Bariatric Surgery in Women with Polycystic Ovary Syndrome

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Review

Bariatric Surgery in Women with Polycystic Ovary Syndrome

Suhaniya N.S. Samarasinghe [a,*], Casper Woods [b], Alexander Dimitri Miras [b,c]

[a] Imperial College Healthcare NHS Trust, UK
[b] Imperial College London, UK
[c] School of Medicine, Ulster University, UK

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrine condition in premenopausal women and is a common cause of anovulatory subfertility. Although obesity does not form part of the diagnostic criteria, it affects a significant proportion of women with PCOS and is strongly implicated in the pathophysiology of the disease. Both PCOS and obesity are known to impact fertility in women; obesity also reduces the success of assisted reproductive technology (ART). With or without pharmacotherapy, lifestyle intervention remains the first-line treatment in women with PCOS and obesity. Bariatric surgery is still an experimental treatment in women with PCOS and subfertility. This review will present an overview of the pathophysiology of PCOS and obesity and the role of bariatric surgery. Although data are sparse regarding the impact of bariatric surgery on subfertility in women with PCOS and obesity, existing studies point to a beneficial role in treating metabolic and reproductive dysfunction.

1. Introduction: polycystic ovary syndrome (PCOS)

1.1. Definition of PCOS

Polycystic ovary syndrome (PCOS) is a common endocrine condition that is the predominant cause of anovulatory subfertility in women of reproductive age [1]. Its incidence ranges 6.2 and 19.5 % depending on diagnostic criteria used [2] and results in subfertility in up to 72 % of women [3]. The International evidence-based guidelines recommend diagnosing PCOS in women with irregular menstrual cycles and clinical/biochemical hyperandrogenism or one of irregular menstruation or hyperandrogenism, alongside ultrasound evidence of polycystic ovarian morphology [4]. The guidelines also recommend excluding alternative causes of these presentations, including congenital adrenal hyperplasia, Cushing's disease and hypogonadotropic hypogonadism [4]. Hypogonadotrophic hypogonadism (also known as secondary hypogonadism) is the result of gonadal failure secondary to abnormal levels of pituitary gonadotrophins [5]; low/normal gonadotropin levels in the presence of a low concentration of oestradiol is diagnostic [5].

PCOS is associated with the development of metabolic syndrome in up to 33 % of women [6]. Tissue-specific Insulin resistance and hyperinsulinemia, seen in 65-70 % of women with PCOS [7], are considered key factors underpinning the pathophysiology of the disease [8]. The primary phenotypic manifestation of PCOS resulting from hypothalamic-pituitary-gonadal (HPG) dysfunction is reproductive compromise, which occurs due to anovulation [1] (Fig. 1). Women with PCOS have a significantly reduced spontaneous conception rate compared to age-matched controls [9], are more likely to require ovulation induction and in vitro fertilisation (IVF) [10] and have higher miscarriage rates [9]. Following conception, women with PCOS are more likely to develop late pregnancy complications such as gestational diabetes mellitus and pregnancy-induced hypertension [11].

A review of the evidence from meta-analyses published in the International Evidence-based Guideline 2023 reported that women with PCOS have a significantly increased risk of endometrial cancer and/or endometrial hyperplasia. The odds of endometrial cancer are higher in women with PCOS when compared to those without PCOS [4].

2. Obesity

Obesity affects between 50 %–80 % of women with PCOS [12]. It is strongly implicated in the pathophysiology of the disease since the severity of obesity correlates with the degree of selective insulin resistance and hyperandrogenism [8]. Furthermore, obesity contributes to metabolic disease and obstructive sleep apnoea (OSA) in PCOS [8]. Importantly, the development of PCOS also leads to further weight gain.

* Corresponding author.
E-mail address: s.samarasinghe@imperial.ac.uk (S.N.S. Samarasinghe).

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The aetiology behind obesity in PCOS has been linked to decreased postprandial thermogenesis, which has been demonstrated in women with PCOS compared to age and BMI-matched controls [13]. Basal metabolic rate may also be lower in women with PCOS, contributing to the development of obesity [14]. This could partially be explained by impaired energy metabolism in skeletal muscle due to mitochondrial dysfunction [15]. Whilst the pathogenesis behind this effect is yet to be fully elucidated, it may be underpinned by androgen excess, which causes mitochondrial abnormalities in vivo [16]. Reduced brown adipose tissue activity has also been identified in several PCOS cohorts and might explain this reduction in energy expenditure [17]. Additionally, white adipose tissue dysfunction, characterised by adipocyte hypertrophy and impaired lipolysis, may predispose to abdominal obesity [18]. These impairments are also likely to result from excess androgen levels, since treatment of adipocytes with testosterone has been shown to impair lipolysis and result in hypertrophy [18]. The specific distribution of body fat in women with PCOS and obesity is significant since fat deposition in visceral and subcutaneous abdominal areas (android deposition), common in women with PCOS, may contribute to hyperandrogenism [19].

2.1. Impact of obesity on fertility

Obesity in the absence of PCOS is also associated with subfertility [20], defined by the inability to conceive after more than one year of regular unprotected intercourse [21]. Obesity impairs ovulation, oocyte quality, endometrial function, implantation, and fertilisation in eumenorrheic women [22]. Increased leptin levels in obesity may impair ovarian steroidogenesis, whilst chronic leptin exposure can also lead to central leptin resistance and subsequent Gonadotropin hormone-releasing hormone (GnRH) insensitivity [23]. Meanwhile, adiponectin, which may have a protective role in folliculogenesis and steroidogenesis, is found in lower serum concentrations in obesity [24]. Hyperinsulinemia and hyperandrogenism are highly correlated in obesity and may also impair ovulation by causing HPG dysfunction, including GnRH insensitivity [25]. Hyperandrogenism results from increased peripheral production in adipocytes and theca cells and decreased sex hormone binding globulin (SHBG) levels [26]. Together, these molecular effects of obesity reduce the success of natural conception, as demonstrated by several prospective studies showing longer time to pregnancy in women with higher BMI than women with normal BMI [27].

Obesity also reduces the success of assisted conception, evidenced by systematic reviews that found that higher threshold doses of gonadotrophins were needed for ovulation induction and a lower chance of pregnancy following IVF in women with BMI >30 kg/m^2 compared to 20–30 kg/m^2 [28]. As a result, NICE guidelines recommend that women must have a BMI <30 kg/m^2 to be eligible for assisted reproduction [29]. Like PCOS, obesity also predisposes to pregnancy complications, including gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, induction of labour, preterm labour, miscarriage and still-birth [30]. One observational study demonstrated that as little as 5 % weight loss improved spontaneous conception rates in women with PCOS and obesity treated with a low-fat diet [31].

2.2. Behavioural modification and pharmacotherapy

Owing to the heterogeneity of the disease, no single treatment is appropriate or effective for managing women with PCOS. International evidence-based guidelines recommend a target weight loss between 5 and 10 % [32], which increases insulin sensitisation [33] and ovulation rates [29]. Lifestyle modifications, such as calorie-restricted diets and exercise, are currently first-line options for achieving this degree of weight loss [34]. As such, several studies have investigated their

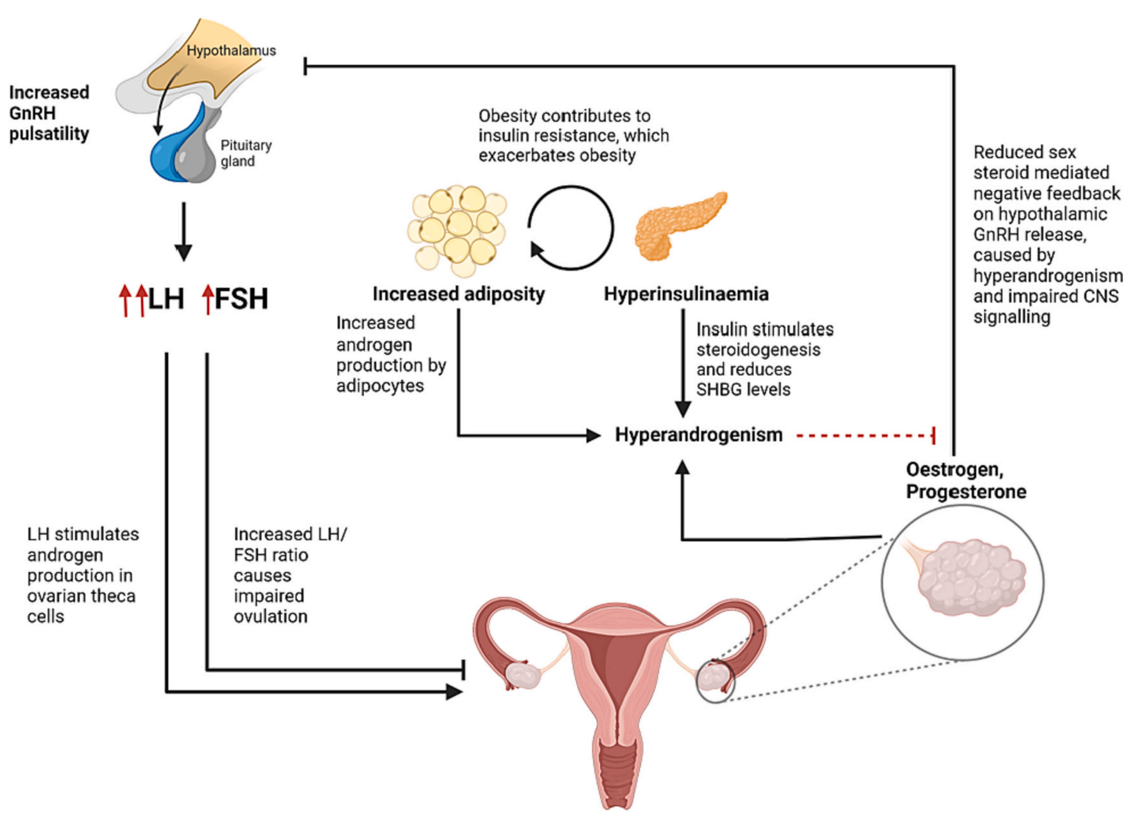

Fig. 1. Pathophysiology of PCOS. GnRH, gonadotrophin-releasing hormone; LH, luteinising hormone; FSH, follicle stimulating hormone; CNS, central nervous system.
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efficacy. In a prospective study, 25 out of 33 women with PCOS achieved weight loss of at least 5 % after following a 1200 kcal/day diet for six months [35]. This resulted in significant improvements in menstrual regularity and anthropometric indices such as waist and hip circumference. Additionally, calorie restriction restored fertility in 10 women who could later conceive naturally. In another cohort, 67 women with PCOS achieved significantly greater weight loss and improved fertility after six months of a weekly lifestyle education programme, compared to 20 who did not complete the course [36]. Women who completed the intervention were also shown to have reduced miscarriage rates and psychological distress compared to baseline. Concerning the impact of lifestyle intervention on metabolic function in PCOS, a meta-analysis of 15 randomised controlled trials revealed that it reduces BMI, biochemical hyperandrogenism, total cholesterol and LDL, but not glucose tolerance relative to minimal intervention [37]. None of these studies lasted longer than 12 months; the majority lasted only 3 months. These findings indicate that short-term lifestyle intervention in women with PCOS effectively induces weight loss and reduces some reproductive and metabolic function indicators.

However, intensive lifestyle modification, including severe caloric restriction utilised in many of the above studies [37], is usually unphysiological and thus unsustainable [38]. Changes, including an increase in appetite and reduced energy expenditure and thermogenesis, have been described in the severely weight-reduced state and limit the ability to maintain weight loss [39]. Though more moderately intensive lifestyle changes may have a higher adherence rate, they also have a more moderate effect on weight [40]. Moderate lifestyle change is unlikely to be an effective long-term management option.

Several medical interventions have been proposed for promoting weight loss in PCOS, including metformin (an insulin sensitiser) and glucagon-like-peptide 1 (GLP-1) receptor agonists [41]. Randomised controlled trials investigating metformin[3] treatment for women with PCOS show that it significantly reduces BMI and other metabolic factors, including fasting glucose, testosterone, and cholesterol levels [42,43]. Similarly, according to trials, GLP-1 agonists, such as liraglutide and exenatide, also effectively reduce weight in women with PCOS [44,45]. A meta-analysis revealed that liraglutide monotherapy reduces weight more effectively than metformin or combination therapy with metformin and liraglutide in women with PCOS [45].

However, the evidence surrounding the use of these insulin sensitisers in reducing reproductive dysfunction is more conflicting. One randomised controlled trial demonstrated that up to 30 weeks of treatment with extended-release metformin resulted in a significantly lower rate of live births in 208 women with PCOS compared to clomiphene in 209 women [46]. Additionally, it found that combined therapy with clomiphene and metformin did not improve ovulation compared to clomiphene alone. Contrastingly, a meta-analysis of 54 trials indicated that metformin monotherapy is less effective than clomiphene in restoring fertility, combining the two medications significantly improves pregnancy rates in WHO group II anovulation [47]. The lipase inhibitor, orlistat, has also been utilised in treating women with PCOS and obesity [48]. Like insulin sensitisers, orlistat also effectively reduces metabolic complications, including insulin resistance and hyperandrogenism [48]. However, a randomised-controlled trial indicated that preconception treatment with orlistat or sibutramine did not significantly improve live birth rates compared to lifestyle modification [49].

2.3. Bariatric surgery

Recently, bariatric surgery has become a treatment of interest in managing PCOS [50]. The most common forms of bariatric surgery procedures include Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG) and gastric banding (BAND) [51]. Bariatric surgery has increased significantly in recent years [52]. According to a recent International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) report, 73.7 % of bariatric surgeries occurred in women between 2014 and 2018, many of whom were of reproductive age [53]. According to NICE guidelines, current indications for bariatric surgery include BMI greater than 40 kg/m^2 or greater than 35 kg/m^2 with significant obesity-related complications such astype 2 diabetes mellitus (T2DM) or hypertension [54]. Alternatively, current American Society for Metabolic and Bariatric Surgery (ASMBS) and IFSO guidelines suggest that lower BMI thresholds of 35 kg/m^2, 30 kg/m^2 in individuals with metabolic disease and 27.5 kg/m^2 in people from specific ethnic groups (e.g. South Asians) should be used [55]. Initially, these procedures were thought to reduce gastric capacity and caloric intake; however, it is now widely accepted that the weight loss mechanism following surgery is more complex [56]. This may result from altering CNS, liver and gut signalling by hormones, including GLP-1, Ghrelin and peptide YY (PYY) [57–60]. Levels of the anorexigenic hormones GLP-1 and PYY are increased following VSG [57,60] and RYGB [59,60] and act centrally to increase satiety [58,60]. Meanwhile, levels of the peptide hormone ghrelin, which induces hunger, are decreased following VSG [58]. Increased secretion of bile acids and fibroblast growth factor 19 (FGF19) has also been demonstrated following RYGB and VSG [61]. These bile acids may increase fatty acid oxidation and suppress appetite by stimulating GLP-1 and PYY [56]. Alongside increased satiety, bariatric surgery may also reduce weight by reducing preference for high-calorie food [58].

2.4. Weight loss and anthropometric indices

Few studies have investigated the efficacy of bariatric surgery in treating women with PCOS, despite the central role that obesity plays in its pathophysiology. There are currently no randomised-controlled trials investigating bariatric surgery specifically in PCOS populations, and most evidence regarding its use comes from prospective cohort studies (Table 1). Almost all studies investigating the effect of bariatric surgery in patients with PCOS have demonstrated significant weight loss (Table 1). Additionally, studies comparing bariatric surgery to medical therapies in women with PCOS and obesity have demonstrated more significant and prolonged weight loss as little as six months after surgery compared to interventions such as a calorie-restricted diet [62,63]. These results parallel findings from the general population [64], indicating that bariatric surgery is also an effective weight loss method for the PCOS population. Importantly, in a prospective cohort study, anthropometric measurements revealed significant reductions in waist and hip circumference 12 months after VSG in 88 women with PCOS and more significant reductions in visceral adipose tissue mass than any other tissue [65]. The visceral adipose tissue loss rate was also higher than in women with obesity following VSG [65]. In another cohort of 13 patients with PCOS, waist and hip circumference were similarly reduced six months after RYGB [66]. These findings demonstrate that bariatric surgery may specifically reduce visceral adiposity in women with PCOS as well as total body weight. Since androgenic fat distribution is implicated in the pathophysiology by driving hyperandrogenism [19], this affect may therefore slow, or reverse, the development of the PCOS phenotype (Fig. 2).

2.5. Metabolic outcomes

Several studies have investigated the impact of bariatric surgery on metabolic parameters in women with PCOS. Tian et al. conducted a meta-analysis of 21 such studies and demonstrated significant reductions in total testosterone levels, fasting blood glucose and insulin [67]. Additionally, the authors found significant reductions in triglyceride levels but no significant change in HDL in post-surgical cohorts [67]. These results indicate that bariatric surgery effectively improves markers of metabolic dysfunction. In a prospective case-control study, improvement of metabolic parameters, including reduced fasting blood glucose, insulin levels and improved lipid profile, in 22 women 12

Table 1
Summary of existing studies investigating the use of bariatric surgery in the treatment of women with PCOS and obesity.

Author and year of publication	Type of study	Number of patients	Type of surgery	Outcomes evaluated	Findings
Abiad- 2018 [68]	Prospective case control	22 (six with PCOS, 16 without)	VSG	FG score, FBG, Insulin, T, SHBG, lipids, CRP, adiponectin at 12 months post-surgery	Decreased FBG in both groups ($p < 0.001$ in non-PCOS, $p = 0.003$ in PCOS). Increased adiponectin levels ($p = 0.001$ in non-PCOS, $p = 0.013$ in PCOS). Decreased CRP in both groups. Non-significant increase in SHBG in both groups Decreased insulin levels in both groups ($p = 0.005$ in PCOS) Decreased LDL-c ($p < 0.001$ in both groups)
Ahmed- 2021 [110]	Retrospective case-matched study	90 (30 with PCOS, 60 without)	RYGB	BMI, HbA1c, SBP and remission rates of OSA at 12 and 24 months post-surgery	Decreased BMI and HbA1c ($p < 0.0001$) at both 12 and 24 months in all patients. Reduced SBP and DBP at 24 months ($p = 0.004$) in all patients Reduced No. patients with OSA - 25 at baseline to three at 24 months ($p < 0.0001$) No significant difference in reductions in any parameter between PCOS and non-PCOS groups
Benito- 2020 [92]	Prospective cohort study	169 (49 with PCOS, 120 without)	RYGB, BAND and VSG	BMI, metabolic markers, and No. pregnancies Within 2 years post-surgery	Decreased weight, BMI, TT, FBG, fasting insulin, HOMA-IR (all $p < 0.05$) in both groups 17 women with PCOS had at least one pregnancy. 23 controls had at least one pregnancy ($\chi^2 = 4.643$, $P = 0.031$) Pregnancy rates were 40.8 % in women with PCOS and 25.0 % without PCOS ($\chi^2 = 4.178$, $P = 0.041$) Lower mean birth weight in women with PCOS ($p = 0.04$), but no significant difference in LBW
Bhandari- 2016 [86]	Prospective observational study	75 (43 with PCOS, 32 without)	VSG	AMH, BMI and menstrual function 6 months post-surgery	BMI reduced in both groups ($p < 0.001$) AMH reduced in both groups ($p < 0.001$). 57.14 % (16 out of 28) of patients with PCOS and 30.43 % (seven out of 23) of patients without PCOS had restored menstruation (NS in both groups)
Bhandari- 2022 [69]	Prospective observational study	1013 (all with PCOS)	BAND	Weight loss, T2DM, lipids, menstrual function, hormones, and hirsutism up to 5 years post-surgery	Mean %total weight loss of 32.4 at 5 years ($p = 0.001$) 936 women had correction in menstrual pattern at 6 months ($p < 0.0001$) Significant reduction in hirsutism ($p < 0.0001$) No significant change in LH/FSH ratio Significant reduction in incidence of T2DM, HTN, dyslipidaemia and OSA ($p < 0.0001$) after 5 years
Buyukkaba- 2022 [85]	Prospective cohort study	70 patients (23 PCOS, 47 non-PCOS)	VSG, RYGB	BMI, HbA1c, HOMA-IR, cholesterol, AMH	Decreased weight and BMI in both groups ($p < 0.001$) Increased AMH ($p < 0.001$) in both groups Decreased HOMA-IR ($p = 0.039$) in both groups No significant difference in total cholesterol, LDL, HDL and Tg in PCOS patients. Reduced Tg ($p = 0.003$) and LDL ($p < 0.001$) in patients without PCOS
Cai- 2021 [65]	Prospective cohort study	153 (83 with PCOS, 70 without)	VSG	Anthropometric measurement 12 months post-surgery	Decreased weight, BMI, waist circumference, visceral adipose tissue mass (all $p < 0.001$) and android/gynoid ratio ($p = 0.004$) in the PCOS group.
Cai- 2023 [83]	Prospective case-control study	164 (88 with PCOS, 76 without)	VSG	Anthropometric measurements, BMI, metabolic parameters, menstrual function, fertility, and pregnancy outcomes 12 months post-surgery Predictors of improvement in menstrual function 6 months post-surgery	Decreased SBP, DBP waist circumference, hip circumference, AST, ALT, TG, HbA1c and HOMA-IR in PCOS and control groups ($p < 0.05$) Increased number of menstruations per year in women with PCOS ($p < 0.001$), no significant difference in women without PCOS. "Spontaneous pregnancy, live birth, and miscarriage rates of 19.31 %, 17.04 % and 2.27 % respectively." Association between time from PCOS diagnosis and recovery of fertility and menstrual function
Casals- 2021 [76]	Retrospective cross-sectional study	217 (43 with PCOS)	VSG, RYGB	Weight loss, BMI, menstrual function, time-to-pregnancy, use of fertility treatments and pregnancy outcomes one-year post-surgery or period required for successful conception	Decreased prevalence of T2DM, HTN and OSA. Increased menstrual regularity. Reduced time-to-pregnancy and low rate of adverse pregnancy outcomes. Reduced mean birth weight. No significant difference between PCOS and non-PCOS groups.
Chiofalo- 2017 [87]	Retrospective cohort study	55 (29 with PCOS, 26 without)	VSG, RYGB	AMH, T, androstenedione, DHEAS, and EWL% 12 months post-surgery	Some data not displayed. Decreased TT, androstenedione, and DHEAS in patients with PCOS ($p < 0.05$) Decreased DHEAS in patients without PCOS ($p < 0.01$)

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Table 1 (*continued*)

Author and year of publication	Type of study	Number of patients	Type of surgery	Outcomes evaluated	Findings
Christ- 2018 [77]	Retrospective case-control study	109 (44 with PCOS, 65 without)	–	BMI, HbA1c, lipids, ovarian volume, and menstrual function an average 1.9 ± 0.3 years (PCOS) or 2.6 ± 0.3 years post-surgery (non-PCOS)	Reduced AMH in women with ($p = 0.02$) and without ($p = 0.04$) PCOS Decreased BMI in both groups ($p < 0.001$) No significant change in ovarian volume or HbA1c in the PCOS group Decreased Tg and VLDL-C ($p < 0.05$) Increased HDL-c ($p < 0.05$) Decreased TT ($p < 0.05$) in the PCOS group Improvement in regularity of menstrual pattern ($p < 0.001$) in the PCOS group.
Christinajoice- 2020 [93]	Retrospective case-control study	45 (29 with PCOS, 16 without)	VSG, RYGB, BAND	BMI, PCOS symptoms, fertility, and pregnancy outcomes three years post-surgery	Weight loss of 66.9 % and 76.6 % decrease in BMI in women with PCOS. Reduced dysfunctional uterine bleeding ($p = 0.001$), and amenorrhoea ($p = 0.001$) No significant change in dysmenorrhoea, oligomenorrhoea, acne, acanthosis, hirsutism 7 live births after surgery ($p = 0.61$) - 3 conceived naturally, and 4 after ART. 9 patients unable to conceive. High incidence of early term (37–38 weeks) pregnancy ($p = 0.005$), but no significant incidence of low birth weight. Increased rate of spontaneous vaginal delivery ($p = 0.019$) compared to C-section.
Dilday- 2018 [111]	Retrospective case-control study	238 (119 with PCOS, 119 without)	VSG	BMI, weight loss and fertility 12 months post-surgery	Decreased BMI in women with PCOS compared to women without ($p = 0.04$) 22 % of women with PCOS achieved pregnancy at follow up.
Eid- 2005 [74]	Retrospective case-control study	24 (all with PCOS)	RYGB	BMI, HbA1c, lipids, GORD, hirsutism, depression, menstrual function after an average 27.5 ± 16 months post-surgery	Decreased BMI (50 ± 7.5 to 30 ± 4.5 kg/m^2) 62 % decrease in HbA1c, 92 % decrease in dyslipidaemia and 77 % decrease in HTN. GORD (12 at baseline) and depression (10 at baseline) ameliorated in all patients. Hirsutism reported in 79 % fewer patients. Normal menstrual frequency restored in all patients
Eid- 2014 [78]	Prospective cohort study	14 (all with PCOS)	RYGB	Metabolic parameters and menstrual irregularity 12 months post-surgery	Reduced testosterone, FBG, insulin, ($P < 0.05$), menstrual regularity restored in all patients at 6 and 12 months after surgery (10 irregular at baseline). Non-significant reduction in ferryman-gallway score
Escobar-Morreale- 2005 [79]	Prospective cohort study	12 (all with PCOS)	BAND, BPD	Weight loss, menstrual function, androgens, and insulin 6 months post-surgery	Weight loss ($P < 0.0001$) Restoration of regular menses in all patients. Decreased testosterone ($p < 0.005$), DHEAS ($p < 0.005$), fasting insulin and HOMA-IR ($p < 0.001$)
Ezzat- 2021 [72]	Prospective cohort study	36 (all with PCOS)	VSG, BAND	Metabolic parameters and ovarian volume 12 months post-surgery	Decreased BMI, free testosterone, total testosterone, and FAI (all $p < 0.001$). Increased SHBG ($p < 0.001$) Decreased ovarian volume ($p < 0.001$)
Gomez-Meade- 2013 [112]	Retrospective cohort study	389 (all with PCOS)	RYGB	BMI, metabolic parameters, AST, and ALT 12 months post-surgery	Decreased BMI and weight ($p < 0.0001$) Decreased Total cholesterol, LDL, Tg, HbA1c, ALT ($p < 0.0001$). Decreased AST ($p = 0.04$). No significant change in HDL.
Hu- 2022 [71]	Prospective non-randomised trial	81 (all with PCOS)	VSG	Weight, anthropometric measurements, metabolic parameters testosterone, menstrual function after surgery compared to 6 months of metformin treatment.	Decreased weight, BMI waist and hip circumference ($p < 0.001$) after surgery, no significant difference after medical treatment. Decreased androstenedione ($p = 0.005$), increased SHBG ($p < 0.001$) after surgery, no significant difference after medical treatment. Decreased fasting insulin and HOMA-IR ($p < 0.001$) after surgery, no significant difference after medical treatment More significantly reduced HbA1c after surgery ($p < 0.001$) compared to medical treatment ($p = 0.023$) 78 % PCOS remission rate Higher rates of regular menstruation in surgical compared to medical group.
Jamal- 2012 [70]	Retrospective case-control study	20 (all with PCOS)	RYGB	Menstrual dysfunction, hirsutism, T2DM, Depression, GORD, and urinary incontinence	Decreased weight and BMI ($p < 0.005$) Decreased hirsutism, HTN, depression, GORD (resolution in 7 subjects, partial improvement in 5) and urinary incontinence (resolution in 5 patients) ($p < 0.005$)

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Table 1 (*continued*)

Author and year of publication	Type of study	Number of patients	Type of surgery	Outcomes evaluated	Findings
Kyriacou- 2014 [80]	Retrospective cohort study	96 (48 with PCOS, 48 without)	RYGB	Weight metabolic parameters and menstrual function	Significant weight loss in both groups, with ($P < 0.0001$). Decreased SBP, DBP and HbA1c ($P < 0.0001$) Reduced oligomenorrhoea ($P < 0.004$) HTN completely ameliorated ($P < 0.001$) No significant difference in glucose tolerance
Lacey- 2023 [75]	Prospective cohort study	77 (all with PCOS)	–	Weight loss and QOL at 12 months post-surgery	Improvements in QOL with weight
Machado Júnior- 2019 [113]	Prospective cohort study	18 (all with PCOS)	VSG	BMI, Oestradiol, fasting insulin, LH, FSH and LH/FSH ratio 3 months post-surgery	Decreased BMI ($p < 0.001$), Decreased fasting insulin ($p = 0.001$) Decreased LH/FSH ratio ($P = 0.008$)
Singh- 2020 [81]	Prospective cohort study	50 (18 with PCOS, 32 without)	VSG, BAND	Weight loss, hirsutism, LH/FSH ratio, menstrual function and ovarian morphology on USS 1 year post-surgery	Significant weight loss ($p < 0.01$). All women with PCOS had menstrual function restored ($p < 0.05$). Decreased hirsutism ($p < 0.04$) No significant change in LH/FSH ratio Complete resolution of ovarian morphology in 7 women
Tatarchuk- 2022 [62]	Prospective, non-randomised study	122 (60 with PCOS, 62 without)	VSG	Weight loss, metabolic parameters and menstrual function compared to conservative treatment	Greater weight loss and reduction in HOMA-IR after surgery compared to conservative treatment in women with and without PCOS ($p < 0.05$). Lower number of intermenstrual days and higher number of confirmed ovulations ($p < 0.05$) after surgery compared to conservative treatment and baseline in women with and without PCOS.
Turkmen- 2016 [66]	Prospective cohort	13 (all with PCOS)	RYGB	Anthropometric measures, metabolic parameters, and ovarian volume 6 months post-surgery	Decreased BMI, waist, and hip circumference ($p < 0.001$) Decreased SBP ($p = 0.008$), decreased FBG ($p = 0.0010$) and HbA1c ($p = 0.002$). Decreased Tg ($p = 0.021$) No significant difference in ovarian volume.
Wang- 2015 [63]	Prospective cohort study	48 (all with PCOS)	VSG	BMI, menstrual changes, and androgen levels 6 months post-surgery, compared to conservative treatment	Lower BMI and more significant improvement in menstruation after surgery compared to lifestyle modification ($p < 0.0001$) Decreased androgens after surgery ($p = 0.012$) and no significant change following lifestyle modification. More significant resolution of hirsutism Fertility therapy effective in three women following surgery.
Yheulon- 2019 [114]	Retrospective cohort study	256 (32 with PCOS, 224 without)	VSG	Weight loss and HbA1c four years post-surgery	Greater %Excess weight loss of PCOS and compared to non-PCOS groups. 0.4 mmol/l mean reduction in Hba1c in PCOS group, compared to 0.776 mmol/l mean reduction in non-PCOS group

VSG, vertical sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; BAND, gastric banding; BPD, biliopancreatic diversion; PCOS, polycystic ovary syndrome; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment for insulin resistance; CRP, c-reactive protein; SHBG, sex hormone binding globulin; LDL, low density lipoprotein; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; OSA, obstructive sleep apnoea; T2DM, type 2 diabetes mellitus; HTN, hypertension; TT, total testosterone; FAI, free androgen index; LBW, low birth weight; AMH, anti-mullerian hormone; LH, luteinising hormone; FSH, follicle stimulating hormone; Tg, triglyceride; AST, aspartate transaminase; ALT, alanine transaminase; DHEAS, dehydroepiandrosterone sulphate; ART, assisted reproductive technology; GORD, gastro-oesophageal reflux disease; QOL, quality of life.

months after VSG was identified alongside reduced C-reactive protein [68].

More recently, a large prospective observational study of 1013 patients with obesity and PCOS demonstrated significant amelioration of T2DM (9.2 % reduction) and hypertension (82.2 % reduction) 12 months after bariatric surgery [69]. OSA (98.5 % reduction) and dyslipidaemia (93.2 % reduction) showed significant resolution after 5 years. Whilst this study did utilise a large cohort, it was restricted to a single centre, and hence women included may not reflect the heterogeneity of the PCOS population. However, a smaller retrospective case-control study evaluating outcomes in 20 women with PCOS following RYGB supported these findings [70]. This study found that RYGB significantly resolved T2DM and hypertension after a mean follow up period of 46.7 ± 35.3 months, as well as other complications including gastro-oesophageal reflux and urinary incontinence. Together these findings indicate that bariatric surgery is likely to reduce long-term metabolic complications and markers of metabolic dysfunction in women with PCOS and obesity.

Notably, a recent prospective non-randomised controlled trial by Hu et al. compared the efficacy of VSG to drug treatment [71]. Medically treated patients received 6 months of combined treatment with an oral contraceptive and metformin for 6 months, followed by metformin alone for 6 months. The authors found significant improvements in metabolic parameters, including insulin resistance, HbA1c, total cholesterol, HDL levels and BMI in the surgically treated group after 12 months. Contrastingly, the drug-treated group only demonstrated significant reductions in HbA1c and BMI after 12 months and achieved significantly less weight loss than the surgical group. Additionally, the direct comparison of HbA1c, insulin resistance and cholesterol levels between groups did not reach statistical significance. However, these findings give some preliminary evidence to suggest that bariatric surgery may be more effective than medical management in reducing metabolic complications in women with PCOS and obesity. The authors did demonstrate that the free androgen index was more significantly reduced in the surgical group. This supports the assertion that surgery may specifically ameliorate androgenic fat distribution and hence, the development of

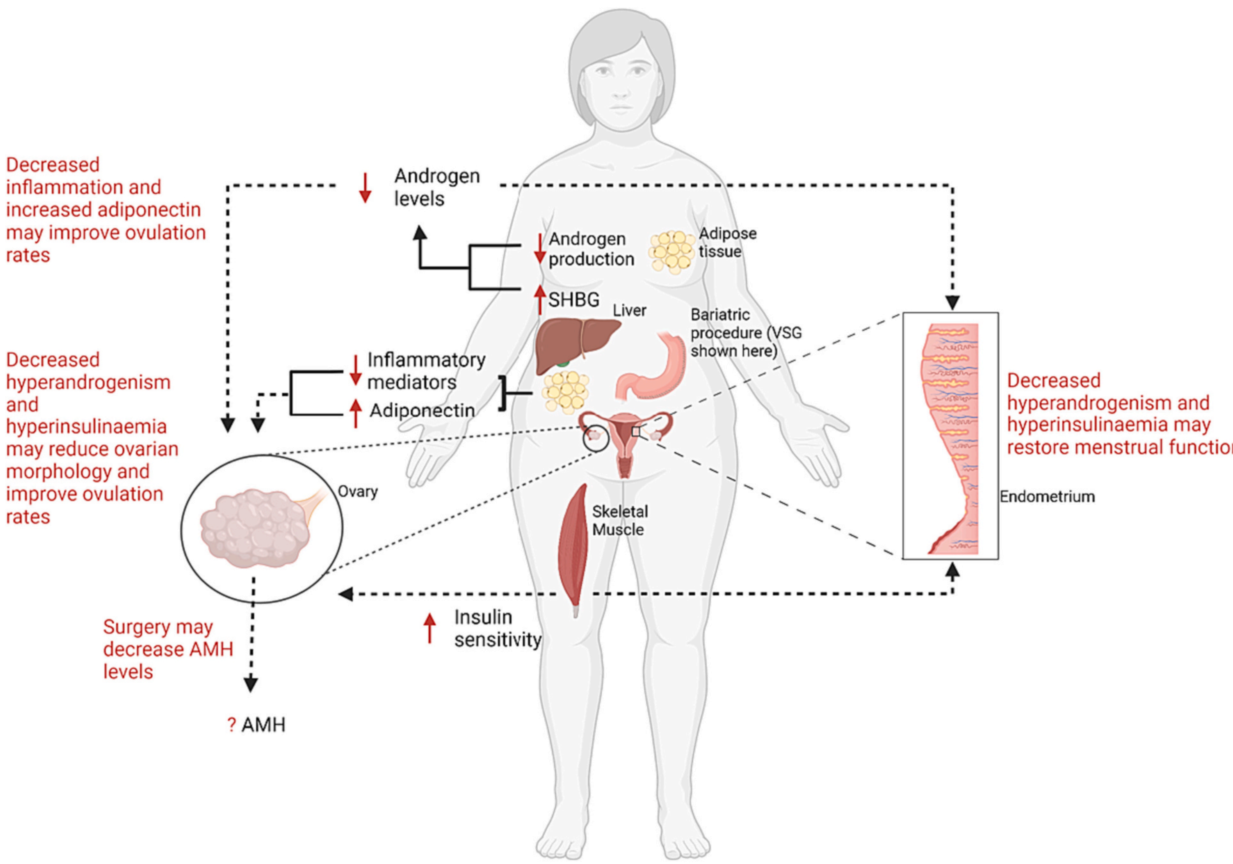

Fig. 2. Potential changes in the pathophysiology of PCOS following bariatric surgery. VSG, vertical sleeve gastrectomy; SHBG, sex hormone binding globulin; AMH, anti-mullerian hormone.
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clinical hyperandrogenism. Alternatively, this reduction in free androgens could be attributed to increased SHBG levels, which were more significantly increased following surgery than drug treatment and increased after VSG and BAND in another prospective study [72].

2.6. *Psychological outcomes and QOL*

Alongside the reduction in biochemical androgen levels, clinical indicators of hyperandrogenism, including self-reported acne and hirsutism, have also been shown to resolve following surgery [67]. Given the association between these manifestations and reduced QOL [73], the psychological sequelae of PCOS might also be expected to improve following bariatric surgery. As a secondary outcome, two retrospective case-control studies investigated the incidence of depression 12 months following RYGB in women with PCOS [70,74]. Both studies demonstrated significant resolution of depression following RYGB, although other mental health disorders, including anxiety, were not recorded, and neither paper detailed how depression was assessed. To our knowledge, only one prospective study in 77 patients with PCOS has directly assessed the impact of bariatric surgery on QOL [75]. This study demonstrated significant improvement in QOL as measured by a health-related QOL questionnaire 12 months post-surgery and an association between the degree of weight loss and improvement in QOL. Together, these reports give some evidence to suggest that bariatric surgery might improve QOL and reduce psychological sequelae in women with PCOS and obesity; however, the evidence is limited, and few studies have investigated this outcome directly.

3. Impact of bariatric surgery on fertility

Owing to the role that obesity plays in exacerbating subfertility in PCOS, it follows that bariatric surgery would be effective in treating PCOS for reproductive outcomes; "Bariatric/metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, ovulation and pregnancy rates in women with PCOS" [4].

Several studies have investigated the impact of bariatric surgery on menstrual function in PCOS, and most have identified that it leads to the restoration of normal menstruation [67,69,76–83]. Following gastric sleeve resection, reproductive function was compared to medical therapy in a prospective non-randomised trial [62]. Here, compared to medical therapy, bariatric surgery was found to lower the number of intermenstrual days in 33 women and increase the number of ovulations, confirmed using transvaginal ultrasound and serum progesterone levels [62]. In a single-centre, prospective, non-randomised trial, Hu et al. showed that VSG restored regular menstruation more effectively than metformin monotherapy, which was given after combined treatment with metformin and an oral contraceptive [71]. These findings indicate that bariatric surgery may improve menstrual regularity and ovulation rates in women with obesity and PCOS more efficaciously than lifestyle modification and drug therapy. Interestingly, adiponectin which has a protective role in folliculogenesis, was shown to be significantly increased 12 months following VSG in one prospective study [68]. This indicates that the change to normal ovulation in women with PCOS following surgery may partly be attributed to restoring normal adipokine secretion [84]. Alternatively, it could be explained by the reversal of hyperinsulinemia and hyperandrogenism [25].

Fewer studies have investigated bariatric surgery's impact on fertility markers in PCOS other than menstrual regularity. Investigation of the impact on AMH levels, a marker of ovarian reserve, has given conflicting results. One prospective cohort study found significantly increased AMH 6 months post RYGB or VSG [85], whilst others found significantly decreased levels six [86] and twelve [87] months post-surgery. AMH levels were significantly lower at baseline in the study, which found an increase (1.46 ± 0.81 ng/ml compared to 4.68 and 5.44 ± 3.94 ng/ml). This indicates that findings may be partially attributed to inherent cohort characteristics. Data surrounding the effect of other weight loss strategies, including lifestyle, on AMH levels in women with PCOS is similarly conflicting. Some studies suggest that weight loss has no effect [88] whilst others suggest it decreases AMH levels [89,90]. Importantly, AMH levels strongly correlate with the chances of success in in-vitro fertilisation (IVF) [91]. Therefore, any reduction following surgery may have implications for the chances of successful contraception with assisted reproductive technology (ART). In addition to AMH, there have also been contrasting reports of the effect of surgery on ovarian volume. This has been shown to decrease twelve months post-surgery [72] or show no significant change at six months [66] and an average 1.9 ± 0.3 years post-surgery [77]. However, studies that showed no significant change did show numerical reductions in volume, indicating that there may have been some resolution of ovarian morphology in these cohorts.

Regardless of its impact on fertility markers, bariatric surgery has significantly improved pregnancy rates in previously nulliparous women with obesity in several prospective cohort studies [83,92,93]. One report identified a correlation between time since PCOS diagnosis and resolution of PCOS phenotype after bariatric surgery, but no association with age [83].

Given the above findings that it significantly ameliorates insulin resistance and hypertension, it seems likely that surgery might prevent obstetric complications such as gestational diabetes and pregnancy-induced hypertension in women with PCOS and obesity. However, very few studies have investigated the impact of surgery on pregnancy outcomes specifically in women with PCOS. One such retrospective case-control study showed a significant incidence of early-term pregnancy but no significant change in low birth weight compared to controls in pregnancies within three years of bariatric surgery [93]. Additionally, it demonstrated an increased rate of normal vaginal delivery compared to Caesarean sections in women with PCOS. In another prospective study, the rate of live births was similar between women treated for obesity and PCOS and those treated for obesity without PCOS [92]. Whilst the difference in incidence of low birth weight between groups did not reach significance, there was a numerical difference (17.6 % compared to 3.7 %). These findings indicate that pregnancies following bariatric surgery may be complicated by low birth weight and early delivery. To determine any relationship, more data are needed to directly compare pregnancy outcomes following bariatric surgery and alternative medical treatments in women with PCOS. A recent systematic review and meta-analysis of 33 studies investigating pregnancy outcomes in women without PCOS found that the risk of perinatal mortality (OR 1.38; 95 % CI 1.03–1.85), preterm birth (OR 1.57; 95 % CI 1.38–1.79) and small for gestational age (OR 2.72; 95 % CI 2.32–3.20) was increased following bariatric surgery [94]. This suggests that births complicated by low birth weight following bariatric surgery may not be isolated to women with PCOS but also the wider population undergoing surgery.

To our knowledge, no studies have directly assessed the impact of bariatric surgery on reproductive outcomes following ART. Currently, preferred ART methods in PCOS include artificial intrauterine insemination, IVF, and intracytoplasmic sperm injection (ICSI) [95]. In one cohort, 25 % of previously infertile women conceived using ART within three years of surgery [93]. Similarly, three women from another cohort could conceive six months after IVF surgery, having previously been unable to conceive with ART [63]. These findings suggest that bariatric surgery may improve the efficacy of ART in women with obesity and PCOS. However, the evidence remains anecdotal and randomised controlled trials are required to corroborate these findings. In women without PCOS, existing studies have indicated that IVF is safe [96] and may be more effective following bariatric surgery. A large retrospective case-control study in 153 women undergoing IVF after bariatric surgery found that women had similar pregnancy rates and live birth rates in the first cycle compared to controls with the same BMI at the time of treatment [97]. These findings were replicated in several smaller retrospective cohort studies [98–101]. Together, this suggests that bariatric surgery may improve the chances of successful conception after ART by reversing the effect of obesity.

There are no head-to-head RCTs to support the superiority of one operation over another for the purpose of improved fertility. In the first year after any surgical procedure, most women should lose enough weight to restart ovulation and to reduce the complications of a future pregnancy. Collectively, the available data suggest that RYGB is superior to VSG for people with T2DM and the metabolic syndrome [102]. The BYBAND Sleeve RCT will soon inform us about the most effective and cost-effective procedure for people with obesity [103]. Insulin sensitisers like metformin and obesity pharmacotherapy can be given together with surgery, in order to enhance its effects [104,105]. Whether the combination of pharmacotherapy plus surgery leads to superior outcomes in this cohort of women is unknown. What is probably more important than the type of surgery is the timing of conception. The current evidence regarding the risks of early pregnancies after surgery (i.e. within the first year) are conflicting, especially when it comes to the incidence of babies small for gestational age [106]. The advice given to most women is to delay pregnancy for at least one year after surgery [106]. This is the time point weight stability is reached, making the recommendation reasonable. During pregnancy mothers and babies should be monitored in a unit with the relevant expertise.

4. Mechanisms underlying effects of effects of bariatric surgery on PCOS

Chronic menstrual irregularities in PCOS are correlated with hyperinsulinaemia, which stimulates secretion of excess androgens from ovarian theca cells [107]. In a cross-sectional study of patients with PCOS and non-PCOS controls, there was a correlation between the severity of IR, increased LH/FSH ratio and androgen levels, and the degree of disturbance in menstrual function [108]. Given that the significant weight loss achieved following bariatric surgery has been shown to ameliorate insulin resistance [65,71,85,92] this effect might partially explain the improvement in menstrual regularity demonstrated post-surgery. Weight loss following surgery may also reverse hyperandrogenism in PCOS by increasing SHBG levels and hence levels of circulating androgens. As well as in several prospective cohort studies [71,72], this effect was demonstrated in a systematic review and meta-analysis of fifty-four studies, which found a significant decrease in total testosterone and a significant increase in SHBG in women following surgery [109]. It should be noted that there was significant heterogeneity in these studies, which also investigated the effect of surgery in men. Regardless, it seems likely that the positive effect of surgery on menstrual function is a direct effect of the amelioration of hyperandrogenism.

5. Conclusions

In this narrative review, we explored the evidence surrounding the use of bariatric surgery in treating women with PCOS. The lack of randomised controlled trials in this area is striking and highlights this important gap in our knowledge. However, existing studies suggest that bariatric surgery is highly beneficial for treating the metabolic sequelae and reproductive dysfunction in women with PCOS and obesity. Currently, evidence surrounding the efficacy of bariatric surgery in reducing pregnancy complications and improving the success of ART is lacking. Trials in this field could compare the impact and safety of bariatric surgery vs. modern obesity pharmacotherapy on ovulation and eventually on the incidence of pregnancy in women with PCOS. Deep phenotyping of these women, prospective follow-up and response to treatment are some of the vital pieces of information needed to enable the stratification of this heterogeneous population upon presentation and personalised therapy using a precision medicine approach.

CRediT authorship contribution statement

SS and AM were responsible for the conception of the work. SS and CW were responsible for data analysis, interpretation, and article drafting. AM performed the critical revision of the article and final approval for publication.

Declaration of competing interest

Alexander D. Miras has received honoraria for educational events from Novo Nordisk, Astra Zeneca, Currax, Boehringer Ingelheim, Screen Health and GI dynamics.

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