

Bariatric Surgery in the Management of Adolescent and Adult Obese Patients with Polycystic Ovarian Syndrome

Firass Abiad¹, Hussein A. Abbas^{1,2}, Caroline Hamadi³ and Ghina Ghazeeri^{3*}

¹Department of General Surgery, American University of Beirut Medical Center, Beirut, Lebanon

²Medicine Department, American University of Beirut Medical Center Beirut, Lebanon

³Department of Obstetrics and Gynecology, American University of Beirut Medical Center, Beirut, Lebanon

Abstract

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. Obesity in PCOS patients is associated with significant morbidities. Obesity in PCOS abrogates the menstrual cycle and fertility, and can independently increase the risk of metabolic syndrome and the latter's long-term cardiac and health complications. The degree of obesity as reflected by the body mass index (BMI) can have a significant impact on the associated risk with its morbidities. Thus, weight reduction is highly encouraged for obese patients with PCOS as early as in adolescence to avoid long-term complications. Conservative methods of weight reduction, such as diet and lifestyle modifications, have been used in PCOS patients but their effects can be short-lived, especially in the morbidly obese populations. To that end, bariatric surgery has been proposed as an alternative modality for the treatment of obese patients with PCOS in order to decrease the risk of metabolic syndrome. Nevertheless, bariatric surgery utilization in the adolescent population of PCOS patients is still not well evaluated. Bariatric surgery is considered in patients with very high BMI levels and those patients who had multiple failed attempts of weight reduction using more conservative methods. In this review, we focused on the metabolic manifestations of PCOS and discussed studies highlighting the usage of bariatric surgery as an attempt to reduce weight in obese patients with PCOS with primary focus on the adolescent population.

Keywords: Bariatric surgery; Polycystic ovarian syndrome; Obesity; Metabolic syndrome; Adolescent

Synopsis: Bariatric surgery should be entertained in qualified patients with PCOS who desire weight reduction and amelioration of long term complications where conservative measures have failed.

Introduction

Polycystic ovarian syndrome (PCOS) is the commonest endocrine disorder in reproductive age women, with an estimated worldwide prevalence reaching a staggering 15% [1]. The Rotterdam consensus criteria are used to diagnose PCOS and require two of the following: (1) biochemical or clinical evidence of androgen excess, (2) chronic oligo-ovulation or anovulation, (3) polycystic ovaries on an ultrasound examination, and the exclusion of other known disorders [2]. Although not part of the diagnostic criteria, patients with PCOS are at an increased risk of developing several metabolic disorders including impaired glucose tolerance, type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, hypertension, and insulin resistance [1,3]. Signs and symptoms of PCOS, primarily obesity and menstrual abnormalities, are manifested as early as in adolescent years. Hence, it is warranted to identify treatment modalities that can be initiated as early as adolescence to alleviate the long-term complications of PCOS.

Since obesity is a major contributor to the metabolic syndrome and other biological pathways, it is prudent to encourage women with PCOS to lose weight. According to the PCOS/Troglitazone Study Group, risk of metabolic syndrome in PCOS women is more evident with BMI above 27 kg/m² suggesting that the degree of overweight and obesity should factor into the risk of developing complications [4]. However, conservative weight reduction methods are not always successful. Bariatric surgery is as an alternative method to achieve faster and more stable weight loss in obese individuals. In this review, we will examine the contribution of obesity to the metabolic syndrome, cardiovascular disease and other metabolic abnormalities in PCOS patients. Further, we will discuss the utilization of bariatric surgery as weight reduction approach in PCOS patients as early as in adolescence.

Obesity in PCOS

Obesity in the general population: Owing to sedentary lifestyle, high-calorie diet and genetic factors, more than 2 billion people are considered overweight or obese [5,6]. Further, approximately 4% of adolescents and children between the age of 2 and 19 years are obese [5,6]. Conservative weight reduction methods, such as diet and life style modifications, are important in management of obesity and are associated with an average loss of 10 kilograms of body weight, which can be significantly lower than the target weight reduction [7,8]. Alternatively, bariatric surgery is superior to conservative methods and medical therapy for weight loss management in the general population [9-12]. Noteworthy, the extent of weight loss after undergoing bariatric surgery depends on the extent of pre-intervention overweight. The utilization of bariatric surgery in obese PCOS patients is gaining momentum.

Prevalence and pathogenesis of obesity in PCOS women: Stein and Leventhal (1935) noted a strong association between polycystic ovaries and obesity [13]. Today, more than 25% and 35% of overweight and morbidly obese women, respectively, have PCOS, compared to only 5% of the lean women population [14]. The prevalence of overweight and obesity in women with PCOS varies between 35% and 80% depending on the population under study [15-17]. In fact, obesity in post-adolescence was predictive for the development of PCOS [18].

***Corresponding author:** Ghina Ghazeeri, Associate Professor of Clinical Obstetrics and Gynecology, American University of Beirut Medical Center, PO Box 11-0236, Riad El-Solh 1107 2020, Beirut, Lebanon, Tel: 00961-3-788624; Fax: 00961-1-370829; E-mail: gg02@aub.edu.lb

Received February 16, 2016; **Accepted** March 09, 2016; **Published** March 12, 2016

Citation: Abiad F, Abbas HA, Hamadi C, Ghazeeri G (2016) Bariatric Surgery in the Management of Adolescent and Adult Obese Patients with Polycystic Ovarian Syndrome. J Obes Weight Loss Ther 6: 303. doi:10.4172/2165-7904.1000303

Copyright: © 2016 Abiad F, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Further, PCOS could have been prevented in at least 30% of patients if the patients had normal body weight [19].

The development of obesity in PCOS patients is proposed to start as early as during embryogenesis [20]. Specifically, hyperandrogenism induces visceral fat deposition, and the latter positively feedback into androgen hyper-secretion creating a vicious cycle [20,21]. Some genetic alterations have also been implicated in obesity and PCOS. For instance, a single nucleotide polymorphism in *FTO* increases the risk of obesity and has been associated with obese, but not lean body weight, women with PCOS [22]. Hence, obesity in PCOS can be initiated as early as during fetal life and is primarily related to hyperandrogenism via a positive feedback loop mechanism.

Obesity exacerbates PCOS metabolic comorbidities, and impairs several endocrine and metabolic pathways. For instance, the hypothalamic-pituitary-ovarian axis can be altered by several mechanisms in obese women with PCOS [23]. Compared to women with PCOS who have lean body weight, obese women with PCOS have abrogated inflammatory and growth factor pathways that can lead to increased insulin resistance and higher levels of androgens [24,25]. Sex hormone binding globulin (SHBG) levels are inversely correlated with body mass index (BMI) [26]. Thus, obesity induce major hormonal changes that can exacerbate or even induce metabolic abnormalities. Management of obesity can possibly hinder the progression of these disorders or even prevent it.

Effects of obesity on metabolic abnormalities in PCOS: The occurrence of metabolic syndrome in PCOS women has been of interest to endocrinologists and gynecologists. Metabolic syndrome is defined as a constellation of central obesity and at least two of the following: low HDL-C, hypertension, high triglycerides and high fasting blood glucose [27]. Patients with metabolic syndrome have an increased risk of mortality due to cardiovascular disease and T2DM. Women with PCOS are at two to four fold increased risk of developing metabolic syndrome compared to the general women population at all age groups and independently of body weight, and are subsequently at an increased risk of developing cardiovascular diseases [28,29]. Interestingly, there are several similarities between women with metabolic syndrome and women with PCOS, including reproductive problems, insulin resistance and obesity [30].

The origin of metabolic syndrome in PCOS women has not been well elucidated. However, obesity has been entertained as an underlying factor in instigating metabolic syndrome in women with PCOS [30]. Faloia et al. found that 37% of the overweight or obese women with PCOS exhibited metabolic syndrome, compared to none of the PCOS women with lean body weight [31]. Another study found that metabolic syndrome is not manifested in women with PCOS with a BMI less than 27 Kg/m² neither in women having normal waist circumference [4]. On the other hand, other studies did not find obesity as a risk factor for developing metabolic syndrome in PCOS women [32,33]. The variation in these results could be attributed to the lack of consensus in defining the metabolic syndrome. Noteworthy, other metabolic disorders of PCOS manifest as early as in adolescence and include menstrual cycle irregularities, infertility, dyslipidemia, Insulin resistance, acne, weight gain, hirsutism and mental health disturbances [30,34,35]. Because insulin resistance, hyperandrogenism and obesity can alter lipid metabolism, it is not surprising that dyslipidemia is one of the most common metabolic abnormalities in women with PCOS [28]. Approximately 10% and 30% of women with PCOS have T2DM or impaired glucose tolerance, respectively [23]. Because obesity underlies significant comorbidities of PCOS women, management of obesity as

early as possible can be an effective measure to prevent and treat these manifestations.

Treatment of obesity in PCOS

Significance of weight loss in obese women with PCOS: Weight loss is a first line management in PCOS women who are obese [18]. To prevent the consequences of metabolic disorders in PCOS women, treatment should be initiated as early as diagnosis. Most importantly, preventing metabolic disorders by encouraging weight loss would be highly beneficial as early as in adolescence [21]. Further, because almost 80% of overweight adolescents remain overweight as adults, it is warranted to have weight reduction interventions as soon as possible [36].

Adolescents with PCOS who lose weight have fewer PCOS complications. For instance, weight loss can improve fertility rate via changes in SHBG levels and reduction of LH pulse amplitude, both mechanisms which lead to decreased androgens [37]. Not surprisingly, weight loss is the first line management in obese women who are infertile [38]. Further, improved response to fertility treatment is evident in PCOS women who lose weight compared to obese [39]. A 5% decrease in body weight can restore menses, and reduce insulin resistance and testosterone levels in obese women with PCOS [40-42]. Losing 10% of initial body weight in obese PCOS women improves insulin resistance and metabolic disorders [43]. These findings strongly implicate the importance of weight loss in obese women with PCOS.

Conventional treatment of obesity in PCOS: Lifestyle modifications including diet control and regular exercise to achieve weight loss are widely used methods to attain weight loss. However, the effects are rarely durable and success rates are low. To that end, medical intervention for weight loss has been entertained. Metformin decreased BMI in obese women with PCOS and improved fertility [44]. Other medications implicated in weight loss of PCOS patients who are obese include orlistate, sibutramine and rimonabant [18,45,46]. However, the effectiveness of these drugs varied among studies and significant side effects to the medications emerged [18]. To that end, identifying a more durable approach for weight loss in PCOS is highly warranted.

Bariatric surgery

Bariatric surgery as an alternative approach for weight loss: Lifestyle modifications and medical therapy are most of the times unsuccessful in achieving significant weight loss. In fact, more than 90% of obese people who used conservative treatment to attain weight loss return to their original weight eventually [47]. Surgical therapy for weight loss is an alternative durable approach. Bariatric surgery is considered the most effective weight reduction method, and has long-term survival benefit [48,49]. Not only bariatric surgery reduces the cardiovascular and diabetes complications of obesity, but it also improves fertility [50]. More than 70% of anovulatory women achieved normal ovulatory cycles post bariatric surgery [51]. To note, although more studies have been conducted on the adult population, bariatric surgery was demonstrated to be effective in both adults and adolescents women with PCOS [52-54].

Currently, there are no predictive guidelines of pre-surgical psychological assessments for bariatric surgery in PCOS [55]. Nevertheless, similar to non-PCOS patients, obese women with PCOS who plan to undergo bariatric surgery for weight reduction are encouraged to also undergo neuropsychological assessment such as detailed clinical interview, evaluations for objective mood and brief cognitive function, reasoning for seeking surgery, and certain

personality measurement tools such as the commonly used Minnesota Multiphasic Personality Inventory-2-RF.

Types of bariatric surgery: The most commonly performed bariatric procedures performed include adjustable gastric banding (AGB), Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG). AGB utilizes a saline-filled silicon band that is placed near the esophageal junction around the stomach. The RYGB is a modification of the original gastric bypass first done by Mason and Ito but has a different approach in order to reduce bile reflux. In VSG at least 80% of the stomach is removed. The effectiveness of each of these methods varies among studies and populations under study. However, AGB and RYGB are among the most widely used methods nowadays [56]. Noteworthy, assisted robotic approach in gastric bypass procedures are commonly used because of better visualization, reduced morbidity, and improved accuracy and positioning. Detailed reviews comparing these three methods in adolescents and adults are available in reference list [53,56].

Bariatric surgery in adolescence: The rate of bariatric surgery in the adolescent population has significantly increased in the last two decades [57,58]. Eligibility criteria are not well defined but necessitates that adolescents have a BMI above 40 Kg/m². The American Academy of Pediatrics provided the following guidelines for adolescents under consideration for weight loss surgery: (1) patients should have failed 6 or more months of organized attempts at Weight management; (2) the patient should have attained physiological or skeletal maturity which usually occurs at age 13 years for girls and 15 years for boys; (3) patients should be severely obese with BMI exceeding 40 Kg/m² with severe obesity-related problems, or have a BMI > 50 Kg/m² with lesser obesity-related problems [59]. Further, adolescents are encouraged to abstain from getting pregnant for 1 year after surgery. In a study comparing 716 adults and 24 adolescent patients who underwent gastric banding in the US, there were no significant differences between the preoperative BMI, operating room time, estimated blood losses and length of hospital stay between the adult and the adolescent populations [60]. Among the adolescent patients, the average excess weight loss ranged from 22% to 42% at 3 and 36 months post follow-up, respectively [60]. Around 30% of patients had complications and included staple line leak, pouch enlargement in adolescents (25%), hematomas and pneumonia [60,61]. The definite significance of early bariatric surgery for obese women on overall survival is still under investigation. Nevertheless, bariatric surgery in adolescence ameliorates diabetes, insulin resistance, sleep apnea, obesity and dyslipidemia as discussed further below [54,57,62, 63]. Some work suggests that it is safer to conduct bariatric surgery in adolescence than in adulthood [64].

Benefits of bariatric surgery in adolescents

Weight loss: Among the studies in the adolescent population, the Pediatric Bariatric Study Group and other researchers demonstrated the effectiveness of RYGB and AGB in weight reduction, and their results are correlated with pre-operative BMI level [65-67]. Adolescents undergoing bariatric surgery lose 50% of their weight [53]. AGB is probably a better approach for weight loss in a 5-year follow-up analysis, as well as in inducing remission of the metabolic syndrome [67,68].

Diabetes: Adult overweight and obese patients who have type 2 diabetes mellitus and underwent bariatric surgery have a significantly better overall remission rates compared to those patients who follow conventional, non-surgical weight loss regimens [11]. Fewer studies have been conducted in the adolescent population to that end. RYGB improved the diabetes profile (fasting insulin and fasting glucose) in

obese adolescents as early as 6 months post-surgery although many patients were still obese [65,66,69]. The effectiveness of diabetes reduction is influenced by the duration and severity of diabetes preoperatively, and the age of individual at the time of surgery [70].

Cardiovascular disease risk reduction: Because bariatric surgery in adolescents is relatively a recent procedure, only few studies have been done to assess the cardiovascular disease outcome post-surgery. However, it is apparent that bariatric surgery, mainly RYGB, improves systolic and diastolic blood pressure, ameliorates hypertension, enhances the lipid profile including reduction in total cholesterol and increasing HDL, and reduces left ventricular mass [65,66,69,71].

Reproductive improvement: As discussed earlier, weight loss is the first line of management for obese women who are infertile [57]. Not only obesity increases the risk of infertility and PCOS, it poses significant obstetrical risk including gestational diabetes and hypertension, Caesarian delivery, and large for gestational age babies, among others. Due to the physiological and psychological improvements, higher pregnancy rates and fewer obstetrical complications were reported following RYGB in obese adolescents females [57,63,69,72]. Young women choosing to get pregnant after bariatric surgery will expect improvement in both maternal health and fetal outcomes [72,73]. Yet, systematic studies have not yet been conducted to study the maternal and fetal outcomes of adolescents post bariatric surgery. It is still controversial whether bariatric surgery increases Caesarian section deliveries [73,74]. Also, it is possible that bariatric surgery may induce nutritional deficiencies in pregnant women and increase the risk for small for gestational age babies [73]. Adolescent females undergoing bariatric surgery may have higher rates of unintended pregnancies compared to the national average [72]. Hence, it is reasonable to offer appropriate birth control measures for these patients to decrease teen pregnancy. However, obesity may decrease the effectiveness of hormonal contraceptives in women [75].

Bariatric surgery in PCOS management

Rationale for surgery: Because obesity in PCOS may be the culprit in developing metabolic disorders, it is not surprising that surgical approach for weight reduction in PCOS has been investigated in several reports. However, an intervention *per se* may not be sufficient to ameliorate the complications. What is also needed is an *early* intervention. It was found that in both the US and UK, 13% of women of childbearing age who undergo bariatric surgery has PCOS, and subfertility is the main underlying reason for undergoing the procedure [76,77]. Yet, studies that aim at assessing the efficacy of bariatric surgery in obese PCOS women are scarce. Interestingly, obese rats with PCOS have improved metabolic and reproductive outcomes after undergoing bariatric surgery [78].

Bariatric surgery is efficacious in ameliorating complications of obesity in PCOS women

One of the first studies assessing the surgical intervention for weight reduction in PCOS women came from Eid et al. who conducted a retrospective analysis on adult obese PCOS women who underwent RYGB. The authors found significant improvement in hirsutism, menstrual dysfunction and decreased rates of common comorbidities such as diabetes, dyslipidemia and hypertension [79]. Further, 5 women in their study who were declared as infertile were able to conceive spontaneously after the procedure [79]. A longitudinal prospective non-randomized clinical study was conducted on 36 obese women, 17 of which had PCOS, undergoing bariatric surgery. Eleven

and 4 of the PCOS women underwent biliopancreatic diversion and laparoscopic bypass, respectively [14]. All women with PCOS had significant weight reduction (mean weight loss of 41 kg), decreased hirsutism score, decreased levels of testosterone, androstenedione, and dehydroepiandrosterone sulfate, and improved indexes of insulin resistance [14]. These findings were translated clinically by achieving normal menses and ovulatory cycles, and improvement of hypertension and diabetes post-surgery [14]. These initial studies were also recently reproduced by Stroh et al. in Germany and Gomez-Meade et al. in the US [80,81]. While the study by Stroh et al., was conducted on 3 patients with PCOS only, Gomez-Meade et al. took a retrospective approach to identify 389 adult women with PCOS who underwent RYGB between 2001 and 2009. The conclusions were similar among all studies where there was a significant reduction in BMI and metabolic profile in adult obese patients who underwent PCOS. Much fewer studies were conducted in the adolescent population.

Concluding Remarks

PCOS is the commonest endocrinological disorder in women of childbearing age. Further, obesity is strongly associated with PCOS and can significantly contribute to the metabolic disorders associated with PCOS including the metabolic syndrome, anovulation, infertility, dyslipidemia and hypertension. Hence, it is warranted to implement stringent weight reduction methods for patients with PCOS as an attempt to ameliorate complications. Further, since PCOS is a disease that can manifest as early as in adolescent years, and since most of the complications are better prevented at an earlier stage, weight reduction methods in adolescence may provide better results. However, conventional, non-surgical methods in weight reduction have limited results. For PCOS patients who are unable to manage their weight with conservative management and metabolic manifestations of PCOS are exacerbated by obesity, bariatric surgery should be discussed. Bariatric surgery is the most efficacious methods in managing morbid obesity in adolescent and adult population and it also improves survival [60]. To that end, it is warranted to attempt bariatric surgery in obese adolescents with PCOS. In fact, recent evidence suggests that even moderately overweight and non-morbidly obese women can benefit from bariatric surgery [82]. Although guidelines for bariatric surgery in adolescent women with PCOS are not established yet, results of bariatric surgery in adolescents have been promising. Yet, bariatric surgery should be the last possible solutions for weight reduction after multiple failed attempts of conservative weight reduction methods. It is crucial to have randomized clinical trials to assess the benefits and risks of bariatric surgery in this population.

References

1. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, et al. (2012) Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril* 97: 28-38.
2. Rotterdam EA-SPCWG (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and sterility* 81: 19-25.
3. Ehrmann DA, Kasza K, Azziz R, Legro RS, Ghazzi MN; PCOS/Trogilazone Study Group (2005) Effects of race and family history of type 2 diabetes on metabolic status of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 90: 66-71.
4. Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, et al. (2006) Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 91: 48-53.
5. Grundy SM (2008) Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol* 28: 629-636.
6. Kann L, Kinchen S, Shanklin SL, Flint KH, Kawkins J, et al. (2014) Youth risk behavior surveillance—United States, 2013. *MMWR Suppl* 63: 1-168.
7. Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, et al. (2005) Randomized trial of lifestyle modification and pharmacotherapy for obesity. *N Engl J Med* 353: 2111-2120.
8. Lass N, Kleber M, Winkel K, Wunsch R, Reinehr T (2011) Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima-media thickness in obese adolescent girls. *J Clin Endocrinol Metab* 96: 3533-3540.
9. Colquitt JL, Picot J, Loveman E, Clegg AJ (2009) Surgery for obesity. *The Cochrane database of systematic reviews* CD003641.
10. Maggard-Gibbons M, Maglione M, Livhits M, Ewing B, Maher AR, et al. (2013) Bariatric surgery for weight loss and glycemic control in nonmorbidly obese adults with diabetes: a systematic review. *JAMA* 309: 2250-2261.
11. Ribaric G, Buchwald JN, McGlennon TW (2014) Diabetes and weight in comparative studies of bariatric surgery vs conventional medical therapy: a systematic review and meta-analysis. *Obes Surg* 24: 437-455.
12. Nidhi R, Padmalatha V, Nagarathna R, Amritanshu R (2011) Prevalence of polycystic ovarian syndrome in Indian adolescents. *J Pediatr Adolesc Gynecol* 24: 223-227.
13. Stein I, Leventhal M (1935) Amenorrhea associated with bilateral polycystic ovaries. *American journal of obstetrics and gynecology* 181-191.
14. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millan JL (2005) The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *The Journal of clinical endocrinology and metabolism* 90: 6364-6369.
15. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, et al. (2004) Androgen excess in women: experience with over 1000 consecutive patients. *J Clin Endocrinol Metab* 89: 453-462.
16. Cupisti S, Kajaia N, Dittrich R, Duezleni H, M WB, et al. (2008) Body mass index and ovarian function are associated with endocrine and metabolic abnormalities in women with hyperandrogenic syndrome. *Eur J Endocrinol* 158: 711-719.
17. Glinborg D, Henriksen JE, Andersen M, Hagen C, Hangaard J, et al. (2004) Prevalence of endocrine diseases and abnormal glucose tolerance tests in 340 Caucasian premenopausal women with hirsutism as the referral diagnosis. *Fertility and sterility* 82: 1570-1579.
18. Vrbikova J, Hainer V (2009) Obesity and polycystic ovary syndrome. *Obes Facts* 2: 26-35.
19. Laitinen J, Taponen S, Martikainen H, Pouta A, Millwood I, et al. (2003) Body size from birth to adulthood as a predictor of self-reported polycystic ovary syndrome symptoms. *International journal of obesity* 27: 710-715.
20. Escobar-Morreale HF, San Millán JL (2007) Abdominal adiposity and the polycystic ovary syndrome. *Trends Endocrinol Metab* 18: 266-272.
21. Escobar-Morreale HF (2012) Surgical management of metabolic dysfunction in PCOS. *Steroids* 77: 312-316.
22. Wählén K, Sjölin E, Hoffstedt J (2008) The common rs9939609 gene variant of the fat mass- and obesity-associated gene FTO is related to fat cell lipolysis. *J Lipid Res* 49: 607-611.
23. Legro RS (2012) Obesity and PCOS: implications for diagnosis and treatment. *Semin Reprod Med* 30: 496-506.
24. Repaci A, Gambineri A, Pasquali R (2011) The role of low-grade inflammation in the polycystic ovary syndrome. *Mol Cell Endocrinol* 335: 30-41.
25. Ciampelli M, Fulghesu AM, Cucinelli F, Pavone V, Ronisvalle E, et al. (1999) Impact of insulin and body mass index on metabolic and endocrine variables in polycystic ovary syndrome. *Metabolism* 48: 167-172.
26. Glass AR, Burman KD, Dahms WT, Boehm TM (1981) Endocrine function in human obesity. *Metabolism* 30: 89-104.
27. Alberti KG, Zimmet P, Shaw J (2006) metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetic medicine* 23: 469-480.
28. Cussons AJ, Stuckey BG, Watts GF (2007) Metabolic syndrome and cardiometabolic risk in PCOS. *Curr Diab Rep* 7: 66-73.

29. Essah PA, Nestler JE (2006) Metabolic syndrome in women with polycystic ovary syndrome. *Fertil Steril* 86 Suppl 1: S18-19.
30. Caserta D, Adducchio G, Picchia S, Ralli E, Matteucci E, et al. (2014) Metabolic syndrome and polycystic ovary syndrome: an intriguing overlapping. *Gynecological endocrinology* 30: 397-402
31. Faloià E, Canibus P, Gatti C, Frezza F, Santangelo M, et al. (2004) Body composition, fat distribution and metabolic characteristics in lean and obese women with polycystic ovary syndrome. *Journal of endocrinological investigation* 27: 424-429.
32. Apridonidze T, Essah PA, Luomo MJ, Nestler JE (2005) Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 90: 1929-1935.
33. Azziz R (2006) How prevalent is metabolic syndrome in women with polycystic ovary syndrome? *Nat Clin Pract Endocrinol Metab* 2: 132-133.
34. Awwad JT, Farra C, Mitri F, Abdallah MA, Jaoudeh MA, et al. (2013) Split daily recombinant human LH dose in hypogonadotrophic hypogonadism: a nonrandomized controlled pilot study. *Reproductive biomedicine online* 26: 88-92.
35. Moran LJ, Lombard CB, Lim S, Noakes M, Teede HJ (2010) Polycystic ovary syndrome and weight management. *Womens Health (Lond Engl)* 6: 271-283.
36. Freedman DS, Khan LK, Dietz WH, Srinivasan SR, Berenson GS (2001) Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. *Pediatrics* 108: 712-718.
37. Holte J, Bergh T, Berne C, Wide L, Lithell H (1995) Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome. *The Journal of clinical endocrinology and metabolism* 80: 2586-2593.
38. KC A, ME L, DB S (2009) Obesity and reproductive functioning: psychiatric considerations. *Primary Psychiatry* 16: 35-40.
39. Koulouri O, Conway GS (2008) A systematic review of commonly used medical treatments for hirsutism in women. *Clin Endocrinol (Oxf)* 68: 800-805.
40. Nissen SE, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356: 2457-2471.
41. Huber-Buchholz MM, Carey DG, Norman RJ (1999) Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab* 84: 1470-1474.
42. Gambineri A, Pelusi C, Genghini S, Morselli-Labate AM, Cacciari M, et al. (2004) Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome. *Clinical endocrinology* 60: 241-249.
43. Arslanian SA, Lewy VD, Danadian K (2001) Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and beta-cell dysfunction and risk of cardiovascular disease. *The Journal of clinical endocrinology and metabolism* 86: 66-71.
44. Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ (1994) Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism* 43: 647-654.
45. Cho LW, Kilpatrick ES, Keevil BG, Coady AM, Atkin SL (2009) Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary syndrome. *Clinical endocrinology* 70: 233-237.
46. Lindholm A, Bixo M, Bjorn I, Wolner-Hanssen P, Eliasson M, et al. (2008) Effect of sibutramine on weight reduction in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Fertility and sterility* 89: 1221-1228.
47. Weigle DS, Brunzell JD (1990) Assessment of energy expenditure in ambulatory reduced-obese subjects by the techniques of weight stabilization and exogenous weight replacement. *International journal of obesity* 14 Suppl 1: 69-77
48. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, et al. (2007) Long-term mortality after gastric bypass surgery. *N Engl J Med* 357: 753-761.
49. Buchwald H, Estok R, Fahrbach K, Banel D, Sledge I (2007) Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery* 142: 621-632.
50. Merrell J, Lavery M, Ashton K, Heinberg L (2014) Depression and infertility in women seeking bariatric surgery. *Surgery for obesity and related diseases* 10: 132-137.
51. Teitelman M, Grotegut CA, Williams NN, Lewis JD (2006) The impact of bariatric surgery on menstrual patterns. *Obes Surg* 16: 1457-1463.
52. Abu-Abeid S, Gavert N, Klausner JM, Szold A (2003) Bariatric surgery in adolescence. *J Pediatr Surg* 38: 1379-1382.
53. Stefater MA, Jenkins T, Inge TH (2013) Bariatric surgery for adolescents. *Pediatr Diabetes* 14: 1-12.
54. Sugerman HJ, Sugerman EL, DeMaria EJ, Kellum JM, Kennedy C, et al. (2003) Bariatric surgery for severely obese adolescents. *J Gastrointest Surg* 7: 102-107.
55. Votruba K, Marshall D, Finks J, Giordani B (2014) Neuropsychological factors and bariatric surgery: a review. *Curr Psychiatry Rep* 16: 448.
56. Stefater MA, Wilson-Perez HE, Chambers AP, Sandoval DA, Seeley RJ (2012) All bariatric surgeries are not created equal: insights from mechanistic comparisons. *Endocrine reviews* 33: 595-622.
57. Miller RJ, Xanthakos SA, Hillard PJ, Inge TH (2007) Bariatric surgery and adolescent gynecology. *Curr Opin Obstet Gynecol* 19: 427-433.
58. Apovian CM, Baker C, Ludwig DS, Hoppin AG, Hsu G, et al. (2005) Best practice guidelines in pediatric/adolescent weight loss surgery. *Obes Res* 13: 274-282.
59. Inge TH, Krebs NF, Garcia VF, Skelton JA, Guice KS, et al. (2004) Bariatric surgery for severely overweight adolescents: concerns and recommendations. *Pediatrics* 114: 217-223.
60. Dillard BE 3rd, Gorodner V, Galvani C, Holterman M, Browne A, et al. (2007) Initial experience with the adjustable gastric band in morbidly obese US adolescents and recommendations for further investigation. *J Pediatr Gastroenterol Nutr* 45: 240-246.
61. Nocca D, Nedelcu M, Nedelcu A, Noel P, Leger P, et al. (2014) Laparoscopic sleeve gastrectomy for late adolescent population. *Obes Surg* 24: 861-865.
62. Kalra M, Inge T, Garcia V, Daniels S, Lawson L, et al. (2005) Obstructive sleep apnea in extremely overweight adolescents undergoing bariatric surgery. *Obesity research* 13: 1175-1179.
63. Strauss RS, Bradley LJ, Brolin RE (2001) Gastric bypass surgery in adolescents with morbid obesity. *J Pediatr* 138: 499-504.
64. Tsai WS, Inge TH, Burd RS (2007) Bariatric surgery in adolescents: recent national trends in use and in-hospital outcome. *Archives of pediatrics & adolescent medicine* 161: 217-221.
65. Inge TH, Jenkins TM, Zeller M, Dolan L, Daniels SR, et al. (2010) Baseline BMI is a strong predictor of nadir BMI after adolescent gastric bypass. *The Journal of paediatrics* 156: 103-108e
66. Lawson ML, Kirk S, Mitchell T, Chen MK, Loux TJ, et al. (2006) One-year outcomes of Roux-en-Y gastric bypass for morbidly obese adolescents: a multicenter study from the Pediatric Bariatric Study Group. *Journal of pediatric surgery* 41: 137-143
67. O'Brien PE, Sawyer SM, Laurie C, Brown WA, Skinner S, et al. (2010) Laparoscopic adjustable gastric banding in severely obese adolescents: a randomized trial. *JAMA* 303: 519-526.
68. Franco JV, Ruiz PA, Palermo M, Gagner M (2011) A review of studies comparing three laparoscopic procedures in bariatric surgery: sleeve gastrectomy, Roux-en-Y gastric bypass and adjustable gastric banding. *Obesity surgery* 21: 1458-1468.
69. Inge TH, Miyano G, Bean J, Helmrath M, Courcoulas A, et al. (2009) Reversal of type 2 diabetes mellitus and improvements in cardiovascular risk factors after surgical weight loss in adolescents. *Pediatrics* 123: 214-222.
70. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, et al. (1995) Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Annals of surgery* 222: 339-350
71. Ippisch HM, Inge TH, Daniels SR, Wang B, Khoury PR, et al. (2008) Reversibility of cardiac abnormalities in morbidly obese adolescents. *J Am Coll Cardiol* 51: 1342-1348.

72. Roehrig HR, Xanthakos SA, Sweeney J, Zeller MH, Inge TH (2007) Pregnancy after gastric bypass surgery in adolescents. *Obes Surg* 17: 873-877.
73. Magdaleno R Jr, Pereira BG, Chaim EA, Turato ER (2012) Pregnancy after bariatric surgery: a current view of maternal, obstetrical and perinatal challenges. *Archives of gynecology and obstetrics* 285: 559-566.
74. Dell'Agnolo CM, Carvalho MD, Pelloso SM (2011) Pregnancy after bariatric surgery: implications for mother and newborn. *Obes Surg* 21: 699-706.
75. Merhi ZO (2013) Revisiting optimal hormonal contraception following bariatric surgery *Contraception* 87: 131-133.
76. Gosman GG, King WC, Schrope B, Steffen KJ, Strain GW, et al. (2010) Reproductive health of women electing bariatric surgery. *Fertil Steril* 94: 1426-1431.
77. Pournaras DJ, Manning L, Bidgood K, Fender GR, Mahon D, et al. (2010) Polycystic ovary syndrome is common in patients undergoing bariatric surgery in a British center. *Fertility and sterility* 94: e41
78. Wilson-Pérez HE, Seeley RJ (2011) The effect of vertical sleeve gastrectomy on a rat model of polycystic ovarian syndrome. *Endocrinology* 152: 3700-3705.
79. Eid GM, Cottam DR, Velcu LM, Mattar SG, Korytkowski MT, et al. (2005) Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 1: 77-80.
80. Gomez-Meade CA, Lopez-Mitnik G, Messiah SE, Arheart KL, Carrillo A, et al. (2013) Cardiometabolic health among gastric bypass surgery patients with polycystic ovarian syndrome. *World journal of diabetes* 4: 64-69.
81. Stroh C, Hohmann U, Lehnert H, Manger T (2008) [PCO syndrome--is it an indication for bariatric surgery? *Zentralbl Chir* 133: 608-610.
82. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, et al. (2008) Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA* 299: 316-323.