Human Reproduction, Vol.37, No.10, pp. 2474–2481, 2022
Advance Access Publication on July 29, 2022 https://doi.org/10.1093/humrep/deac164

human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Outcomes of *in-vitro* fertilization after bariatric surgery: a national register-based case–control study

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Submitted on February 17, 2022; resubmitted on June 4, 2022; editorial decision on June 27, 2022

STUDY QUESTION: Does previous bariatric surgery (BS) in women affect cumulative live birth rate in IVF?

SUMMARY ANSWER: Women having had BS seem to have the same cumulative live birth rate as non-operated women of the same BMI at IVF treatment.

WHAT IS KNOWN ALREADY: Because of the perinatal risks of obesity to mother and infant as well as impaired outcomes of IVF, obese women are advised to reduce their weight, but it is not clear whether previous BS could affect IVF results.

STUDY DESIGN, SIZE, DURATION: This national register-based case–control study included all cases of BS (n = 30 436) undergoing IVF (n = 153) from 2007 until 2017.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Swedish women between 18 and 45 years operated with BS, with at least one first started cycle of IVF after surgery, were included. For each woman having IVF after BS (n = 153), up to five non-operated control women (n = 744) starting their first IVF cycle during the study period were matched for age, parity and BMI at treatment. The primary outcome in this study was the cumulative live birth rate (CLBR) after the first IVF cycle, defined as all live births after the first cycle including fresh and frozen embryo transfers.

MAIN RESULTS AND THE ROLE OF CHANCE: There was no significant difference in CLBR between the BS group and the matched controls (29.4% compared to 33.1%), even though the number of retrieved oocytes (7.6 vs 8.9, $P = 0.005$) and frozen embryos (1.0 vs 1.5, $P = 0.041$) were significantly fewer in the BS group. There was no association between cumulative live birth and BS, adjusted odds ratio 1.04, 95% CI (0.73, 1.51). However, the birth weight was significantly lower in the children born to mothers with previous BS, mean (SD) 3190 (690) vs 3478 (729) g, $P = 0.037$.

LIMITATIONS, REASONS FOR CAUTION: Confounders such as age, BMI and previous childbirth were accounted for by the matching design of the study, but there were no data on indication for IVF, anti-Müllerian hormone, smoking or previous comorbidities. The study was exploratory and did not reach sufficient power to detect potential smaller differences in live birth rates.

WIDER IMPLICATIONS OF THE FINDINGS: The findings concur with those in previously published smaller studies and provide somewhat reassuring results considering IVF outcomes after BS with a CLBR comparable to that of controls, despite a lower mean birth weight.

STUDY FUNDING/COMPETING INTEREST(S): This research was funded by grants from the Southern Health Care Region of Sweden. The authors have no competing interests to declare.

TRIAL REGISTRATION NUMBER: N/A.

Key words: IVF / ART / obesity / fertility / infertility / bariatric surgery

Introduction

Over the past decades, obesity, defined as BMI above 30, has increased worldwide, and in Sweden, the prevalence is around 14% in women aged 30–44 years (Public Health Agency of Sweden, 2020; WHO, 2022). The pregnancy rate is lower in women with obesity, and obesity is associated with a doubled time to pregnancy as compared with normal weight women, for couples trying to conceive spontaneously (Hassan and Killick, 2004). When seeking medical care for involuntary childlessness, obesity is also associated with poorer outcomes of *in-vitro* fertilization (IVF) such as implantation failure, pregnancy loss and overall lower live birth rates compared to women with normal weight (ASRM, 2015; Sermondade *et al.*, 2019). Because of this, and the perinatal risks of obesity to mother and infant, Swedish clinics apply BMI limits for access to fertility care and patients are advised to reduce their weight (Legro, 2016). Bariatric surgery (BS) with its beneficial metabolic consequences (Herzog *et al.*, 2020) is the most effective treatment for obesity (Maciejewski *et al.*, 2016), with large numbers of reproductive age women seeking treatment (Scandinavian Obesity Surgery Registry, SOReg, 2020). Women seem to have high expectations on regained fertility (Nilsson-Condori *et al.*, 2019), and several studies are pointing towards increased fertility among women having gone through BS (Milone *et al.*, 2016), in particular in women with PCOS (Benito *et al.*, 2020). However, obesity-related infertility is not considered an indication for BS (ACOG, 2009; ASRM, 2015).

Anti-Müllerian hormone (AMH), a marker of ovarian reserve, is positively correlated with the number of retrieved oocytes and cumulative live birth rate (CLBR) after IVF (Hu *et al.*, 2020). However, several studies have shown lower AMH levels after BS (Chiofalo *et al.*, 2017; Nilsson-Condori *et al.*, 2018; Vincentelli *et al.*, 2018), and it is not clear whether previous BS could negatively impact the results of IVF. Two large randomized controlled studies on changes in lifestyle and diet in obese women before going through IVF (Mutsaerts *et al.*, 2016; Einarsson *et al.*, 2017) have also failed to show significant improvements in live birth rates despite substantial weight loss. In addition, IVF and BS are associated with an increased risk of adverse birth outcomes, such as preterm birth (PTB) (Johansson *et al.*, 2015; Ginström Ernstad *et al.*, 2016). Previous studies on IVF after BS are few and include few patients after BS (Tsur *et al.*, 2014; Milone *et al.*, 2017; Grzegorczyk-Martin *et al.*, 2020). Findings include a decreased need of gonadotropins and a shorter length of stimulation, and the largest study (Grzegorczyk-Martin *et al.*, 2020) (n = 83 patients with previous BS) found no difference in CLBR after IVF when compared to non-operated matched controls.

The aim of this study was to investigate whether outcomes of IVF differ between women with a history of BS compared with non-operated control women matched for post-surgery BMI.

Materials and methods

Registers and study population

Between 1 January 2007 and 31 December 2017, 30 436 women aged 18–45 years having gone through BS were identified via the Scandinavian Obesity Surgery Registry (SOReg). The SOReg was established in 2007 and its coverage of performed BS has gone up from 80% in 2008 to >99% since 2010 (Hedenbro *et al.*, 2015).

All women treated with IVF between 1 January 2007 and 31 December 2017, excluding those using donated germ cells, were identified via the Swedish National Quality Register for Assisted Reproduction (Q-IVF). Q-IVF was established in 2007 and has a coverage close to 100% including both private and public clinics, since the reporting of fertility treatments to the registry is mandatory (Q-IVF, 2020). Linkage between the two registers was possible via the unique personal identification numbers assigned to all individuals in Sweden. Figure 1 depicts the register linkages and the selection of women with prior BS and controls, respectively. Cases (n = 310) having gone through both BS and IVF during 2007–2017 were identified. From the Q-IVF, we aimed at retrieving five controls per case, matched for age in years at treatment and BMI class according to World Health Organization at treatment. If BMI at treatment was missing for the cases, BMI registered 1 year after BS was used. Linkage to the Swedish Medical Birth Register (MBR) (covering 98–99% of all births in Sweden) (Källén *et al.*, 2003) was performed in order to obtain status of previous parity and matching was made to previous births (yes or no). For some cases, we could not reach the desired number of controls (see Fig. 1). After matching and exclusion of non-matched cases, treatment not being the first cycle, cases with BS after IVF and cycles with stimulation for other reasons such as oncological oocyte freezing, the study population consisted of 153 BS cases and 744 non-operated controls contributing with 897 first fresh cycles and 410 subsequent frozen transfers. Of the 153 cases, 142 were operated with gastric bypass and 11 with sleeve gastrectomy.

Outcome measures: data on fertility treatments and birth outcomes

The primary outcome in this study was the CLBR after the first IVF cycle, defined as all live births after the first cycle including fresh and frozen embryo transfers. Deliveries of multiple pregnancies were counted as one live birth. Secondary outcomes were cancellation rates, number of oocytes retrieved, number of frozen embryos and rate of pregnancy loss. Pregnancy loss included biochemical pregnancies not leading to a viable pregnancy, extrauterine pregnancies, miscarriages before 22 weeks of gestation and terminations. All outcomes of IVF were retrieved from the Q-IVF. Birth outcomes, including gestational age, birth weight, small-for-gestational age (SGA), PTB and mode of delivery, were retrieved from the MBR. For the analysis of birth outcomes, multiple pregnancies (twins) (n = 6) were excluded to avoid bias due to the inherent higher risk of adverse birth outcomes in this group. Single embryo transfers have also been the general rule in Sweden since 2003 (Q-IVF, 2020). SGA was defined as those infants with a birth weight less than the 10th percentile (Marsál *et al.*, 1996). PTB was defined as <37 completed weeks of gestation.

Statistical analyses

Data were expressed as mean ± SD or as percentages. Groups of data were assessed for distribution using the Kolmogorov–Smirnov test. Demographics and treatment outcomes were compared using independent *t*-test for the comparison of means of normally distributed quantitative variables since there were a variable number of matched

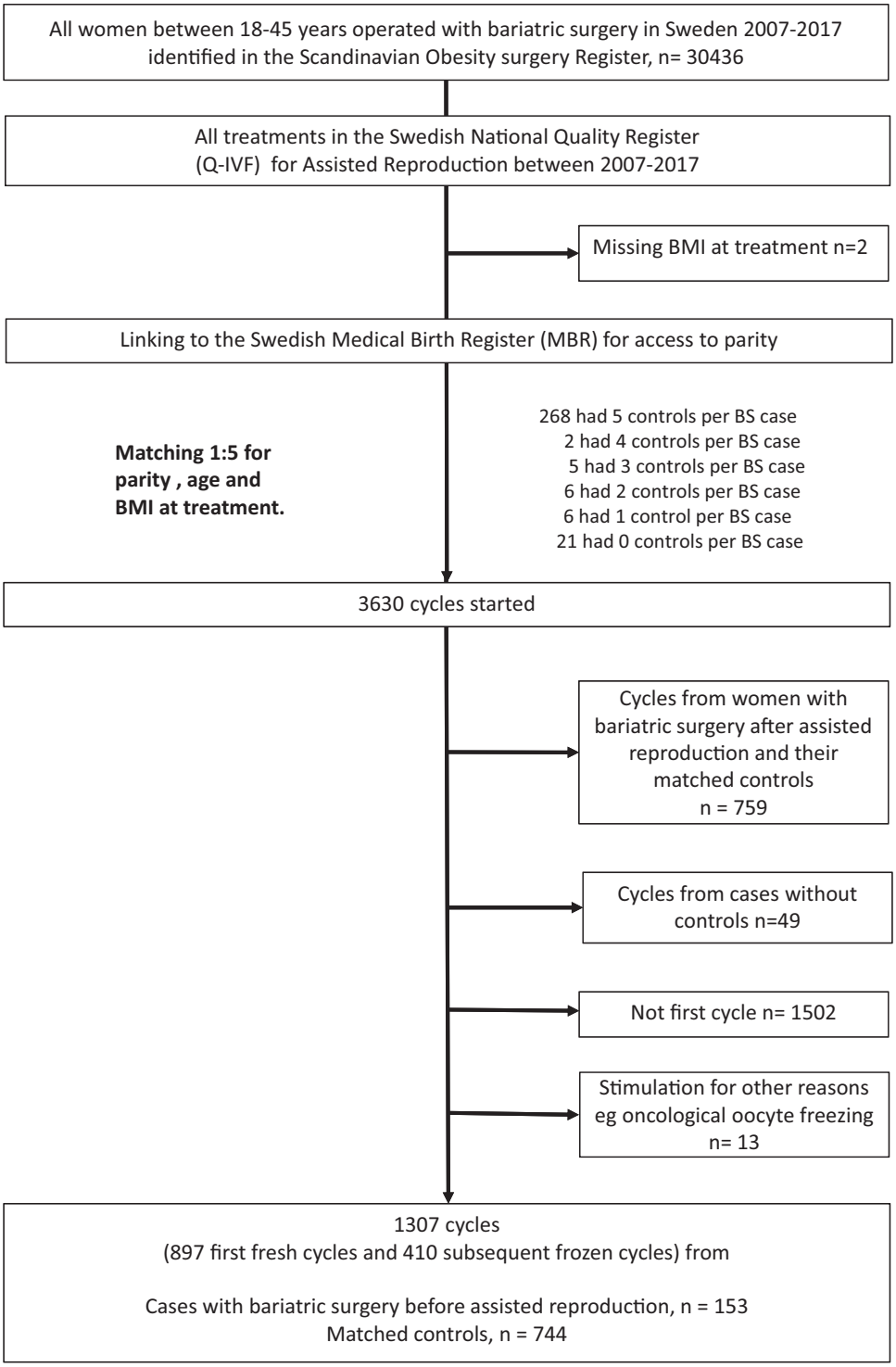

Figure 1. Flowchart depicting registry linkages and the selection of women with prior bariatric surgery and controls, respectively.

controls, likewise the Mann–Whitney *U*-test was used for non-normally distributed variables. Categorical variables were compared with the Chi-square test and Fisher exact test. Chance of birth in the first cycle and the risk of SGA and PTB were explored through logistic regressions, generating odds ratios and 95% CI. Age and BMI are known risk factors for lower birth rates after IVF, and previous childbirth increases chances of success. These confounders were accounted for by the matching in the study. A Directed Acyclic graph revealed that year of treatment should be included as a confounder to adjust for potential cohort effects. Adjusted odds ratios (aORs) were

calculated including the matching variables: age at treatment, parity, BMI classes and treatment calendar year intervals.

Power calculation

The study was exploratory, since it was previously unknown how many women had had IVF after BS. Analyses were performed using IBM SPSS Statistics, version 24 (IBM Corp, Armonk, NY), G*Power, Version 3.1.9.2 (Franz Faul, Universität Kiel, Germany) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical approval

Ethical approval was granted by the National Ethics Board Department Lund (No: 2018/1140). The three separate data sets were merged by the National Board of Health and Welfare and anonymized, according to data protection restrictions.

Results

Demographics for cases and controls are presented in Table I. The mean BMI was comparable: 28.4 among the BS patients and 28.2 in the matched controls. The mean age was 32.7 years for BS patients and 33.0 years for the controls. There was no significant difference in parity, with 80.4% of BS patients being nulliparous, as compared with 83.2% in the controls.

The IVF results are shown in Table II. Cancellation rates before the first cycle were comparable, and oocyte retrieval was performed in 141 cases and 691 controls. The number of retrieved oocytes was significantly lower in the BS group, 7.6 vs 8.9 ($P = 0.005$), as was the number of frozen embryos 1.0 vs 1.5 ($P = 0.041$). There was no significant difference in CLBRs, 29.4% in the BS group compared with 33.1% in the controls.

We also investigated birth outcomes of the first IVF cycles, excluding multiple pregnancies, as shown in Table III. There was a lower mean birth weight, 3190 g compared with 3478 g in controls ($P = 0.037$), but no difference in the frequency of SGA or PTB.

Adjusted outcomes by the presence of BS before IVF are shown in Table IV. There was no association between live birth in first cycle and BS (aOR 1.04, 95% CI (0.73, 1.51)); neither was there any association between BS and preterm birth (aOR 1.0, 95% CI (0.38, 2.78)).

Discussion

In this national register-based case–control study, we found no negative effect of previous BS on IVF outcomes. CLBRs in surgery-treated patients were on par (29.4%) with the rates among matched controls

Table I. Descriptive characteristics of the patients in the exposed and non-exposed groups.

	Bariatric surgery patients n = 153	Non-operated matched controls n = 744	Between group comparisons *P*-Value[a]
Age at treatment, mean (SD)	32.7 (4.5)	33.0 (4.6)	0.431
Age classes, total valid	153 (100)	744 (100)	
<25	4 (2.6)	16 (2.2)	
25–29	35 (22.9)	168 (22.6)	
30–35	67 (43.8)	303 (40.7)	
36–37	25 (16.3)	135 (18.1)	
38–39	15 (9.8)	72 (9.7)	
40–41	4 (2.6)	34 (4.6)	
>42	3 (2.0)	16 (2.2)	
Nulliparous, n (%)	123 (80.4)	619 (83.2)	0.403
BMI, mean (SD)	28.4 (3.7)	28.2 (4.1)	0.491
BMI classes, total valid, n (%)	153 (100)	744 (100)	
<18.5	0	0	
18.5–24.9	31 (20.3)	144 (19.4)	
25–29.9	67 (43.8)	311 (41.8)	
30–34.9	49 (32.0)	269 (36.2)	
35–39.9	6 (3.9)	20 (2.7)	
>40	0	0	
IVF treatment year, total valid, n (%)	153 (100)	744 (100)	
2007–2009	3 (2.0)	50 (6.7)	
2010–2012	24 (15.7)	249 (33.5)	
2013–2015	41 (26.8)	188 (25.3)	
2016–2017	85 (55.6)	257 (34.5)	

[a]Independent *t*-test was used for the comparison of means of quantitative variables and chi-square test was used for the comparison of categorical variables.
BMI, body mass index; IVF, *in-vitro* fertilization.

Table II. IVF outcomes.

	Bariatric surgery patients	Non-operated matched controls	Between group comparisons *P*-Value[a]
First cycles intended for transfer	153	744	
IVF outcomes			
Cycle cancelled before oocyte retrieval (of first cycles); n (%)	12 (7.8)	53 (7.0)	0.755
Oocyte retrievals; n	141	691	
Number of retrieved oocytes; mean (SD)	7.6 (5.2)	8.9 (5.6)	0.005
Number of frozen embryos after first fresh cycle; mean (SD)	1.0 (1.7)	1.5 (2.2)	0.041
Fresh cycle results			
Transfers in first fresh cycle; n (%)	117 (76.5)	570 (76.6)	0.970
Number of embryos transferred in first fresh cycle, mean (SD)	0.82 (0.5)	0.84 (0.5)	0.648
Pregnancy rate per started first fresh cycle; n (%)	44 (28.8)	226 (30.4)	0.691
Pregnancy loss[b] first fresh cycle; n (%)	10 (6.5)	67 (9.0)	0.321
Live birth rate after first fresh cycle; n (%)	34 (22.2)	159 (21.4)	0.815
Pregnancy rate per first fresh embryo transfer; n (%)	44 (37.6)	226 (39.6)	0.680
Pregnancy loss per first fresh embryo transfer; n (%)	10 (8.5)	67 (11.8)	0.316
Live birth rate per first fresh embryo transfer n (%)	34 (29.1)	159 (27.9)	0.798
Cumulative results for first cycle, fresh and frozen transfers			
Total numbers of, fresh and frozen, embryo transfers in first cycle; n	163	904	
Cumulative pregnancy rate in first cycle; n (%)	62 (40.5)	365 (49.1)	0.062
Cumulative pregnancy loss in first cycle; n (%)	17 (11.1)	119 (16.0)	0.138
Cumulative live birth rates in first cycle; n (%)	45 (29.4)	246 (33.1)	0.395
Cumulative pregnancy rate per transfer in first cycle; n (%)	62 (37.3)	365 (40.4)	0.464
Cumulative live birth rate per transfer in first cycle; n (%)	45 (27.1)	246 (27.2)	0.978

[a]Independent *t*-test or Mann–Whitney *U*-test was used for the comparison of means of quantitative variables, and chi-square test and Fisher exact test were used for the comparison of categorical variables.
[b]Pregnancy loss was defined as biochemical pregnancies, extrauterine pregnancies, miscarriages before 22 weeks of gestation and terminations.
IVF, *in-vitro* fertilization.

(33.1%), even though the number of retrieved oocytes, 7.6 vs 8.9, and frozen embryos, 1.0 vs 1.5, were significantly lower. The perinatal outcomes were also generally comparable. There was no increase in the prevalence of preterm birth or SGA; however, the mean birth weight was significantly lower in the children of BS patients.

These results concur with the findings in previously published smaller studies (Tsur *et al.*, 2014; Milone *et al.*, 2017; Grzegorczyk-Martin *et al.*, 2020), which have also pointed towards comparable outcomes of IVF within the same BMI class for BS patients and non-operated women. The results suggest that women after BS and the ensuing substantial weight loss can expect live births after IVF treatment that are comparable with those in nonoperated patients within the postoperative BMI class. aORs for live birth rates in the BMI class 25–29.9 were, in a large study (Provost *et al.*, 2016), significantly higher (0.94) than that of the BMI class 40–44.9 (0.73), which is presumably corresponding to the preoperative BMI of our BS group. Similarly, higher live birth rates were shown in patients with a lower BMI, independently of BS, as compared with women of a higher BMI (Grzegorczyk-Martin *et al.*, 2020).

Together with decreases in levels of testosterone, androstenedione and DHEAS, AMH is reduced after BS (Nilsson-Condori *et al.*, 2018). CLBR is associated with AMH; however, a larger proportion of women with polycystic ovary syndrome (PCOS), and the associated very high AMH values, could rather benefit from normalized levels as suggested previously (Hu *et al.*, 2020).

Even though we found a lower mean birth weight, we did not find a higher prevalence of preterm birth or SGA. Lower birth weight, SGA and preterm birth are known to be associated with pregnancies after BS (Johansson *et al.*, 2015), and the mechanism has been proposed to be the malabsorption of nutrients in the mother. On the other hand, it is conceivable that the BS group differs from other obese women in other ways such as a higher prevalence of women with PCOS (Gosman *et al.*, 2010) and that the risks of adverse birth outcomes are rather related to this condition. In a study on pregnancy and perinatal outcomes in women with PCOS who had had BS, the birth weight was lower than in the non-PCOS controls who also had had BS (Benito *et al.*, 2020). PCOS has been related to adverse neonatal outcomes following frozen-thawed embryo transfers (Lin *et al.*, 2021) and to preterm birth also in population-based studies, where epigenetic changes in the placenta via placental-derived extracellular vesicles have been a hypothesized mechanism (Robinson and Yeung, 2021).

Table III. Perinatal outcomes for first cycle, fresh and frozen transfers, singletons only.

	Bariatric surgery patients n = 44	Non-operated matched controls n = 241	Between group comparisons *P*-Value[a]
Gestational age; weeks, mean (SD)	38.3 (2.8)	38.9 (3.1)	0.254
Preterm birth[b]; n (%)	5 (2.4)	26 (2.4)	0.969
Birth weight; grams, mean (SD)	3190 (690)	3478 (729)	0.037
Small for gestational age[c]; n (%)	0	6 (2.5)	0.242
Vaginal delivery; n (%)	21 (47.7)	126 (52.3)	0.578

[a]Independent *t*-test was used for the comparison of means of quantitative variables and chi-square test was used for the comparison of categorical variables.
[b]Preterm birth was defined as <37 completed weeks of gestation.
[c]Small for gestational age was defined as those infants with a birth weight less than the 10th percentile.

Table IV. Odds ratios (OR) with 95% CI for outcomes by the presence of bariatric surgery before IVF.

	Cumulative results for first cycle, fresh and frozen transfers			
	Bariatric surgery patients n = 153	Non-operated matched controls n = 744	Crude OR (95% CI)	Adjusted[a] OR (95% CI)
Live birth	45	246	0.96 (0.67, 1.38)	1.04 (0.73, 1.51)
Preterm birth[b]	8	29	0.98 (0.37, 2.56)	1.0 (0.38, 2.78)
Small for gestational age[c]	0	6	N.A.	N.A.

[a]Adjustments were made for age at treatment, parity, body mass index intervals and treatment year intervals.
IVF, *in-vitro* fertilization.
[b]Preterm birth was defined as <37 completed weeks of gestation.
[c]Small for gestational age was defined as those infants with a birth weight less than the 10th percentile.

Strengths and limitations of this study

This study is based on data encompassing the entire Swedish population of 10 million inhabitants and it is, to our knowledge, the largest study on IVF outcomes after BS. During the time period of the study, some minor modifications to the techniques of IVF and BS have been introduced, but this study represents a generalizable cohort, rather than a sample from one institution only. We adjusted for the most important confounders. However, all sources of confounding cannot be excluded since we had no data on indication for IVF, FSH doses, AMH, smoking or previous comorbidities. BS patients constitute a group with a high rate of comorbidities including, e.g. depression (Dreber *et al.*, 2017), which is even more prevalent in women with both infertility and obesity (Merrell *et al.*, 2014). Thus, it is uncertain whether the surgery itself, the comorbidities or other unknown underlying factors account for the difference in infant birth weight that has previously been shown in large cohorts (Johansson *et al.*, 2015).

We cannot exclude that some of the controls had gone through BS before the start of SOReg the year of 2007, or abroad during the study time period. We did stratify our data depending on year of treatment, but since the incidence of BS increased in the late 2000s and peaked year 2012 (Scandinavian Obesity Surgery Registry, SOReg, 2020) and treatment with surgery in Sweden is publicly funded, we believe that women having had BS among the controls are few. We did not compare IVF results before and after BS, which would have needed a different design, as performed in a different study (Milone *et al.*, 2017). Thus, there might be differences between the operated cases and non-operated controls that cannot be accounted for. Neither did we have a control group matched on pre-surgery BMI. Since most IVF clinics in Sweden, publicly as well as privately funded, have BMI limits in the range between 30 and 35, it would be almost impossible to find matching controls. The BMI limit and difficulties in finding matched controls is also the reason behind the higher numbers of IVF treatment in the latter part of the study period within the BS group, as well as the varying number of controls we were able to find for this study. Finally, we tried to evaluate the efficacy of treatment by comparing the cancellation rate of cycles; however, lacking data on FSH dosage, as well as complications such as OHSS, this study cannot evaluate the efficacy nor safety of ART after BS.

BS is an increasing trend accompanying the obesity epidemic. Since studies on lifestyle intervention in obese women have failed to show improved pregnancy rates (Mutsaerts *et al.*, 2016; Einarsson *et al.*, 2017), BMI limits for IVF have been argued not to be evidence based (Legro, 2016; Tremellen *et al.*, 2017), even though a high BMI is strongly associated with a lower live birth rate (Sermondade *et al.*, 2019). Pregnancy is generally advised against during the first 12 months after BS (ASRM, 2015). However, based on the now existing studies (Milone *et al.*, 2017; Grzegorczyk-Martin *et al.*, 2020), for those patients having time on their side to abstain from trying to conceive

after surgery as generally recommended (ASRM, 2015), BS does not seem to have a negative effect on the live birth rate. It cannot be excluded that BS even might have the potential to improve the chances of a successful IVF treatment. Although it is difficult to show improved IVF results with the design of our study, a CLBR comparable to that of non-operated women matched on post-surgery BMI is better than the results shown in a large study of non-operated women with a BMI over 40 (Provost et al., 2016).

This study provides reassuring results considering IVF outcomes after BS, but despite including all BS patients having subsequently used IVF from a complete national sample, the study did not reach sufficient power to detect potential smaller differences in live birth rates, nor regarding differences in birth outcomes. To detect a clinically significant reduced CLBR of 5%, with an allocation ratio of 5, a type I error of 0.05, a power of 0.80, and an expected CLBR of 33.1% in matched controls, with Fisher exact test, 651 cases and 3255 controls would have been needed. As previously suggested (Grzegorczyk-Martin et al., 2020), larger studies with details regarding causes of infertility, or randomized controlled studies, are needed to answer the question of whether BS could be indicated for obesity-related infertility.

Data availability

The datasets generated and analysed during the current study are not available publicly, due to national data protection laws and restrictions imposed by the ethics committee to ensure the privacy of study participants.

Authors' roles

All authors conceptualized and contributed to study design. E.N.-C. obtained funding and acquired the data; E.N.-C. and K.M. did the statistical analyses and E.N.-C. drafted the manuscript. All authors interpreted the results. All authors critically revised the manuscript for important intellectual content. E.-N.C. and KM had full access to the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analyses.

Funding

The Southern Health Care Region of Sweden.

Conflict of interest

The authors have no competing interests to declare.

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