrieved, female cause of infertility (ovulatory disorder), female secondary infertility and initial multiple pregnancies leading to singleton live births. Female age, oocyte numbers ≤3, 4–9, 16–20, endometriosis as a cause of infertility, male factor cause of infertility, unexplained infertility and number of embryos transferred were not predictors for either PTB or LBW (Tables II and III). The event rates are summarized as 32 separate probabilities for PTB and 16 separate probabilities for LBW as shown in Tables IV and V.

Discussion

The study results demonstrate an association between the number of oocytes retrieved and adverse obstetric outcomes of PTB and LBW following IVF treatment. It demonstrates that women with >20 oocytes retrieved have a higher risk of adverse obstetric outcomes. Women with poor ovarian response did not have an increased risk of the

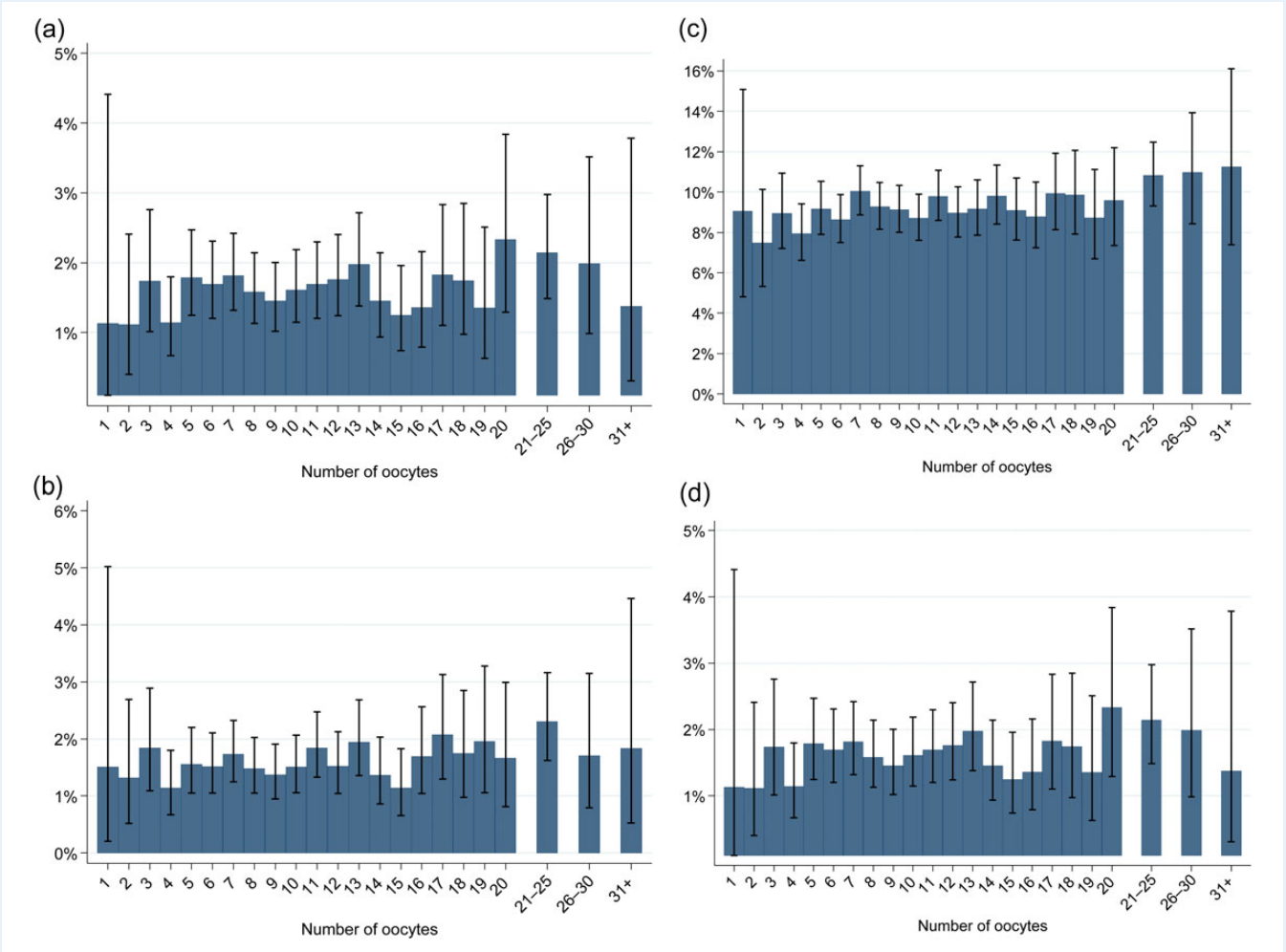

Figure 3 Association between oocyte number and adverse obstetric outcomes. (**a**) Pre-term birth. (**b**) Early preterm birth (**c**) Low birthweight (**d**) Very low birthweight.

adverse obstetric outcomes. The study demonstrated that female age is not the most important cause of the adverse obstetric outcomes following IVF. On the other hand, very high number of oocytes retrieved is a predominant factor influencing the risk of adverse obstetric outcomes following IVF. The risk of PTB, LBW was higher in women undergoing IVF with a female cause for the infertility. Although women who had multiple embryos transferred did not have an increased risk of the adverse obstetric outcomes, women with pregnancies which initially started as multiple gestations and led to singleton live births had a much higher risk of PTB or LBW compared with those starting as singleton pregnancies.

Excessive response has its own underlying pathogenesis based on high ovarian reserve and without doubt a high prevalence of women with polycystic ovary syndrome (PCOS) can be found in this category. Women with PCOS have an increased prevalence of adverse obstetric outcome including PTB and LBW (Boomsma *et al.*, 2008; Qin *et al.*, 2013), which is in line with the conclusion of our current study but which did not allow specific identification of women with PCOS. This is the largest study addressing the association between ovarian response to stimulation (determined as number of oocytes retrieved) and obstetric outcomes following IVF. A previous study on factors affecting obstetric outcome of singletons born following IVF based on Swedish registry data with 8941 singleton live births found no correlation between number of oocytes and the obstetric outcome of early PTB (Sazonova *et al.*, 2011). The discrepancy in findings could be related to the smaller numbers in the previous study. Moreover, the previous study categorized number of oocytes as <5, 5–14 and >15 which varied from the current study which found a higher incidence of PTB and LBW with very high number of oocytes (>20) when compared with the reference group of 10–15 oocytes which is generally considered as the appropriate response group. A subsequent systematic review and meta-analysis concluded that there was low-quality evidence that the dose of gonadotrophins or the number of oocytes retrieved does not affect perinatal outcome (Pinborg *et al.*, 2013). The strength of our study lies in the vast dataset which allows generalizability of the findings. However, the disadvantage of registry studies is that not all variables needed to explain a finding will be available. The limitation with this study was that there was no information on likely confounders such as smoking, BMI and medical history (e.g. presence of diabetes, hypertension) of women during pregnancy. The HFEA data, being anonymized,

Table II Relationship between risk factors and preterm birth (<37 weeks) following IVF.

Risk factor	Odds ratio	95% confidence interval	*P*-value
Number of oocytes retrieved			
1–3	0.88	0.76–1.01	0.71
4–9	0.99	0.93–1.05	0.65
16–20	1.02	0.93–1.11	0.67
>20	1.15	1.03–1.28	0.01
Female age in years			
35–37	0.99	0.93–1.06	0.92
38–39	0.97	0.89–1.07	0.57
≥40	1.04	0.93–1.17	0.48
Treatment period			
1996–2000	0.78	0.72–0.86	0.000
2001–2005	0.75	0.69–0.82	0.000
2006–2008	0.77	0.69–0.85	0.000
Female infertility type			
Primary infertility	0.88	0.83–0.0.93	0.000
Infertility cause			
Tubal disease	1.16	1.07–1.26	0.000
Ovulatory disorder	1.18	1.08–1.29	0.000
Male factor	0.98	0.91–1.04	0.43
Unexplained	0.96	0.89–1.04	0.31
Endometriosis	1.06	0.95–1.18	0.31
Number of embryos transferred			
≥2	0.94	0.82–1.07	0.32
Initial singleton or multiple pregnancy			
Multiple pregnancy to singleton live birth	1.97	1.76–2.20	0.000

Table III Relationship between risk factors and low birthweight (<2500 g) following IVF.

Risk factor	Odds ratio	95% confidence interval	*P*-value
Number of oocytes retrieved			
1–3	0.92	0.79–1.06	0.24
4–9	0.99	0.93–1.05	0.76
16–20	1.02	0.93–1.11	0.72
>20	1.18	1.06–1.31	0.003
Female age in years			
35–37	0.94	0.88–1.00	0.58
38–39	0.90	0.82–0.99	0.024
≥40	1.02	0.90–1.14	0.79
Treatment period			
1996–2000	0.87	0.79–0.95	0.002
2001–2005	0.84	0.77–0.92	0.000
2006–2008	0.85	0.77–0.94	0.002
Female infertility type			
Primary infertility	0.98	0.93–0.0.99	0.004
Infertility cause			
Tubal disease	1.07	0.99–1.17	0.65
Ovulatory disorder	1.17	1.07– 1.27	0.001
Male factor	0.95	0.89–1.02	0.16
Unexplained	0.98	0.90–1.06	0.61
Endometriosis	0.98	0.88–1.18	0.31
Number of embryos transferred			
≥2	0.95	0.83–1.08	0.42
Initial singleton or multiple pregnancy			
Multiple pregnancy to singleton live birth	2.21	1.98–2.46	0.000

Analysis by logistic regression with Wald tests for significance and confidence intervals.

did not permit analysis of one IVF cycle per woman. Therefore, a limitation of this data is that individual women would have contributed to more than one cycle and outcome in the data set which means that the true sample size is unknown, and the conventional significance tests may be in error, giving *P*-values that are too small and CIs that are too wide. However, all results are either highly significant ($P \leq 0.01$) or not close to significance ($P > 0.1$), so the study is protected against false positive results.

The findings of this study, which did not demonstrate an increased risk of adverse obstetric outcomes in poor responders, concur with previous studies of poor responders and women with reduced ovarian reserve (van Disseldorp *et al.*, 2010; Calhoun *et al.*, 2011). Poor ovarian response is a manifestation of ovarian ageing and, similar to chronological ageing, is associated with reduced chance of IVF success. However, when pregnancy is achieved and ongoing, no effect on duration of gestation or fetal weight has been found in women with poor ovarian response. The present study showed that pregnancies starting as a multiple gestation and ending as a singleton live birth had a significantly higher risk of PTB and LBW. This finding of a higher risk of adverse outcomes with a 'vanishing twin' is in accordance with previous literature (Pinborg *et al.*, 2005, 2007).

In summary, this study demonstrates that ovarian stimulation leading to very high number of oocytes influences the risk of adverse obstetric outcomes of PTB and LBW in IVF. Elucidating the probable causes of this association warrants further research. Likely reasons for women with very high number of oocytes having a higher incidence of adverse outcomes could be related to the effect of the supraphysiological estradiol levels and possible effect on the oocytes, implanting embryos or the endometrium. This needs further unravelling and could be studied further by comparing clinical outcomes following natural IVF cycles, stimulated fresh IVF cycles and frozen-thawed embryo replacement cycles.

Finally, the findings of the study are of clinical relevance to IVF practice in tailoring ovarian stimulation regimens. Controlled ovarian stimulation regimens should be adapted to avoid women having an excessive response (>20 oocytes) with the resultant complications of OHSS

Table IV Association between IVF risk factors and preterm birth (<37 weeks).

	Tubal disease		No tubal disease	
	Ovulatory disorder *n/N* (%)	No ovulatory disorder *n/N* (%)	Ovulatory disorder *n/N* (%)	No ovulatory disorder *n/N* (%)
Primary infertility; ≤20 oocytes; initial single pregnancy	37/383 (9.7%)	394/4347 (9.1%)	310/3342 (9.3%)	1591/20 743 (7.7%)
Secondary infertility; ≤20 oocytes; initial single pregnancy	47/424 (11.1%)	661/6261 (10.6%)	178/1742 (10.2%)	989/11 515 (8.6%)
Primary infertility; ≤20 oocytes; initial multiple pregnancy	3/20 (15%)	28/161 (17.4%)	23/146 (15.8%)	101/783 (12.9%)
Secondary infertility; ≤20 oocytes; initial multiple pregnancy	4/20 (20.0%)	41/235 (17.4%)	17/85 (20.0%)	71/523 (13.6%)
Primary infertility; >20 oocytes; initial single pregnancy	9/39 (23.1%)	40/321 (12.5%)	49/400 (12.3%)	111/1435 (7.7%)
Secondary infertility; >20 oocytes; initial single pregnancy	7/39 (17.9%)	51/463 (11.0%)	24/207 (11.6%)	73/817 (8.9%)
Primary infertility; >20 oocytes; initial multiple pregnancy	1/1 (100.0%)	1/10 (10.0%)	1/22 (4.5%)	14/71 (19.7%)
Secondary infertility; >20 oocytes; initial multiple pregnancy	2/6 (33.3%)	5/21 (23.8%)	4/14 (28.6%)	9/47 (19.1%)

Table V Association between IVF risk factors and low birthweight (<2500 g).

	Ovulatory disorder	No ovulatory disorder
Primary infertility; ≤20 oocytes; initial single pregnancy	347/3725 (9.3%)	1985/25 090 (7.9%)
Secondary infertility; ≤20 oocytes; initial single pregnancy	225/2166 (10.4%)	1650/17 776 (9.3%)
Primary infertility; ≤20 oocytes; initial multiple pregnancy	26/166 (15.7%)	129/944 (13.7%)
Secondary infertility; ≤20 oocytes; initial multiple pregnancy	21/105 (20.0%)	112/758 (14.8%)
Primary infertility; >20 oocytes; initial single pregnancy	58/439 (13.2%)	151/1756 (8.6%)
Secondary infertility; >20 oocytes; initial single pregnancy	31/246 (12.6%)	124/1280 (9.7%)
Primary infertility; >20 oocytes; initial multiple pregnancy	2/23 (8.7%)	15/81 (18.5%)
Secondary infertility; >20 oocytes; initial multiple pregnancy	6/20 (30.0%)	14/68 (20.6%)

and adverse obstetric outcomes, as demonstrated by this study. Lastly, this evidence could also perhaps make clinicians and researchers in IVF/ART consider what defines success in IVF, not just the occurrence of a live birth but also alleviating adverse outcomes.

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Authors' roles

S.K.S. conceived the hypothesis. S.K.S. directed the data analysis by P.T.S. and drafted the manuscript. P.T.S., A.L.M. and Y.K. appraised the manuscript.

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Conflict of interest

None declared.

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