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ORIGINAL ARTICLE *Infertility*

IVF outcomes in patients with a history of bariatric surgery: a multicenter retrospective cohort study

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STUDY QUESTION: How does a history of dramatic weight loss linked to bariatric surgery impact IVF outcomes?

SUMMARY ANSWER: Women with a history of bariatric surgery who had undergone IVF had a comparable cumulative live birth rate (CLBR) to non-operated patients of the same BMI after the first IVF cycle.

WHAT IS KNOWN ALREADY: In the current context of increasing prevalence of obesity in women of reproductive age, weight loss induced by bariatric surgery has been shown to improve spontaneous fertility in obese women. However, little is known on the clinical benefit of bariatric surgery in obese infertile women undergoing IVF.

STUDY DESIGN, SIZE, DURATION: This exploratory retrospective multicenter cohort study was conducted in 10 287 IVF/ICSI cycles performed between 2012 and 2016. We compared the outcome of the first IVF cycle in women with a history of bariatric surgery to two age-matched groups composed of non-operated women matched on the post-operative BMI of cases, and non-operated severely obese women.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The three exposure groups of age-matched women undergoing their first IVF cycle were compared: Group 1: 83 women with a history of bariatric surgery (exposure, mean BMI 28.9 kg/m^2); Group 2: 166 non-operated women (non-exposed to bariatric surgery, mean BMI = 28.8 kg/m^2) with a similar BMI to Group 1 at the time of IVF treatment; and Group 3: 83 non-operated severely obese women (non-exposed to bariatric surgery, mean BMI = 37.7 kg/m^2). The main outcome measure was the CLBR. Secondary outcomes were the number of mature oocytes retrieved and embryos obtained, implantation and miscarriage rates, live birth rate per transfer as well as birthweight.

MAIN RESULTS AND THE ROLE OF CHANCE: No significant difference in CLBR between the operated Group 1 patients and the two non-operated Groups 2 and 3 was observed (22.9%, 25.9%, and 12.0%, in Groups 1, 2 and 3, respectively). No significant difference in average number of mature oocytes and embryos obtained was observed among the three groups. The implantation rates were not different between Groups 1 and 2 (13.8% versus 13.7%), and although lower (6.9%) in obese women of Group 3, this difference was not statistically significant. Miscarriage rates in Groups 1, 2 and 3 were 38.7%, 35.8% and 56.5%, respectively ($P = 0.256$). Live birth rate per transfer in obese patients was significantly lower compared to the other two groups (20%, 18%, 9.3%, respectively, in Groups 1, 2 and 3, $P = 0.0167$). Multivariate analysis revealed that a 1-unit lower BMI increased the chances of live birth by 9%. In operated women, a significantly smaller weight for gestational age was observed in newborns of Group 1 compared to Group 3 ($P = 0.04$).

LIMITATIONS, REASONS FOR CAUTION: This study was conducted in France and nearly all patients were Caucasian, questioning the generalizability of the results in other countries and ethnicities. Moreover, 950 women per group would be needed to achieve a properly powered study in order to detect a significant improvement in live birth rate after bariatric surgery as compared to infertile obese women.

WIDER IMPLICATIONS OF THE FINDINGS: These data fuel the debate on the importance of pluridisciplinary care of infertile obese women, and advocate for further discussion on whether bariatric surgery should be proposed in severely obese infertile women before IVF. However, in light of the present results, infertile women with a history of bariatric surgery can be reassured that surgery-induced dramatic weight loss has no significant impact on IVF prognosis.

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Key words: bariatric surgery / sleeve gastrectomy / gastric bypass / lifestyle intervention / obesity / weight loss / BMI / IVF / ART / neonatal outcome

Introduction

Obesity is defined by the World Health Organization (WHO) as a BMI >30 kg/m^2 (WHO, 2017). Its prevalence among women of reproductive age has been reported to be 14–20% (Ng et al., 2014). Although huge variations exist between areas and countries, this prevalence keeps increasing in most countries (WHO, 2017). Among the several health consequences of female obesity, most studies conducted in infertile women report significantly poorer clinical outcome than in normal weight women (Sermondade et al., 2019). More specifically, obese women require higher gonadotrophin doses and a longer duration of ovarian stimulation, and experience lower implantation, clinical pregnancy and live birth rates, as well as higher miscarriage rate, as compared to normal BMI patients (Maheshwari et al. 2007; Luke et al., 2011; Moragianni et al. 2012; Kaiyrlykyzy et al., 2015; Kawwass et al. 2016; Provost et al. 2016). The impact of obesity on pregnancy and neonatal outcomes is also well established, with higher prevalence of miscarriage, gestational hypertension, pre-eclampsia, gestational diabetes, post-partum hemorrhage, cesarean sections, and fetal and neonatal deaths (Bhattacharya et al., 2007; Koning et al., 2010).

Bariatric surgery, along with lifestyle modifications, has been shown to be effective for long-term weight loss (Acosta et al., 2014). Bariatric surgery is currently proposed in women with a BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with associated co-morbidities (NHLBI Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 1998; Colquitt et al. 2014), and generally led to a rapid and intense weight loss (patients can lose up to 23% of their total body weight within 2 years) (Sjöström et al., 2012). In the context of increasing prevalence of obesity, these clinical benefits have led to a dramatic increase of bariatric surgery procedures over the last 10 years (Angrisani et al., 2015). Interestingly, 83% of operated patients are women, of whom 20% are under the age of 30 years (Schaaf et al., 2015), highlighting the relevance of specifically evaluating bariatric surgery in this group of women of reproductive age.

In women who become pregnant naturally, bariatric surgery is associated with significantly reduced obesity-related obstetric complications (Johansson et al., 2015). Literature concerning ART results after bariatric surgery is very sparse (Doblado et al., 2010; Christofolini et al., 2014; Tsur et al., 2014; Milone et al., 2017). All these studies were conducted in small series of patients (range n = 5–40). Moreover, their design and outcome measures were heterogeneous. Therefore, the available literature provides limited information on the clinical relevance of bariatric surgery in obese infertile women, and advocates for further studies in larger populations.

The aim of the present retrospective cohort study was to evaluate how a history of bariatric surgery influences cumulative live birth rates (CLBR) after IVF by comparing operated infertile women to women of similar age and BMI without any history of bariatric surgery, and to severely obese women.

Materials and methods

Cases and controls

Data from 10 287 IVF/ICSI cycles performed in three IVF centers (two university-based and one private ART center) between 2012 and 2016 were extracted and retrospectively analyzed with their follow-up. Donor cycles were excluded.

Three cohorts undergoing the first IVF cycle with oocyte retrieval and of similar age (±2 years) were analyzed:

- Group 1: 83 women aged 18–43 years old with a history of bariatric surgery. Average weight loss was calculated using preoperative BMI as notified in the surgery report and weight at first IVF consultation.
- Group 2: 166 non-operated women with BMI matched on Group 1 post-operative BMI.
- Group 3: 83 non-operated severely obese women (BMI ≥ 35 kg/m^2), with BMIs approaching preoperative BMIs of Group 1. Of note, the pre-bariatric surgery BMI of Group 1 was even higher than the BMI of Group 3 (Table I) since women with very high BMI were not eligible for IVF in our centers.

Treatment modalities

Patients underwent controlled ovarian stimulation with either long GnRH agonist or antagonist protocol, according to standard practice. In both protocols, hCG was administered when at least three follicles reached a mean diameter ≥17 mm. Transvaginal oocyte retrieval was performed 36 h later. Metaphase II oocytes were inseminated or micro-injected according to semen characteristics and couple history.

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

	Group 1 (bariatric surgery patients) (*n* = 83)	Group 2 (non-operated BMI-matched patients) (*n* = 166)	Group 3 (non-operated obese patients) (*n* = 83)	Between-group comparisons *P*-value
Age (y), mean ± SD	33.1 ± 4.4	33.0 ± 4.4	32.8 ± 4.6	0.94
Primary infertility (%)	72.3	69.9	61.4	0.27
Weight (kg), mean ± SD	80.1 ± 14.4	78.7 ± 13.6	100.1 ±10.0	<1/10^6[a,c]
BMI, kg/m^2, mean ± SD	28.9 ± 4.7	28.8 ± 4.5	37.7 ± 2.8	<1/10^6[a,c]
Polycystic ovary syndrome (%)	25.3	9.0	24.1	0.0007[b,c]
Origin of infertility (%)				0.2512
Ovulatory	16.7	14.7	16.9	
Tubal	15.4	11.5	9.6	
Male	32.1	38.5	42.2	
Idiopathic	16.7	17.9	20.5	
Endometriosis	2.6	8.3	1.2	
Mixed	16.7	9.0	9.6	
Anti-Müllerian Hormone level (ng/ml), mean ± SD	4.6 ± 5.4	3.3 ± 2.4	3.9 ± 4.0	0.08
Antral Follicule Count, mean ± SD	17.1 ± 11.5	13.9 ± 9.9	19.7 ± 12.1	0.0008[c]
Female smokers (%)	25.3	24.1	15.7	0.240

Chi^2 test was applied for comparing qualitative variables and ANOVA for quantitative variables.
[a]Comparing Group 1 to Group 3; [b]comparing Group 1 to Group 2; [c]comparing Group 2 to Group 3.

Fresh embryo transfer occurred on Day 2, 3 or 5. Cleavage-stage embryos were considered as good quality on the basis of stage-specific cell number and regularity, <25% fragmentation rate, and no evidence of multinucleation (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). Blastocysts were classified according to Gardner's classification (Gardner *et al.*, 1999) and considered as good quality starting from an expansion grade 3 and inner cell mass and/or trophectoderm scores of B or higher.

Single or double embryo transfer was chosen jointly by the couple and medical staff. Luteal phase support was performed with 400 mg/day of micronized intravaginal progesterone until pregnancy test, and continued up to ultrasonography confirmation of the intrauterine pregnancy at 7 weeks of gestation if the test was positive. Supernumerary developing embryos or blastocysts were vitrified and transferred in a subsequent frozen-thawed embryo transfer cycle after hormone replacement treatment.

Outcome measures

The primary outcome measure was the CLBR, defined by the number of live births taking into account the fresh and all subsequent frozen embryo transfers of the first IVF cycle.

Secondary outcomes were the pregnancy rates (pregnancy defined by French Agence de Biomédecine as a positive βHCG test >100 mUI/ml), the average number of mature oocytes and embryos obtained, number of babies born per embryo transferred, miscarriages rates, birthweight and gestational age. Small for gestational age (SGA) newborns were those with a birthweight below the 10th percentile for the gestational age (Ego *et al.*, 2016).

Statistical analysis

Data were expressed as mean ± SD, or as percentages. Demographic characteristics and ovarian stimulation characteristics were compared between the three groups using a chi-square test for qualitative variables and means comparison/ANOVA for quantitative variables. A *P*-value <0.05 was considered as statistically significant. Univariate generalized linear model (GLM) was carried out in order to search for variables potentially related to the occurrence of live birth after the first IVF. Covariates that were significant at an alpha level of 20% were retained in the multivariate analysis. Then, a multivariate GLM with a random effect relative to the study center plus a treatment effect (operated versus non-operated) covariate forced in the model was carried out in order to explain the occurrence of live birth after the first IVF in bariatric surgery patients (Group 1) compared to non-operated Groups 2 and 3. A stepwise procedure using the Akaiké information criterion was applied. Two strategies of comparisons were retained, Group 1 (exposed to bariatric surgery) versus Group 2 (non-operated women of similar BMI), and Group 1 versus all non-exposed women (Groups 2 + 3). Only the second multivariate model is provided here since both models gave the same results. The first model is reported in Supplementary Tables SI and SII. Women with a history of bariatric surgery were compared with two age- and BMI-matched women of Group 2, but were only compared to one obese age-matched women of Group 3 because of the limited number of severely obese women eligible for IVF. Statistical analyses were carried out using R statistical software, version 3.6.0 (R Core Team, 2019).

This study is exploratory, since a properly powered prospective non-inferiority study to detect a level of reduction of effectiveness between operated and non-operated women as being clinically significant, stating a maximum difference of 5% of CLBR, a type I error of 0.05, a power of 0.80, with an expected proportion of cumulative birth of 25.9% in age- and BMI-similar groups, with a one-sided test, would have needed to include 950 women per group (EpiDysplay R Studio).

Ethical approval

Before undergoing IVF, patients sign a written consent form allowing anonymous data to be used for retrospective studies. Only patients having given their written consent were included.

The study was approved by our Institutional Review Board and registered in *clinicaltrials.gov* under the number: NCT02884258.

Results

Patients' demographic characteristics in the three groups are presented in Table I. Among the 83 operated women (Group 1), surgery procedures consisted of 60 sleeve gastrectomies, 13 adjustable gastric bands, and 10 gastric bypasses. Preoperative BMI of women undergoing bariatric surgery (Group 1) was 43.6 kg/m^2 (range 39–54). Average weight loss was 41.8 ± 16.7 kg, and the mean delay between surgery and the first IVF cycle was 2.98 ± 1.9 years. No significant difference was found between the three groups in terms of age and type of infertility. However, the prevalence of polycystic ovary syndrome (PCOS) was significantly higher in Group 1 and obese Group 3 compared to Group 2. Accordingly, mean antral follicle count (AFC) was higher in Groups 1 and 3 when compared to Group 2.

The ovarian stimulation and laboratory parameters are presented in Table II. No statistical difference was found between the three groups, except for the total dose of gonadotrophin and ovarian stimulation duration, which were significantly higher in Group 3 (severely obese controls) than in Group 1 (bariatric surgery) and Group 2. The proportion of patients without embryo transfer (owing to absence of oocytes retrieved, mature oocytes, or embryo development) was 13.3%, 6.6% and 19.3% in Groups 1, 2 and 3, respectively ($P = 0.01$).

IVF cycle outcomes are presented in Table III. CLBR after the first IVF cycle was 22.9 in Group 1 versus 12.0 in Group 3, but this difference did not reach statistical significance. A significant difference in CLBR between Groups 2 and 3, however, was observed (25.9% versus 12.0%; $P = 0.042$). Moreover, a significant difference in live birth rate per transfer was observed between groups, with the worst result in obese patients (20%, 18%, 9.3%, respectively, in Groups 1, 2 and 3, $P = 0.0167$). Group 1 had a slight, but significantly lower average number of transfers than Group 2. No difference in average number of transfers was observed between Groups 1 and 3, or between Groups 2 and 3.

Implantation and miscarriage rates followed the same tendency toward poorer results in obese Group 3 than Groups 1 and 2, although the differences did not reach statistical significance.

No differences were observed in live birth depending on the length of time in years from the bariatric surgery to the first embryo transfer (Supplementary Table SI).

Mean birthweight was significantly lower in Group 1 than in Groups 2 and 3 (Table III). A higher proportion of SGA newborns (defined by a weight for gestational age <10th percentile) was found in operated women of Group 1, but this difference was not statistically significant (31.3%, 13.5% and 10.0% in Groups 1, 2 and 3, respectively; $P = 0.14$ for Group 1 versus Group 2, $P = 0.35$ for Group 1 versus Group 3).

Multivariate analysis

The univariate model was used in order to search for variables potentially related to the occurrence of live birth after the first IVF, and the results are presented in Table IV. The multivariate GLM model showed that female BMI was significantly and independently associated with live birth (Table V). A lower BMI had a positive impact on the chance of live birth following IVF (odds ratio 0.92 (0.87; 0.97), $P = 0.002$), which could be translated into a 9% live birth rate gain for

Table II IVF procedure.

	Group 1 (bariatric surgery patients) (*n* = 83)	Group 2 (non-operated BMI-matched patients) (n = 166)	Group 3 (non-operated obese patients) (n = 83)	Between-group comparisons *P*-value
IVF without ICSI (%)	45.8	47.6	41.0	0.611
Agonist protocol (%)	41.0	42.8	25.3	0.022[a,b]
Total Gonadotrophin doses (IU), mean ± SD	2453 ± 876	2420 ± 836	2919 ± 1151	0.0005[a,b]
Number of stimulation days, mean ± SD	10.8 ± 1.7	10.6 ± 1.8	11.5 ± 2.2	0.0016[a,b]
End-of-cycle estradiol level, mean ± SD	1662±973	1931±1084	1549 ± 1117	0.0027[b]
Number of retrieved oocytes, mean ± SD	8.8 ± 5.9	9.7 ± 5.7	8.5 ± 5.9	0.251
Number of mature oocytes, mean ± SD	6.9 ± 4.9	7.4 ± 4.9	6.6 ± 4.4	0.474
Number of embryos, mean ± SD	4.4 ± 4.2	4.8 ± 3.8	4.2 ± 3.5	0.422
Number of good-quality embryos, mean ± SD	2.6 ± 2.5	3.0 ± 2.7	2.3 ± 1.9	0.092

Chi^2 test was applied for comparing qualitative variables and ANOVA for quantitative variables.
[a]Comparing Group 1 to Group 3; [b]comparing Group 2 to Group 3.

Table III Pregnancy outcome after the first IVF cycle.

	Group 1 (bariatric surgery patients) (*n* = 83)	Group 2 (non-operated, BMI-matched, patients) (*n* = 166)	Group 3 (non-operated obese patients) (n = 83)	Between-group comparisons *P*-Value
Total number of embryos transferred, mean ± SD	1.9 ± 1.5	2.2 ± 1.3	1.7 ± 1.3	0.057
Number of embryos per transfer, mean ± SD	1.7 ± 0.5	1.5 ± 0.5	1.3 ± 0.4	0.46
Number of transfers, mean ± SD	1.14 ± 0.73	1.44 ± 0.86	1.30 ± 0.93	0.034[b]
Proportion of transfers at the blastocyst stage	4	3	10	0.062
Cumulative pregnancy rates after first IVF cycle (%)	37.3	40.4	27.7	0.204
Implantation rate after first IVF (%)	13.8	13.7	6.9	0.09
Live birth rate per transfer (%)	20.0	18.0	9.3	0.0167[a,c]
Cumulative live birth rates after first IVF cycle (%)	22.9	25.9	12.0	0.042[c]
Number of remaining cryopreserved embryos for patients having delivered a live baby mean ± SD	2.16 ± 2.83	2.09 ± 2.69	0.7 ± 0.48	0.273
Number of remaining cryopreserved embryos for patients not having delivered a live birth mean ± SD	0.50 ± 1.41	0.80 ± 1.82	0.55 ± 1.45	0.398
Pregnancy loss (%)	38.7	35.8	56.5	0.256
Gestational age at delivery (weeks), mean ± SD	38.3 ± 3.3	39.1 ± 1.0	39.7 ± 1.2	0.419
Birthweight (g) mean ± SD	2753 ± 734	3170 ± 863	3482 ± 263	0.044[a]
Twin birth rate (%)	15.8	14.0	0	0.609
Vaginal delivery (%)	68.4	69.0	70.0	1

Chi^2 test was applied for comparing qualitative variables and ANOVA for quantitative variables.
[a]Comparing Group 1 to Group 3; [b]comparing Group 1 to Group 2; [c]comparing Group 2 to Group 3.

Table IV Univariate generalized linear model analysis of live birth occurrence Group 1 versus Groups 2 + 3.

Variable	Odds ratio	95% CI	*P*-value
Age	0.94	[0.98; 1.00]	0.058
BMI	0.91	[0.86; 0.96]	<0.001
History of bariatric surgery	1.10	[0.59; 1.97]	0.758
Anti-Müllerian hormone level	0.97	[0.88; 1.05]	0.551
Antral follicule count	1.01	[0.99; 1.04]	0.225
IVF without ICSI	0.88	[0.52; 1.49]	0.640
Agonist protocol	1.05	[0.61; 1.79]	0.853
Total gonadotrophin doses	0.9996	[0.9992; 0.99993]	0.016
Number of stimulation days	0.90	[0.77; 1.03]	0.135
End-of-cycle estradiol level	1.0003	[1.00003; 1.0005]	0.025
Number of retrieved oocytes	1.05	[1.003; 1.09]	0.036
Number of mature oocytes	1.08	[1.02; 1.14]	0.005
Number of embryos obtained	1.11	[1.05; 1.19]	0.001
Number of good-quality embryos	1.26	[1.13; 1.40]	0.001
Cumulative embryos transferred	1.13	[0.93; 1.35]	0.215
Total number of transfers	1.30	[0.96; 1.74]	0.084

each loss of 1 BMI unit. We observed the same result when restricting the model to comparing Group 1 with Group 2 (Supplementary Table SII).

Discussion

In this retrospective multicenter cohort study, we found that IVF patients with a history of bariatric surgery had chances of live birth that were comparable to non-operated patients of the same BMI and age. Although the difference between non-operated severely obese and operated women did not achieve statistical significance, a trend toward lower CLBR in non-operated severely obese women was found, as demonstrated by a significant negative association between BMI and live birth rate. Additionally, severely obese patients showed a significantly lower live birth rate per transfer compared to the other two groups, suggesting a possible negative affect of obesity on implantation. Finally, these live birth results of all three groups were lower than those observed in patients with a normal BMI (20< BMI <25 kg/m^2) undergoing their first IVF cycle in the study centers during the same period (32.5%), as bariatric surgery patients did not subsequently reach a normal BMI (28.9 ± 4.7 kg/m^2); thus reemphasizing the important impact of BMI on IVF results.

The prevalence of obesity among women of reproductive age has dramatically increased over the last two decades, reaching 15% in 2016 (WHO, 2016), and 10% are morbidly obese in the USA (BMI ≥40 kg/m^2) (Hales et al., 2018). The negative impact of obesity on time to pregnancy is driven by several infertility factors (e.g. ovulation disorders, lower implantation, higher miscarriages rates) and has often been demonstrated (Maheshwari *et al.* 2007; Brewer and Balen, 2010; Moragianni *et al.* 2012; Kaiyrlykyzy *et al.*, 2015; Kawwass *et al.* 2016; Provost *et al.* 2016). In addition, obstetric and neonatal outcome is

Table V Multivariate generalized linear model analysis* of live birth occurrence Group 1 versus Groups 2 + 3.

Variable	Odds ratio	95% CI	P-value
BMI	0.92	[0.87 ; 0.97]	0.002
Number of good-quality embryos	1.24	[1.11 ; 1.38]	<0.001
History of bariatric surgery	0.93	[0.49 ; 1.75]	0.819

Number in model = 328, Number of study centers = 3, Akaike Information Criterion (AIC) = 322.5, C-statistic = 0.702.
*Generalized linear model with a Center effect as random effect, and a treatment effect (bariatric surgery (Y/N)) forced in the model.

poorer in obese pregnant women than in normal weight pregnant women (Catalano and Shankar, 2017). Therefore, weight loss strategies are of utmost importance in obese women of reproductive age in order to optimize their chances of pregnancy, either naturally or after ART, and limit the risk of obstetric and neonatal complications. In this respect, a multidisciplinary approach is essential to implement weight loss strategies, ideally involving nutritional, endocrinological and psychological supports, as well as surgical interventions such as bariatric surgery (Einarsson et al., 2017). The time necessary to implement these strategies, and thus their benefit-risk balance in terms of live birth rate, should obviously be put into perspective with female age when considering obese infertile women, as IVF procedure might be delayed, potentially exacerbating the age-related decline in fertility (Goldman et al., 2019). To our knowledge, the recent available literature concerning lifestyle approaches to combat obesity prior to fertility treatment reported weight losses of 4.4 kg after a 6-month period, with a discontinuation rate of 21.8% (Mutsaerts et al., 2016). This contrasts with the substantial weight loss induced by bariatric surgery. To our knowledge, no study compared lifestyle interventions for weight loss before IVF to bariatric surgery.

Bariatric surgery has several consequences on female physiology and particularly during pregnancy where nutritional deficiencies have been observed (e.g. in vitamin A, B1, B6, B12, iron, calcium) (Rottenstreich et al., 2019). Fertility issues after bariatric surgery have to be taken into account, as up to 80% of women having undergone bariatric surgery are of reproductive age (Schaaf et al., 2015). Although bariatric surgery has been shown to be associated with significantly reduced obesity-related obstetric complications in women who conceive naturally (Johansson et al., 2015), the impact of dramatic weight loss following bariatric surgery on IVF clinical outcome is unclear. So far, only four studies dealing with IVF in women after bariatric surgery have been reported, including small cohorts of women, from 5 (Doblado et al., 2010) to 40 (Milone et al., 2017). Importantly, none of them was designed to evaluate the impact of bariatric surgery on live birth rate following IVF. Among them, three used the patients as their own controls (Doblado et al., 2010; Tsur et al., 2014; Milone et al., 2017). As patients were not pregnant before surgery, this design did not allow the comparison of pregnancy outcome before and after bariatric surgery. The design of the fourth study included bariatric patients matched to women of normal weight and obese patients (Christofolini et al., 2014). These authors found a lower number of mature oocytes retrieved in operated patients than in controls, but with no impact on pregnancy rates. However, the low number of patients, as well as the lack of clear definition of pregnancy should lead to cautious interpretation of these results. In this respect, and to the best of our knowledge, our study is the first to report CLBR in infertile women after bariatric surgery, and its comparison with clearly defined BMI and/or age-matched patients.

In the present study, no difference in terms of CLBR was observed between the three surgical techniques (24.1% for sleeves, 15.8% for gastric bandings, 20% for bypasses, $P = 0.911$). Conclusions, however, cannot be drawn with respect to the impact of surgery technique on IVF results because of the much lower number of gastric banding and bypasses compared to sleeve gastrectomies. Further studies conducted with larger samples are needed to guide patients and clinical staff to the most relevant surgical approach in this context.

Beyond the bariatric surgery group, we observed that non-operated severely obese patients undergoing IVF had low CLBRs, and high miscarriage rates. We also found that these severely obese women required a higher gonadotrophin dose and longer ovarian stimulation than thinner women: they also presented high cycle cancelation rates (19.3%). The mean number of remaining embryos cryopreserved after the study period in patients having delivered a baby was higher in Groups 1 and 2 as compared to Group 3; however, this difference did not reach statistical significance (Table III). These results are in line with the tendency toward a poorer prognosis in obese IVF patients compared to the two other groups. This is consistent with a recent meta-analysis comparing IVF outcome in obese patients and normal weight women (Sermondade et al., 2019).

We observed that mean AFC and PCOS incidence were similar in Group 1 (operated women) and Group 3 (severely obese non-operated women), and both significantly higher than in Group 2 (non-operated women of similar Group 1 post-surgery BMI). However, multivariate analysis showed that PCOS status was not independently associated with odds of live birth. Our study, however, was not designed to deal with this question. The literature concerning IVF prognosis in PCOS patients is discordant. Although our results are concordant with some previous findings showing no difference in IVF prognosis in PCOS patients (Esmailzadeh et al., 2005; Sermondade et al., 2013), the debate is still ongoing (Sha et al., 2019).

Of note, in the bariatric surgery group newborns had a significantly lower birthweight for gestational age than in the two other non-operated groups. More importantly, a greater number of SGA newborns were observed after bariatric surgery. This confirms past findings regarding birthweights of children born to mothers after bariatric surgery (Kjaer et al., 2013; Roos et al., 2013; Galazis et al., 2014; Johansson et al., 2015; Hazart et al., 2017), and advocates for further studies on neonatal outcome in infertile women undergoing IVF after bariatric surgery.

Our work has the following strengths. First, this multicenter study reports the largest population of women undergoing IVF after bariatric surgery. The comparison, on the one hand, to non-operated patients of similar BMI, and on the other hand to obese patients, constitutes a significant contribution to the scarce literature. Finally, we chose CLBR after the first IVF cycle as the primary outcome. This outcome is probably the most relevant in order to evaluate the impact of an intervention (here bariatric surgery) in terms of ART outcome.

We also acknowledge that our study has some limitations. First, it would have been optimal to compare operated patients to non-operated obese patients of similar preoperative BMI. However, this was not feasible, as some operated patients had very high preoperative BMI, i.e. up to 54 kg/m^2. Second, embryo transfer policy was not standardized in all participating centers in this multicenter retrospective cohort, with a low proportion of blastocyst stage transfers. However, the embryo transfer strategy was similar in the three centers during the study period. Furthermore, our results should be interpreted with care according to the exploratory character of the retained design, together with the limited number of patients included in the study, leading to limited statistical power. However, a properly powered prospective non-inferiority study to detect a level of reduction of effectiveness between operated and non-operated women as being clinically significant, would have needed to include 950 women per group. This calculation shows that an important investment would be necessary to set up a properly powered prospective study.

Conclusion

IVF patients with a history of bariatric surgery can be reassured regarding their chances of conception following IVF, as they have the same chances of live birth compared to non-operated patients of same BMI. In this study, obese women displayed the poorest IVF outcomes. Overall, female BMI was negatively associated with live birth rate, with a 9% decrease for each additional BMI unit. Female age should obviously be taken into account when considering bariatric surgery in infertile women, as the delay necessary to obtain the targeted weight loss can also be associated with decreased chances of live birth. Of course, obstetric and neonatal outcomes remain part of the decision-making process. Although this study evaluating IVF outcome after bariatric surgery is the largest available up to now, its statistical power remains limited. However, a confirmatory prospective study would require a large number of patients, which might impede its feasibility.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

V.G.-M. initiated, designed and coordinated the study, included patients, collected results and wrote the manuscript. T.F. participated in interpretation of results and wrote the manuscript. A.F. initiated and coordinated the study, collected and verified results with the statistical team and wrote the manuscript. E.B. collected and verified all data, carried out the statistical analysis, participated in interpretation of results and in manuscript revision. I.C.-D. participated in patient inclusion and collected results from Bondy center and participated in manuscript revision. M.M. participated in data collection from Bondy and Poissy ART centers. J.R. participated in data collection and manuscript revision. V.R. participated in data collection and manuscript revision. R.W. participated in data collection. C.A. designed the study, participated in data collection and manuscript revision. P.L. carried out the statistical analysis, participated in interpretation of results and in manuscript writing and revision.

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Conflict of interest

None declared. Preliminary results of this work were presented at the 33rd Annual ESHRE meeting in Geneva July 2017.

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