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REVIEW ARTICLE

The Impact of Bariatric Surgery on Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis

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Abstract Bariatric surgery has been proven to be a successful management strategy for morbid obesity, but limited studies exist on its effect on polycystic ovary syndrome (PCOS). A comprehensive search of electronic databases was completed. Meta-analysis was performed on PCOS, hirsutism, and menstrual irregularity outcomes following bariatric surgery. Thirteen primary studies involving a total of 2130 female patients were identified. The incidence of PCOS preoperatively was 45.6 %, which significantly decreased to 6.8 % ($P<0.001$) and 7.1 % ($P<0.0002$) at 12-month follow-up and study endpoint, respectively. The incidences of preoperative menstrual irregularity and hirsutism both significantly decreased at 12-month and at study end follow-up. Bariatric surgery effectively attenuates PCOS and its clinical symptomatology including hirsutism and menstrual irregularity in severely obese women.

Keywords Bariatric surgery · Obesity · Polycystic ovary syndrome

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Introduction

Over 2.1 billion people worldwide are overweight or obese and the prevalence of obesity is still increasing [1]. It is well known that obesity is associated with numerous comorbidities including cardiovascular disease, metabolic syndrome, obstructive sleep apnea, asthma, and cancer [2]. Obesity has also been found to exacerbate other disease processes including polycystic ovary syndrome (PCOS).

PCOS, as defined by the Rotterdam criteria, is a complex endocrine syndrome defined by oligo/anovulaton, hyperandrogenism, and polycystic ovaries [3]. PCOS is the most common endocrine disease affecting reproductive age women [4] with a prevalence of approximately 8 % [5]. PCOS occurs in both obese and non-obese women. Similarly, obese women may or may not have PCOS. Current estimates indicate that obesity is present in at least 30 % of women with PCOS [6]. The connection between PCOS and obesity remains under debate, and a recent systematic review by Hoeger and Oberfield suggests that the relationship is currently indeterminate [7].

Lifestyle management is a first-line treatment for PCOS, and significant clinical improvements in PCOS have been shown with only 5 % weight loss [8–10]. Unfortunately, adequate weight loss can be difficult to achieve and maintain, especially for the morbidly obese. Bariatric surgery is proven to result in significant and permanent weight loss in the morbidly obese and thus may be an effective treatment modality for PCOS [11].

Limited studies presently exist regarding bariatric surgery's effect on PCOS. Our aim was to investigate the efficacy of bariatric surgery in the treatment of PCOS and the clinical sequelae of PCOS including menstrual irregularity, hirsutism, and infertility.

Methods

A comprehensive search of electronic databases (e.g., MEDLINE, EMBASE, Scopus, Web of Science, and the Cochrane Library) using search terms "bariatric*, sleeve gastrectomy, gastric band*, or gastric bypass" and "polycystic ovary syndrome, polycystic ovary*, or PCOS" was completed. All randomized controlled trials, non-randomized comparison study, and case series with greater than five patients were included. All human studies limited to English were included. The reference list of included studies was also checked to identify missing studies in the primary search. Two independent reviewers screened abstracts, reviewed full-text versions of all studies, and classified and extracted data. All comparison studies included in the systematic review were assessed independently by two reviewers for methodological quality using the Cochrane Risk of Bias (RoB) tools. Disagreements were resolved by re-extraction or third-party adjudication.

Assessment of Study Eligibility

Articles were systematically reviewed based on the following criteria: (1) there were no study format restrictions, (2) studies contained at least one of the outcomes of interest listed below, and (3) enrolled at least five patients.

Outcomes of Interest

The primary outcomes of interest included PCOS, hirsutism, menstrual irregularity, and infertility. Secondary outcomes included age, pre- and postoperative BMI and weight, percentage of excess weight loss (EWL%), and type of bariatric surgery procedure.

Statistical Analysis

Study or patient characteristics and follow-up data were summarized and described as mean (SD) or percentage. Meta-

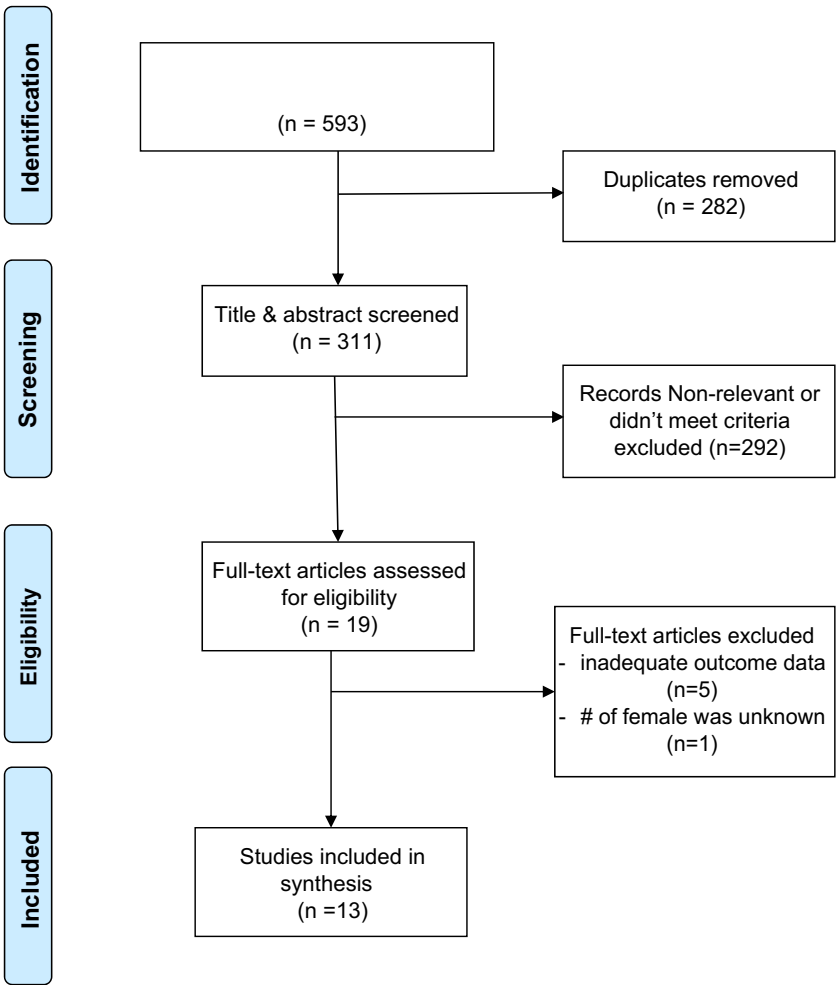

Fig. 1 PRISMA diagram of the systematic review

analysis was conducted where possible and appropriate including polycystic ovary syndrome, hirsutism, menstrual irregularity, and infertility outcomes following bariatric surgery. For dichotomous outcomes, the intervention effect sizes were reported as odds ratio (OR) with their associated 95 % confidence intervals (CI).

Heterogeneity was assessed and the cut points for heterogeneity were as follows:

(1) >25 %: low
(2) >50 %: moderate
(3) >75 %: high

Results

Five hundred ninety-three titles were identified through primary search and 311 titles or abstracts were screened after removing duplicates. Out of 311 titles and abstracts, 292 were excluded due to a failure to meet selection criteria or due to irrelevance. Of the 19 remaining studies, 5 were excluded due to inadequate outcome measures and 1 was excluded because the number of female study subjects was unknown. A total of 13 primary studies (10 full manuscripts and 3 abstract studies) consisting of no randomized controlled trials, 13 case-series [11–23], and no case reports were selected for review and meta-analysis (Fig. 1).

A total of 2130 female patients were identified (Table 1). Mean age was 30.8 years and mean follow-up was 23.8 months. Overall sample weighted preoperative mean BMI was found to be 46.3 kg/m^2, which improved to 34.2 kg/m^2 postoperatively. EWL% ranged from 33.0 to 75.0 %, with a sample weighted mean of 57.2 %. Bariatric operations included the following: gastric bypass, adjustable gastric band, biliopancreatic diversion, sleeve gastrectomy, and gastric vertical plication.

The incidence of PCOS preoperatively was 45.6 % (Table 2), which significantly decreased to 6.8 % ($P<0.001$) and 7.1 % ($P<0.0002$) at 12-month follow-up (Fig. 2) and study endpoint (Fig. 3), respectively. 56.2 % of patients reported preoperative menstrual irregularity (Table 2), which improved significantly following surgery, with the incidence decreasing to 7.7 % ($P<0.0001$) and 7.1 %($P<0.00001$) at 12-month follow-up and study endpoint (Fig. 4), respectively. The incidence of hirsutism preoperatively was 67.0 % (Table 2), which decreased significantly postoperatively to 38.6 % at 12-month follow-up ($P=0.03$) and further to 32.0 % at study end ($P<0.0002$) (Fig. 5). The incidence of preoperative infertility was 18.2 % (Table 2), which significantly decreased to 4.3 % at study end ($P=0.0009$) (Fig. 6). Of note, heterogeneity was significant for all outcomes, except for infertility.

Table 1 Systematic review study characteristics and demographics

Author	Year	Design	Total patients (*n*)	Females (*n*)	Age (mean years)	Preop BMI	Postop BMI	EWL %	Surgery	Follow-up (months)	
										Mean	Latest follow-up
Brancatisano et al. [12]	2008	CS	838	679	44.0	44.0	32.0	54.0	AGB	13	36
Collins et al. [13]	2007	CS	11	7	16.5	50.5	–	60.8	LRYGB	11.5	32
Eid et al. [15]	2005	CS	24	24	34.0	50.0	30.0	56.7	LRYGB	27.5	57
Eid et al. [11]	2014	CS	14	14	36.3	44.8	29.2	66.5	LRYGB	12	12
Escobar Morreale et al. [16]	2005	CS	36	36	31.6	49.5	–	–	Combined[a]	12	12
George et al. [17]	2013	CS	156	156	–	–	–	–	Sleeve	–	12
Jamal et al. [18]	2012	CS	20	20	32.0	52.8	34.3	64.0	LRYGB	46.7	123
Messiah et al. [21]	2013	CS	890	665	18.5	48.4	36.4	–	Combined[a]	–	12
Sugerman et al. [22]	2003	CS	33	19	16.0	52.0	38.0	33.0	Combined[a]	–	168
Kyriacou et al. [19]	2014	CS	96	96	33.0	50.9	32.1	–	LRYGB	–	24
Dixon et al. [14]	2002	CS	107	107	34.0	44.9	36.4	43.0	AGB	–	12
Talebpour [23]	2011	CS	254	254	30.0	43.0	–	75.0	Combined[a]	–	12
Luk et al. [20]	2014	CS	53	53	–	–	–	59.7	–	–	12
Total			2532	2130							
Weighted mean					30.8	46.3	34.2	57.2		14.0	23.8

CS case series, *EWL* excess weight loss, *AGB* adjustable gastric band, *LRYGB* laparoscopic Roux-en-Y gastric bypass

[a] Combination of two or more of laparoscopic Roux-en-Y gastric bypass, adjustable gastric band, sleeve gastrectomy, gastric vertical plication, or biliopancreatic diversion

Table 2 Systematic review preoperative and postoperative primary study outcomes

Author	Preoperative				Postoperative (study end)			
	PCOS (*n*)	Menstrual irregularity (*n*)	Hirsutism (*n*)	Infertility (*n*)	PCOS (*n*)	Menstrual irregularity (*n*)	Hirsutism (*n*)	Infertility (*n*)
Brancatisano et al. [12]	46	–	–	–	22	–	–	–
Collins et al. [13]	3	–	–	–	1	–	–	–
Eid et al. [15]	24	24	23	5	–	0	5	0
Eid et al. [11]	14	10	11	–	–	0	7	–
Escobar Morreale et al. [16]	17	–	–	–	5	–	–	–
George et al. [17]	67	132	96	11	13	0	19	7
Jamal et al. [18]	20	17	14	10	–	3	9	4
Messiah et al. [21]	86	135	–	–	58	89	–	–
Sugerman et al. [22]	1	–	–	–	0	–	–	–
Kyriacou et al. [19]	48	30	–	23	–	10	–	–
Dixon et al. [14]	30	36	31	2	1	14	–	0
Talebpour [23]	27	87	–	14	–	17	–	4
Luk et al. [20]	–	24	–	–	–	3	–	–
Total	383	495	175	65	100	136	40	15
Total incidence (%)	45.6	56.2	67.0	18.2	7.1	7.1	32.0	4.3

PCOS polycystic ovary syndrome

Discussion

Obesity and PCOS independently and additively contribute to an augmented clinical disease state closely related to the metabolic syndrome. Regardless of body habitus, PCOS is independently associated with increased prevalence of impaired glucose tolerance, metabolic syndrome, type 2 diabetes mellitus [24], endometrial cancer [25], and increased risk of cardiovascular disease [26]. When compared to women of normal BMI with PCOS, overweight and obese women with PCOS are known to have increased prevalence of menstrual disturbance, hirsutism, elevated fasting glucose, insulin resistance, obstructive sleep apnea, worsened hormone and lipid profiles, and decreased success with infertility treatments [27–31]. The similarity between PCOS and the metabolic syndrome has lead to the idea that PCOS may actually represent a female subtype of the metabolic syndrome called syndrome XX. This proposed syndrome is defined as the metabolic syndrome with the addition of hyperandrogenemia and anovulation in premenopausal women [32].

The relationship between obesity and PCOS to its clinical manifestations is likely multifactorial and also interrelated. Both obesity and PCOS have been shown to independently contribute to insulin resistance and hyperinsulinemia, which has been implicated in leading to hyperandrogenemia and anovulation [2, 33–35]. Hyperinsulinemia increases androgen production and decreases the synthesis of sex hormone binding globulin (SHBG), thus increasing the availability of free androgens. Together, these mechanisms contribute to hypothalamic-pituitary axis (HPA) dysfunction, ovarian follicle atresia,

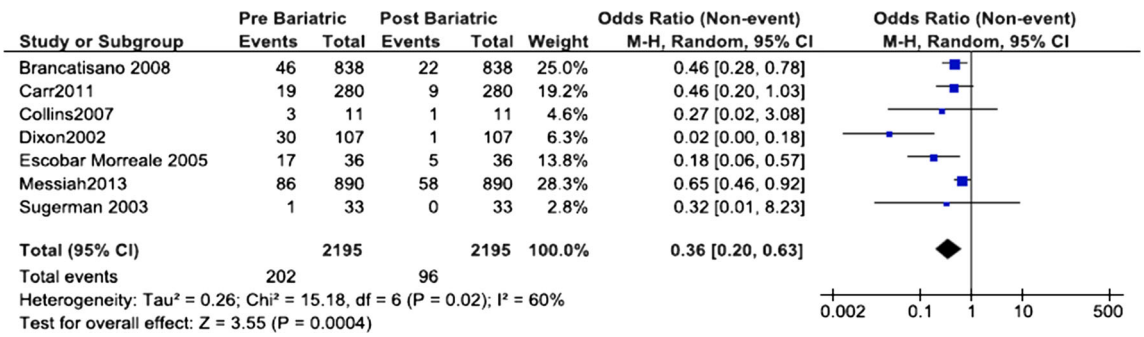

Fig. 2 PCOS 12-month post bariatric surgery

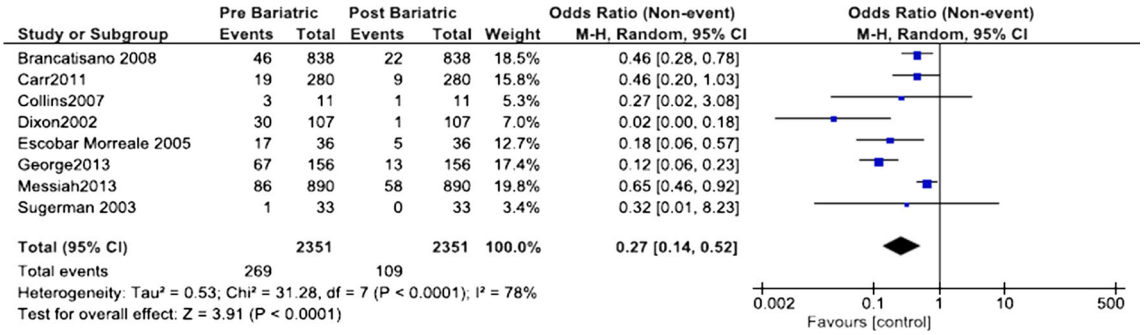

Fig. 3 PCOS at study end post bariatric surgery

and hyperandrogenemia [6, 8, 36]. Other mechanisms proposed involve hyperleptinemia, leptin resistance, and other adipokines. The effect of PCOS on leptin serum levels is less clear [37]; however, studies have shown that PCOS is independently associated with increased serum leptin levels [38] and leptin resistance [37]. A review by Mitchell et al. found that in the context of obesity, adipokines contribute to hyperinsulinemia and also act directly in the ovary to inhibit oocyte maturation ultimately contributing to infertility [39].

Lifestyle management is a first-line treatment for PCOS. Weight loss improves both insulin resistance and serum leptin levels in obese patients with PCOS. Improvement of insulin resistance indices following weight loss is accompanied by increased SHBG levels [8] and reduction in both serum insulin levels, and leptin concentration produces improvement in ovulatory function [40, 41]. Weight loss greater than 5 % has been shown to decrease menstrual irregularity and hirsutism, improve fasting insulin and blood glucose levels, and reduce the number of ovarian microfollicles [8–10].

However, lifestyle changes alone with structured weight loss programs are ineffective, as the average individual is unable to maintain even 5 % weight loss long-term [42]. Bariatric surgery has already been shown to be the most efficacious option for managing weight loss in the morbidly obese; therefore, the transition for its management of PCOS seems natural [43].

Our study found that bariatric surgery markedly improves PCOS and the associated clinical sequelae of menstrual irregularity, hirsutism, and infertility. The incidence of PCOS decreased by nearly 40 % at study endpoint, with nearly 50 % improvement in menstrual irregularity and 30 % improvement in hirsutism. However, the underlying pathophysiology of PCOS is still present and thus an individual is not "cured" of PCOS but rather weight loss simply alleviates components of the insulting pathological process, resulting in decreased symptomatology.

It appears that weight loss induced by bariatric surgery has a similar effect on PCOS through improved insulin resistance and decreased free androgen levels in morbidly obese women [16]. A study by Eid et al. found that improvement in PCOS post bariatric surgery is at least partially independent of weight loss in keeping with bariatric surgery's mechanism in improving other metabolic syndrome pathology [11]. In addition, bariatric surgery improves or resolves several PCOS comorbidities including type 2 diabetes mellitus, hypertension, and dyslipidemia [11, 15]. Importantly, the efficacy of bariatric surgery is unaffected by the presence of PCOS. Kyriacou et al. found that patients with PCOS achieved similar weight loss and improvement in metabolic comorbidities when compared to non-PCOS patients [19].

Given the efficacy of bariatric surgery in alleviating PCOS in obese women, it is important to consider whether PCOS should be an indication for bariatric surgery. Thus far, bariatric

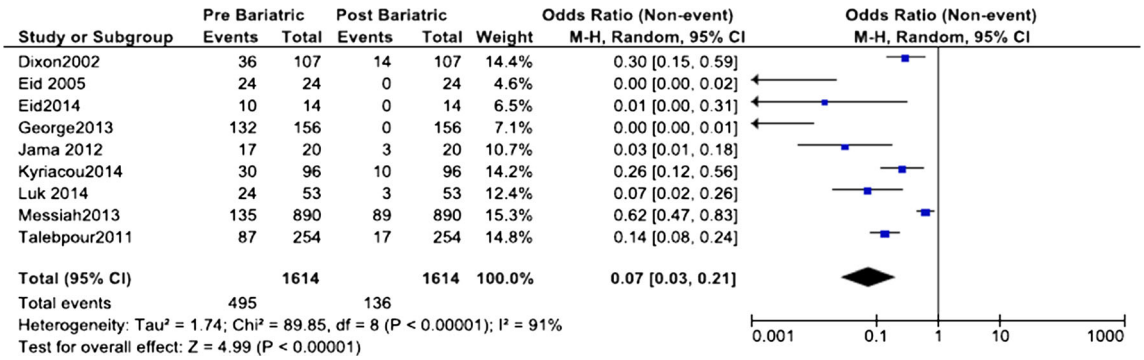

Fig. 4 Menstrual irregularity at study end post bariatric surgery

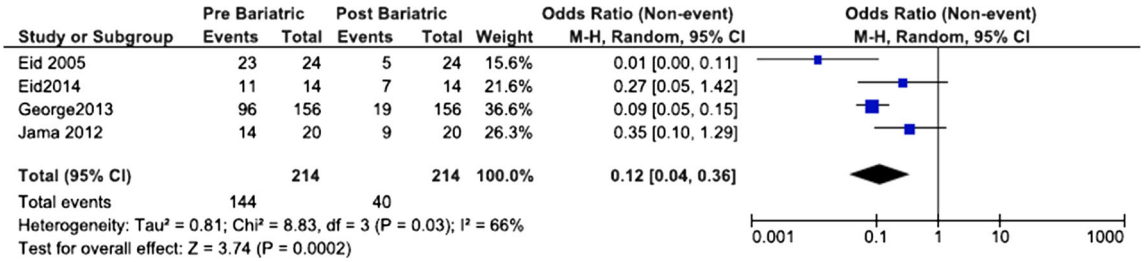

Fig. 5 Hirsutism at study end post bariatric surgery

surgery has only been suggested as a management option for treating obesity and PCOS [11]. Valid arguments for and against the inclusion of PCOS as an indication for bariatric surgery can be made. In Canada, current indications for bariatric surgery include patients with BMI≥40 kg/m^2 or BMI≥ 35 kg/m^2 with comorbid conditions in combination with an appropriate evaluation of the surgical candidate's mental health status, weight loss history, and understanding of the procedure [44]. Considering the effects of PCOS on insulin resistance and similarity to the metabolic syndrome, PCOS could be considered a comorbidity of obesity. This would allow any individual with a BMI≥35 and PCOS to be a legitimate surgical candidate. On the other hand, little is known about the effect of bariatric surgery on PCOS. Long-term data are currently unavailable and it is unknown if PCOS symptoms would remain permanently attenuated. Submitting young reproductive-age women to the risks of bariatric surgery without sufficient longitudinal knowledge could be inappropriate.

Study Limitations and Future Research

This systematic review meta-analysis is not without limitations. First, significant heterogeneity was found amongst studies in all outcome analyses except for infertility. This is not surprising given the absence of RCTs, mixed study designs, variable study populations and settings, and different trial execution qualities. However, it is important to emphasize that this is currently the best available evidence and that synthesized results might be still useful to health professionals.

Another limitation was variable diagnostic criteria for PCOS across studies. For some studies, the diagnostic criteria were unknown while others used dated or variable criteria. Our study strength would be greatly improved if PCOS was consistently diagnosed using the Rotterdam criteria.

The interpretation of infertility was also limited in these studies. Infertility is multifactorial and may be caused by both male and female factors. In particular, male obesity may also decrease fertility. If obese females have obese male partners, higher "infertility" rates amongst obese women may be interpreted as female infertility. Furthermore, it is important to consider patient age when evaluating infertility as fertility is known to decrease with advancing age of the female partner. In order to better characterize the effects of bariatric surgery on infertility in obese females, confounding factors must be considered in future studies.

Ultimately, more focused studies investigating PCOS and bariatric surgery are required. Better study design is needed in the future, and readers need to generalize the conclusion of this study with caution.

Conclusion

While lifestyle intervention remains a first-line management for PCOS, bariatric surgery has been shown to be an effective management modality in severely obese women suffering from PCOS. This is especially true in obese women with PCOS who are either morbidly obese or have failed conservative weight loss management and are otherwise candidates for bariatric surgery.

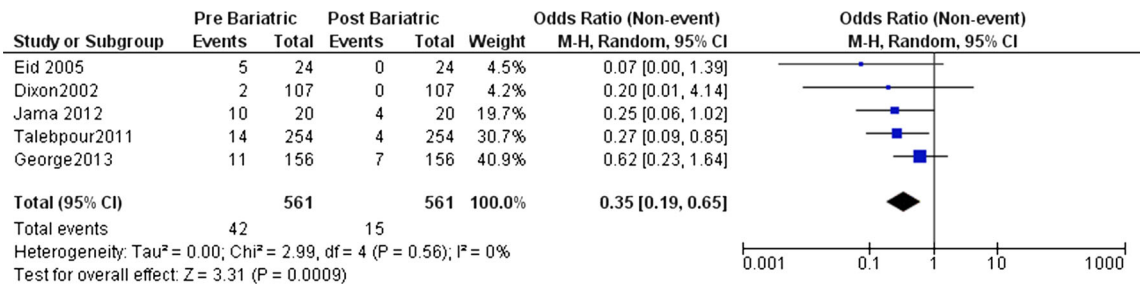

Fig. 6 Infertility at study end

Conflict of Interest The authors declare that they have no competing interests.

Consent to Participate For this type of study, formal consent is not required.

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