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Effects of Lifestyle Modification on Pregnancy Success in Obese and Overweight Women with PCOS

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Abstract

The present review approaches the pregnancy success after lifestyle modification in obese infertile women with Polycystic Ovary Syndrome (PCOS). Lifestyle modification including hypocaloric diet, structured exercise and counseling, in combination with medical intervention, where necessary, is effective on the resumption of menstruation, the amelioration of the reproductive profile and the success of spontaneous pregnancy. Pregnancy rates vary a lot among the studies. There are limitations due to the heterogeneity in the design of the studies, the diagnosis of the syndrome and the type of the intervention. The number of the studies is restricted and raises the need for further evaluation through well designed, controlled trials. Despite the controversies, the evidence supports the lifestyle modification as first line therapy in obese and overweight women with PCOS.

Keywords: PCOS; Lifestyle modification; Pregnancy; Weight loss; Diet

Obesity

Obesity is currently the most widely expanding epidemic disease of the modern world [1]. It is defined as the excessive storage of body fat and it is diagnosed mainly according to the World Health Organization (WHO) Body Mass Index (BMI) criteria. A woman is diagnosed as obese when BMI is ≥ 30 Kg/m^2 and overweight when BMI is between 25-29.9 Kg/m^2. Obesity is a multifaceted, chronic inflammatory disease, characterized by metabolic and endocrine disorders, as well as behavioral declinations. The two prime factors for the manifestation of obesity are the genetic predisposition accounting for 60% and the environmental conditions accounting for another 40% [2].

Obesity is considered chronic recurrent disease and therefore, difficult to confront. It is related to other chronic disorders such as hypothalamus-pituitary-gonadal axis disruptions, hypertension, diabetes mellitus type 2, cardiovascular disease, stroke, and hormone-dependent tumors [2,3].

Adipose tissue, apart from the storage and release of energy, communicates with distant organs and systems, as the central nervous system. In this way, adipose tissue is involved in the co-ordination of diverse biological functions including energy, metabolism, neuroendocrine and immunological reactions and reproduction [4,5].

Polycystic Ovary Syndrome

Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy of women of reproductive age and the most common cause of anovulatory infertility in developed countries. Diagnostic criteria, as suggested in the Rotterdam Consensus Statement (2003) include (i) oligo- and/or anovulation, (ii) hyperandrogenemia and/or hyperandrogenism (clinical signs of high androgen levels: hirsutism, acne, alopecia) and (iii) polycystic ovarian morphology on ultrasound examination. Diagnosis is set when at least two of the three features are present, after the exclusion of other androgen excess disorders [6]. The combination of diagnostic criteria results to four distinct clinical phenotypes of PCOS, according to the combination of manifestations [7]. However, despite the consented criteria there is still uncertainty concerning the importance of each syndrome feature and the severity of the metabolic dysfunction every phenotype implies.

Obesity is closely related to PCOS and the 38-88% of women with the syndrome are overweight or obese [8]. Insulin resistance is another important pathophysiological feature of the syndrome [9]. The majority of the women with PCOS, independent of their body weight, have a type of insulin resistance which is characteristic of the syndrome. Additionally, obese women with PCOS present a further burden upon their insulin resistance which is attributed to their obesity [10].

PCOS is related with significant metabolic disorders that are probably caused by the characteristic insulin resistance of the syndrome [9]. As a result, the prevalence of diabetes mellitus type 2 is ten-fold higher among young women with PCOS compared to healthy women of similar age [10]. Likewise, 30-50% of obese women with PCOS show impaired glucose tolerance or type 2 diabetes, after the age of 30 years [11].

Effects of Obesity and PCOS on Pregnancy Success

Obesity in women with PCOS is recognized as a risk factor for reproductive failure and should be diagnosed and addressed before the initiation of any infertility treatment [12]. Indeed, obesity in PCOS is associated with anovulation, miscarriages, late pregnancy complications, and reduced response to infertility treatments [13]. In a wider spectrum of the general population, obese women have lower pregnancy rates and higher miscarriage, recurrent miscarriage and, irregular cycle rates [13,14].

The impact of obesity on PCOS phenotype is not yet fully known, however, it could be similar to that of obese women without the syndrome. In this regard, the co-existence of PCOS insulin resistance with hyperandrogenism could worsen the negative impact of obesity on reproduction.

Obese women with PCOS have a higher prevalence of menstrual

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disorders than obese women without the syndrome [14]. At the same time, obese women with PCOS have more frequent menstrual abnormalities than normal weight women with the syndrome [15] and less frequent spontaneous and stimulated ovulations and pregnancy rates [16].

Menstrual irregularities in these women reflect the state of chronic oligoovulation or anovulation with which they often present. The earlier the onset of obesity the strongest is the relation with oligo-/anovulation [17]. As a matter of fact, changes in body weight and fat are regulating factors of pubertal development [18]. The onset of menarche and the onset of ovarian failure have been found to be earlier in obese compared to normal weight females [19]. Interestingly, the time of initiation of menstrual irregularities and weight gain are strongly correlated in girls and young women [20]. The fact that weight gain often precedes the clinical expression of PCOS suggests an important role of obesity in the development of the syndrome and related infertility [13].

Although oligo- and anovulation seems to be the prime cause of infertility in obese women with PCOS, the fact that achievement of pregnancy and live-birth is reduced even in obese women without the syndrome suggests that there are, probably, implications also in conception and implantation as well as other factors leading to higher miscarriage rates (Figure 1) [21]. Impaired oocyte quality was observed in obese women with PCOS and was suggested as the main culprit for these complications [22]. Other authors suggest that impaired endometrial receptivity could affect pregnancy success in obese women, but oocyte quality seems to play a more influential role [23].

The combination of obesity and PCOS triggers higher prevalence of insulin resistance, hyperinsulinaimia, hyperandrogenism, lower Sex Hormone-Binding Globulin (SHBG) and higher Luteinizing Hormone (LH) and DeHydroEpiAndrosterone Sulfate (DHEAS) values [24]. Androgen levels increase with increasing obesity and decline after weight loss in obese hyperandrogenemic women [25]. Insulin resistance and hyperinsulinemia that increase with obesity and decline with weight loss could be the cause of hyperandrogenemia, because high insulin levels augment the production of testosterone from the ovarian theca cells [26]. Hyperisulinemia also dampens the function of Insulin-like Growth Factor (IGF) system leading to further ovulatory disorder [27].

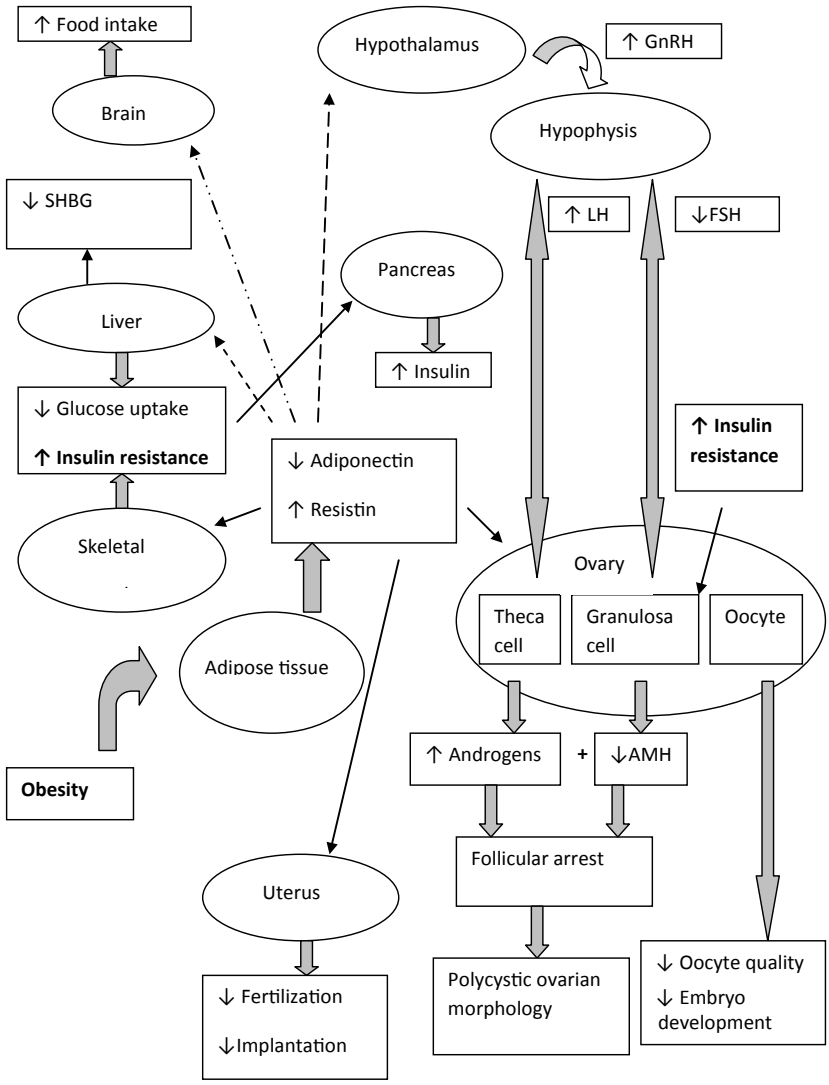

Figure 1: Interactions between obesity, polycystic ovary syndrome, insulin, androgens, adipokines, hypothalamic-hypophysis-ovarian axis, follicles and uterus.

Insulin also decreases SHBG hepatic production, which further increases free testosterone [28]. Overweight and obese women with PCOS have lower SHBG levels than normal weight women with the syndrome [28]. Consequently, obese women with PCOS show a higher Free Androgen Index (FAI), and thus biological active androgens, also, because of the higher testosterone and decreased SHBG levels [17]. Thus, raised androgen concentrations in obese women with PCOS induce anovulation and infertility (Figure 1).

Obese women often manifest altered function of the hypothalamic-pituitary-ovarian axis compared to normal weight women [29]. LH levels in obesity are altered because the amplitude but not the frequency of LH pulses diminishes [30,31]. Still, in obese women with PCOS, LH levels are significantly increased, but can decline after weight loss without changing the pulsatility of LH release [30]. Furthermore, the concentrations of the urinary estradiol metabolites are reduced as well as the urinary progesterone metabolites, during the luteal phase, which is suggestive of the decreased function of corpus luteum [31].

Obesity is also associated with increased risk of development of sexual dysfunction. The main causes of sexual dysfunction are the resistance of peripheral tissues to insulin action, the hyperandrogenemia, the dyslipidemia, and the psychological problems related to obesity [32]. Indeed obesity has a strong negative effect on the sexual desire and the frequency of orgasms [33].

Lifestyle Modification in Obese Women with PCOS

Weight loss is recommended as the first line treatment in overweight and obese women seeking pregnancy [12]. The treatment of obesity involves diet, exercise, medications, behavioral counseling, and bariatric surgery. The term lifestyle modifications usually refers to the combination of diet with exercise that could be enhanced by counseling, psychological support, and pharmacological adjuvant therapy.

Generally, weight loss occurs when energy intake is lower than energy expenditure. In this line, energy intake restriction is essential in all overweight and obese women with PCOS. Currently, there is limited evidence for specific dietary approaches in PCOS [34]. Only two controlled, randomized studies compared the effect of different long term diets in women with PCOS [35,36]. Both of these studies failed to prove significant differences in weight loss or reproductive outcome. Still, the authors concluded that low-fat diets produce a decrease in hyperinsulinemia, which improves metabolic effects [36].

One more randomized trial, comparing the effects of high protein (30% protein, 40% carbohydrate, and 30% fat) and high carbohydrate (15% protein, 55% carbohydrate, and 30% fat) short-term diets in women with PCOS, failed to prove any significant differences between the two dietary patterns [37]. In a recent meta-analysis aiming to assess the effectiveness of lifestyle treatment on reproductive, anthropomentric, metabolic, and quality of life in women with PCOS, there was no significant difference between the distinct approaches [38]. Importantly, the authors highlighted the lack of literature concerning the clinical reproductive outcomes. In conclusion, low calorie diets (energy restriction of 500-600Kcal/per day) with reduced carbohydrate intake are recommended to obese women with PCOS. These diets with reduced glycemic load could be beneficial in alleviating hyperinsulinemia and its metabolic consequences [36]. The success of 5-10% loss of body weight and the effects on hyperinsulinemia are of particular significance to restoration of reproductive potential in women with PCOS [12,39].

Exercise is an important component of any lifestyle modification and weight management program. Women with PCOS self-reported lower baseline activity compared with controls [40]. This attitude could be an additional factor of anovulatory infertility, since increased activity has been associated with lower risk of anovulation [41].

To date, only two studies have examined the direct effects of exercise in women with PCOS [42,43]. The results regarding insulin resistance were divergent and changes in hormone or reproductive parameters were not reported. On the other hand, the combination of diet with physical exercise has been applied in more studies. The drawback is that exercise was not evaluated separately of diet and most of the times was not supervised but self-reported. Finally, the impact of dietary restriction alone and combined with exercise on depression and quality of life was assessed in a recent study that showed similar benefits [44].

However, regular exercise is recommended to all obese women with PCOS, three to five times weekly. The type and frequency of exercise is dependent upon the personal health conditions and limitations of every woman. In any case, even regular walking could be proven beneficial.

The pharmacological agents, used as an adjuvant option with diet, are orlistat and sibutramine, which is currently withdrawn. The primary function of orlistat is the prevention of the absorption of fats from the human diet, and consequently the reduction of caloric intake. The standard prescription dose of orlistat is 120mg three times daily, before meals. It prevents approximately 35% of dietary fat from being absorbed [45]. Orlistat, as well as sibutramine, exerts a weight loss-independent effect on reducing the androgen levels and insulin resistance [46]. Metformin is an oral antidiabetic drug used in diabetes type 2 and other diseases where insulin resistance may be an important factor. Metformin does not enhance weight loss, but, when added to diet, promotes further decline of androgen levels [47].

Behavioral counseling has been proven to contribute to greater weight loss when combined with medical therapy and diet [48]. Counseling includes regular personal or group sessions where support and motivation is provided. Overall goals are psychological strength and stability through better coping strategies and ability to handle every day stress. Behavior therapy is emphasized for weight loss as well as weight maintenance and control. However, despite the great impact of weight loss on PCOS treatment, the support given to PCOS patients to reduce and control their weight is inadequate and needs to be improved [49].

Effects of Lifestyle Modifications on Pregnancy Success in Obese Women with PCOS

Weight loss improves metabolic, endocrine, and reproductive profile of overweight and obese women with PCOS. Even a 5% reduction of body weight can lead to natural conception without the use of any assisted reproduction technique [50-52] and restores ovulation in anovulatory obese women [35,50,51,53]. The mechanism by which weight loss is associated with endocrine and reproductive improvements is not known. However, it has been reported that maximal endocrine ameliorations happened when energy restriction was corresponding to maximal changes in insulin sensitivity, suggesting an intrinsic relation between these two parameters [35]. Probably, the reduction in adipose tissue, and mainly visceral fat, reverses the negative influence on reproductive function. Adipokines seem to play an important role mediating the communication between adipose tissue and reproductive function [54] (Figure 1).

The studies assessing the effect of weight loss and lifestyle modification upon pregnancy success are few and characterized mostly by heterogeneity of the study design and duration, the diagnosis of PCOS, and the type of intervention.

The most recent study of Karimzadeh and Javedani [55] included a high number of infertile women with PCOS diagnosed according to Rotterdam criteria who received either clomiphene or metformin, or clomiphene plus metformin, or lifestyle modifications (diet of 500Kcal less than daily requirements consisted of 50-60% carbohydrates, 25-30% fat and 15-20% proteins as well as 30 minutes of daily exercise even simply walking). Inclusion prerequisite was a minimum 5% of weight loss. The results were menstruation improvements, pregnancies, and significant reduction in waist circumference, insulin, testosterone, SHBG, and LDL levels. Palomba et al. [56] included 40 women with the "classic" PCOS which satisfied both Rotterdam and older NIH criteria. They showed significant improvements of menstrual frequency and ovulation and a decrease in BMI, waist circumference, insulin resistance, and serum levels of testosterone, androstendione, DHEAS and SHBG. They also referred natural conceptions (Table 1).

Lindholm et al. [57] examined the effect of sibutramine combined with low fat normocaloric diet (three meals of reduced fat per day) and modest exercise (at least 10,000 steps daily), in comparison to placebo plus the same lifestyle modification. The primary endpoint was weight loss assessment. The sibutramine group lost more weight in comparison to the placebo group. Three of the women who conceived were on sibutramine and one on placebo. Both treatments resulted in increase of the menstruation frequency while the sibutramine group had lower lipid and higher SHBG levels (Table 1).

Tang et al. [58] performed a randomized, double-blind, controlled study comparing the effect of metformin plus hypocaloric diet (500 Kcal less than daily requirements containing 50% carbohydrates, 10% fat and 40% carbohydrates) to placebo plus the same diet. The patients were advised to increase their normal daily activity (walking, using stairs) by 15 minutes. After six months, there was significant improvement in menstrual frequency and weight reduction in both groups, though more pronounced in the metformin group. Waist circumference and testosterone levels were also significantly reduced only in the metformin group. Surprisingly, there was no amelioration of insulin resistance in any of the groups. There were eight pregnancies (Table 1).

Crosignani et al. [52] evaluated the effect of weight loss through lifestyle modification (1200 Kcal/day diet and aerobic exercise of no specific duration) on fertility rate. The study included 33 anovulatory, overweight plus obese women with PCOS, infertile at least for six months. The maximum study period was 12 months. Twenty five patients lost 5% and eleven of them lost 10% of their body weight. Ovarian volume and number of small follicles were significantly reduced after weight loss. Resumption of menstrual cycles and natural conceptions were also reported (Table 1).

Moran et al. [59] evaluated the effect of dietary composition, namely high or low protein diet (40% carbohydrates, 30% proteins,

Reference	Study objective	Number of women	Study period	PCOS diagnosis	Menstruation improvements	Pregnancy rate after lifestyle
Karimzadeh and Javedani [55]	To compare the effects of clomiphene citrate, metformin and lifestyle modification	343 overweight, infertile women	Six months	Rotterdam criteria [6]	66.6%	20%
Palomba et al. [56]	To compare the effects of an exercise with a diet program on reproductive function	40 obese, infertile women	24 weeks	Both Rotterdam and NIH [64] criteria	45%	22.5%
Lindholm et. [57]	To compare the effects of sibutramine plus low fat diet and exercise vs. placebo plus the same lifestyle modification	42 obese women, (oligomenorrhea and/or hirsutism)	24 weeks	Rotterdam criteria	Yes	10.8%
Tang et al. [58]	To compare the effect of metformin plus hypocaloric diet vs. placebo plus the same diet	143 oligo/amenorrhoeic women	Six months	Oligo/amenorrhoea, PCO*	55.2%	5.6%
Crosignani et al. [52]	To evaluate the effect of weight loss through lifestyle modification	33 overweight anovulatory, infertile with PCOS women	12 months	Chronic anovulation, PCO*	54.5%	30.3%
Moran et al. [59]	To evaluate the effect of dietary composition plus exercise	28 women with PCOS only	16 weeks	NIH criteria [64]	44.0%	10.7%
Huber-Buchholz et al. [30]	To investigate the relationship between insulin sensitivity and ovulation, before and after diet and exercise	18 infertile anovulatory obese women with PCOS (cases) 10 infertile obese women with PCO (controls)	Six months	Menstrual irregularities, biochemical or clinical hyperandrogenemia, PCO	60%	13.3%
Clark et al. [51]	To determine the effect of diet and exercise on reproductive outcome	87 infertile obese women (unspecified number of women with PCOS)	Six months	Not specified	90%	77.6%
Hollmann et al. [53]	To assess the effects of weight loss through hypocaloric diet and exercise on hormonal profile	35 obese infertile women	Three months	Hyperandrogenism, PCO, abnormal LH/FSH	80%	29%
Kiddy et al. [60]	To evaluate the effect of diet on endocrine and ovarian factors	24 obese women with PCOS	Six-seven months	PCO*	81.8%	38%
Pasquali et al. [61]	To investigate the effects of weight loss through diet on clinical and hormonal characteristics	20 obese amenorrhoeic hyperandrogenemic	Six-twelve months		40%	20%

PCOS: polycystic ovarian syndrome, PCO: polycystic ovarian morphology on ultrasound examination, NIH: National Institute of Health.
*according to Adams et al. [65]

Table 1: Studies referring pregnancies in overweight and obese women with PCOS after lifestyle modification.

30% fat vs 55% carbohydrates, 15% proteins, 30% fat, respectively), in a diet of 600 Kcal daily restriction plus exercise (weekly exercise class and advisement of at least three times per week of exercise) on weight loss and reproductive function. The number of infertile women or those who desired pregnancy was not specified. There was improvement in ovulation frequency, and lipid, SHBG, and androgen levels, independent of dietary composition and pregnancies (Table 1).

Huber-Buchholz et al. [30] evaluated the restoration of reproductive potential after weight loss induced by lifestyle modification (group treatment program described by Clark et al. [51]) in obese, infertile women with PCOS compared to age-and weight-matched ovulating women with polycystic ovarian morphology. All anthropometric parameters were improved, mostly in women who lost weight and restored menstruation while three pregnancies were referred (Table 1).

Clark et al. [51] included unspecified numbers of women with PCOS in their study. The causes of infertility varied from anovulation to tubal and male factor. Sixty seven women completed the study and 20 women withdrew and were used as a control group. The patients followed two-hours weekly sessions consisted of one hour low impact aerobic exercise and walk/jog regime or stair climbing and one hour counseling on health, diet, and nutrition rather than calorie counting. Furthermore, women were encouraged to have two more weekly exercise sessions as well as to develop group support and cohesion. After treatment, 90% of the prior anovulatory women resumed ovulation and 78% achieved pregnancy (27% occurred naturally). The authors reported that the resumption of ovulation was noted even after a small weight loss, while the women were still obese. Interestingly, the miscarriage rate was 18% compared to 75% for the same women before the study. Furthermore, the program was proven cost-effective compared to the conventional medical therapy for obese infertile women (Table 1).

Hollmann et al. [53] assessed the effects of weight loss by lifestyle modification (weekly reduction of 5000-10000 Kcal of energy intake with a minimum daily protein intake of 40 g plus increased physical activity) on the hormonal profile. Only one woman was diagnosed as PCOS. However, it could be speculated that there were more participants with PCOS, according to the Rotterdam criteria, as polycystic ovarian morphology and hyperandrogenemia was present in some of them. Weight loss resulted in reduction of glucose, insulin, androstendione, and DHEA levels, and improvement of menstrual function in 80% of the women. They had a pregnancy rate of 29% during and within three months after the study (Table 1).

Kiddy et al. [60] evaluated the effect of a low-calorie (1000 Kcal per day), low-fat (20 g fat per day) diet on endocrine and ovarian factors. Those participants who lost more than 5% of their initial weight showed increased SHBG and decreased total testosterone and insulin levels, menstrual improvements, and some achieved natural conception (Table 1).

Finaly, Pasquali et al. [61] reported the clinical and hormonal changes of obese women with the characteristics of PCOS after a hypocaloric diet of six to twelve months. A decrease in plasma testosterone and LH concentration was noted after weight loss, while menstruation was resumed in eight women, and four natural pregnancies were achieved.

On the whole, about 60-80% of obese anovulatory women with PCOS have been found to resume regular menstrual cycles, though it is not always confirmed if ovulation was restored, and 20-40% of these women achieve pregnancy after following a lifestyle modification for at least six months. Pregnancy could be achieved even after a moderate weight loss of 5% of the body weight, although the possibility rises as weight loss increases.

Hormonal and ultrasound parameters improve with the progression of the weight loss. In this line, it would be interesting to study a more personalized approach for this cohort of overweight and obese women with anovulatory PCOS. Another point to investigate could be the possible different hormonal and metabolic response, of obese anovulatory PCOS women compared to obese ovulatory PCOS women given that the PCOS phenotypes with oligomenorrhea show a higher Visceral Adiposity Index (VAI) score [62] and the PCOS diagnosis, based on hyperandrogenemia and chronic oligoovulation, may resolve after weight loss induced by bariatric surgery [63].

Conclusions

In conclusion, the effects of weight loss by lifestyle modification on pregnancy success in PCOS are encouraging and supportive of the first-line weight loss treatment in obese infertile women with PCOS. The number of the studies is restricted and raises the need for further evaluation through well designed, controlled trials. There are limitations due to the heterogeneity in the design of the studies, the diagnosis of the syndrome and the type of intervention. Despite the controversies, lifestyle modification including hypocaloric diet, structured exercise and counseling, in combination with medical intervention, where necessary, is effective on the resumption of menstruation, the amelioration of the reproductive profile, and the success of natural conception. Inclusion of pregnancy as a primary outcome in studies with PCOS would be of great value in the future.

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