

Ovulation induction in polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common female reproductive endocrine disorders. It is a complex disorder that leads to, among other things, irregular ovulation or anovulation. Weight loss as a strategy to reduce hirsutism has been demonstrated to be effective by several authors in PCOS women. Weight loss, through diet and exercise, improves health in a much more cost-effective manner than drug therapy, eliminating costs for chemical treatments, while still achieving the same result. For lean women with PCOS or those who are unable to lose weight, clomiphene citrate (CC) is the first line of treatment and has been for many years. The discrepancy between ovulation rates and pregnancy rates, the high incidence of clomiphene resistance, and CC's relatively long half life of 5 days has prompted researchers to look for alternative methods for ovulation induction. Metformin is a versatile treatment that can be used in monotherapy, combination therapy or as pre-treatment to ovulation induction with CC. By reducing the dosage of gonadotropins, aromatase inhibitors effectively improve upon the adverse outcomes of this procedure. Surgery is considered the last line of therapy for treating women with PCOS. It is ideal for women who are both clomiphene resistant and unable to respond to FSH therapy.

Key words: ovulation induction, gonadotropins, aromatase inhibitors, surgery, polycystic ovarian syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common female reproductive endocrine disorders [1-3]. It is a complex disorder that leads to, among other things, irregular ovulation or anovulation. In order for a woman to be diagnosed with PCOS, she must exhibit two of the three following manifestations: oligo-ovulation or anovulation, hyperandrogenism, and polycystic ovaries [4, 5]. Obesity and insulin resistance are common features as well. Because PCOS affects about 5 to 10% of women of reproductive age, a great deal of research has been conducted on how to induce ovulation in order to restore hormone levels [3, 6] and/or achieve pregnancy. There are currently a variety of treatments that can be used for these purposes, including lifestyle modifications, drug therapy, and surgery. This paper will discuss the treatment options for induction of ovulation in women with PCOS and critically review the benefits and disadvantages of each.

Lifestyle modifications

Between 35% and 50% of patients with PCOS are either overweight [body mass index (BMI) of 25 kg/m² or higher] or obese (BMI of 30 or higher). Menstrual cycles are dependent upon BMI, so ovulation can be greatly affected by weight [1, 7, 8]. Infertility rates are generally 40% higher in obese women than in women of normal weight [9-13]. This infertility is the consequence of an abnormal menstrual cycle resulting from obesity-induced alterations in physiology. Obesity increases peripheral aromatization to estrogen, thus stimulating estrogenic negative feedback, which in turn reduces follicle stimulating hormone (FSH) levels. It can also decrease the level of sex hormone binding globulin (SHBG), resulting in an increase in free testosterone concentrations [14]. In addition, obesity is associated with high levels of insulin, which stimulate ovarian production of androgens and lead to hyperandrogenemia [15].

Obesity is even linked to poor pregnancy outcomes such as miscarriage, congenital defects, and pre-term labor [12, 16-18]. In a study of 270 women with PCOS conducted by Al-Azemi et al., the overall pregnancy rate was 45.2%. The pregnancy rates for women who were obese and grossly obese (BMI of 25 and above), however, were significantly lower at 30.6 and 14.7%, respectively [1]. Obesity can also negatively affect the outcomes of infertility treatment by reducing the body's response to drug therapy and increasing the need for very high doses of gonadotropins [19]. In the same study by Al-Azemi, only 15.3 and 11.8% of the obese and grossly obese women ovulated after infertility treatment, respectively.

Thus, weight loss should be recommended prior to any sort of pharmaceutical treatment in obese women with PCOS. By losing weight, the body is generally able to correct its altered physiology and resume normal ovulatory function. Ideally, a patient should strive for a BMI of less than 27 kg/m², which will improve ovulation and pregnancy rates [20, 21]. However, even a small weight loss can produce positive results. Huber-Buchholz et al. demonstrated that a weight loss of only 2 to 5% improved menstrual function, largely because any weight loss can lower insulin resistance, resulting in spontaneous ovulation [22]. They studied 15 women with PCOS who had a BMI ranging from 27 to 45 kg/m². These women participated in a 6-month diet and exercise program that promoted healthy lifestyle factors but did not induce rapid weight loss. These 15 women with non ovulatory cycles had greater central obesity, lower insulin sensitivity and lower plasma SHBG compared to women with ovulatory cycles. After the program, 9 of the 15 women regained regular ovulation while experiencing an 11% reduction in central fat with

a 71% improvement in insulin sensitivity. These results strongly suggest that lifestyle modifications without rapid weight loss can assist in lowering insulin resistance and thereby improving ovulatory function [22].

A study conducted by Clark et al. came to similar conclusions. Sixty-seven obese anovulatory women with PCOS engaged in a lifestyle modification program for 6 months. Most of the women who completed the study (60 of 67) resumed spontaneous ovulation after a weight loss of just 4 to 15 kg [20]. Clark et al. also documented improved pregnancy and obstetric outcomes in those who attended greater than two-thirds of the weekly program sessions. Fifty-two women conceived resulting in 45 live births. In contrast, failure to attend the majority of sessions was associated with a less positive reproductive outcome [20].

Thus, it is important to emphasize that for women with PCOS who are obese, weight loss should be the first step in achieving ovulation induction. Weight loss, through diet and exercise, improves health in a much more cost-effective manner than drug therapy, eliminating costs for chemical treatments, while still achieving the same result.

Clomiphene citrate

For lean women with PCOS or those who are unable to lose weight, clomiphene citrate (CC) is the first line of treatment and has been for many years [23-25]. Clomiphene citrate is an estrogen antagonist that binds with estrogen receptors in the hypothalamus, thus obstructing estrogenic negative feedback. By interfering with gonadotropin-releasing hormone (GnRH) secretion, levels of luteinizing hormone (LH) and FSH rise, inducing follicular growth and ovulation [3, 26, 27]. The typical doses of CC range from 50 to 150 mg for 5 days, usually commencing sometime between day 3 and 5 of the menstrual cycle [3, 27]. If ovulation is neither spontaneous nor induced, the dose of CC is incrementally increased by 50 mg/day to a maximum of 250 mg until ovulation occurs. If ovulation fails to occur within 3-4 cycles with high doses of CC, the patient is diagnosed as clomiphene resistant [3]. Clomiphene resistance affects 20 to 25% of women with PCOS and is more common in women who are obese and hyperandrogenemic [28-30]. In cases of clomiphene resistance, other drugs may be used.

Although CC is very successful at inducing ovulation, it is associated with lower implantation rates, partially because it has an adverse effect on cervical mucus and decreases endometrial thickness, making it more difficult for a fertilized embryo to establish pregnancy. This often leads to a large discrepancy between implantation and pregnancy rates [28, 31, 32]. In addition, CC can

cause luteal phase defects, breast tenderness, and hot flashes [27, 32-34]. A much more significant side effect, however, is multiple pregnancies, which occurs in about 5% of patients taking this drug [27, 35]. These multiple pregnancies lead to significant complications for both the mother and fetus and even leads to increase in the newborn mortality rate [36]. The discrepancy between ovulation rates and pregnancy rates, the high incidence of clomiphene resistance, and CC's relatively long half life of 5 days has prompted researchers to look for alternative methods for ovulation induction [37].

Tamoxifen is another anti-estrogen that works similar to CC. It has been used to induce ovulation in women with PCOS, but is used much less frequently because of other better options [2].

Metformin

Insulin resistance is a common feature of PCOS, especially in obese women, and is usually accompanied by compensatory hyperinsulinemia [3]. The high levels of insulin seen in women with PCOS induce physiological changes that ultimately result in hyperandrogenism and anovulation. When levels of insulin are high, the hepatic production of insulin-like growth factor-1 (IGF-1) binding protein is inhibited, leading to an increase in free IGF-1. An interaction between high levels of free IGF-1 and high levels of LH, which are present in women with PCOS, is suspected to be the mechanism that stimulates the production of androgens in theca cells [38]. Subsequently, high levels of androgen causes hormonal imbalance leading to anovulation. Thus, hyperinsulinemia contributes to hyperandrogenism and is supported by studies that show that a decrease in insulin levels is accompanied by a decrease in ovarian androgen production. High levels of insulin also inhibit the production of SHBG in the liver, which binds to sex hormones like testosterone. This increases the availability of free testosterone, which adversely affects ovulation as well [39]. By targeting insulin resistance in PCOS patients, insulin sensitivity can be improved.

For women with PCOS who are clomiphene resistant and have a BMI between 27 and 35 kg/m², metformin is an effective treatment for inducing ovulation. Typically, the severely obese (BMI over 35) do not respond well [6, 40, 41]. Metformin is an oral hypoglycemic agent and is the most commonly used insulin sensitizing agent [3]. It increases glucose uptake in muscles and decreases both intestinal glucose absorption and liver glucose production. By doing so, it augments the effect of insulin on glucose uptake without increasing insulin secretion [42-45]. By decreasing hyperinsulinemia, hyperandrogenism decreases, SHBG levels rise, and free testosterone levels decrease, thereby restoring

ovulation. There is also a possibility that metformin has a direct effect on hyperandrogenism by reducing 17- α -hydroxylase activity (CYP17). Insulin resistance increases CYP17 activity, which leads to increases in androgen production. So by lowering CYP17 activity, metformin is able to obstruct ovarian androgen production and subsequently alleviate hyperandrogenism [46-48].

Metformin is a versatile treatment that can be used in monotherapy, combination therapy or as pre-treatment to ovulation induction with CC. Nestler et al. clearly demonstrated its effectiveness in combination therapy in comparison with placebo for ovulation induction. In their study of obese women with clomiphene resistance, 90% ovulated with metformin and CC treatment compared with 8% who received a placebo and CC [42]. As a pre-treatment, metformin has been found to have a significant affect on ovulation and pregnancy rates as well. In a randomized double blind placebo controlled study by Vandermolen et al., 75% of women with metformin pre-treatment ovulated in contrast with 27% of women with placebo pre-treatment. Pregnancy rates were also significantly higher with metformin pre-treatment vs. placebo, 55 and 7%, respectively. Additionally, they found that metformin pre-treatment helped clomiphene-resistant women respond to CC treatment [49].

Many researchers are currently exploring metformin and its action to surpass CC as the first line of treatment for women with PCOS. Studies have argued that it is equally as effective as CC for inducing ovulation but surpasses CC treatment because it results in higher pregnancy rates, lower miscarriage rates, and consequently higher live-birth rates [25, 50-52]. Palomba et al. compared metformin with CC for treatment in anovulatory lean women with PCOS and found no significant difference in the ovulation rates. However, the pregnancy rate in the metformin group was significantly higher, 15.1 vs. 7.2%, and the rate of miscarriage was significantly lower, 9.7%, compared with 37.5% in CC group. Consequently, metformin was associated with higher birth rates [50]. In contrast, several studies maintain that metformin has no greater effect than CC. One 6-month trial found no statistically significant difference in cumulative pregnancy rates between women taking CC and those taking metformin (49 and 63%). Legro et al. reported higher live birth rates in patients treated with CC [35, 51]. Comparing these studies, however, can be quite difficult because they may differ in patients inclusion criteria, methods of measuring insulin sensitivity, the BMI of the patients, and the dose and length of treatment [45].

Metformin is initially administered at a low dose, which is then increased up to 1500 to 2000 mg per

day [45]. It is less costly than other available drug treatments and reduces the risk of ovarian hyperstimulation syndrome (OHSS), multiple births, and ovarian cysts [25, 53]. Interestingly, conception in women who are being treated with metformin can occur at anytime throughout the first year of treatment whereas conception for those being treated with CC only occurred within the first 6 months with a reduction in effectiveness as time progressed [54, 55]. Additionally, Neveu et al. found that successful ovulation with metformin was independent of the dosage. If corroborated by future studies, this could be beneficial for women who are intolerant of high doses of the drug. As an alternative to starting these women on a new treatment, the dosage may merely be reduced [25]. Many have suggested that metformin has the potential to reduce the rate of early pregnancy loss in those women who conceive during treatment and continue with treatment during pregnancy. However, more data is needed [29].

The side effects of metformin are generally involving the gastrointestinal system and include nausea, vomiting, and diarrhea. However, lactic acidosis is a rare side effect that can occur in women with renal insufficiency. It causes lactate to accumulate in high concentrations, resulting in severe hypoxia and mitochondrial dysfunction [29, 45]. Although metformin and other insulin-sensitizing agents are not yet FDA approved for ovulation induction, they are still acknowledged as an effective form of treatment for ovulation induction [45].

Other insulin-sensitizing agents

Another category of insulin-sensitizing agents used for ovulation induction in women with PCOS are thiazolidinediones. Like metformin, they increase insulin sensitivity and decrease the circulating levels of insulin by using different mechanism action. Thiazolidinediones bind to peroxisome proliferator activated receptor γ (gene encoded for insulin action) which decreases insulin resistance by activating lipoprotein lipase, an enzyme that hydrolyzes lipids [3, 56-58]. Consequently, this improves insulin sensitivity and accordingly decreases hyperandrogenemia, which restores ovulation. Since the extent of hyperinsulinemia is enhanced by weight, this treatment is most effective in overweight and obese women with PCOS [59].

The first effective thiazolidinedione was troglitazone. Although studies testing its effectiveness demonstrated high dose-dependent ovulation rates, it was found to cause severe side effects like drug induced hepatitis. Therefore, the United States Food and Drug Administration (FDA) pulled it from the market in 2000 [3, 59-61].

Currently, new thiazolidinediones such as rosiglitazone and pioglitazone are being investigated because they do not cause hepatotoxicity as a side effect. Rosiglitazone is even arguably more effective than troglitazone because of its 100-fold greater binding affinity to peroxisome proliferator activated receptor γ [60]. Ghazeeri et al. found that combination treatment with rosiglitazone and CC induced ovulation in 77% of clomiphene resistant women vs. 33% with rosiglitazone alone [59]. Another study had similar findings with an ovulation rate of 72.7% with CC and 42.3% alone [62]. Thus, many studies used it in the combination therapy than monotherapy. Thus it has even been suggested that rosiglitazone may be a more effective drug than metformin. Rouzi et al. found that rosiglitazone and CC produced significantly higher ovulation rates than metformin and CC, 91.7 vs. 76.9%, respectively. Additionally, rosiglitazone decreases hepatic fat and increases insulin sensitivity in muscles [63].

In contrast to metformin with its gastrointestinal side effects, which can cause negative patient compliance with the drug, patients receiving rosiglitazone have reported only fluid retention, peripheral edema, and slight decreases in hematocrit levels. In some cases, weight gain has also been noted in patients, possibly due to fluid retention. Additionally, rosiglitazone is classified as a pregnancy category C treatment because of evidence suggesting that it can retard fetal growth in animals during mid-to-late gestation [58, 61, 64-66].

Aromatase inhibitors

Third-generation aromatase inhibitors such as letrozole and anastrozole are currently being investigated as an alternative for ovulation induction in women with PCOS. This treatment targets the aromatase enzymes, which catalyzes the synthesis of estrogen from androgen [2]. Like CC, aromatase inhibitors affect the estrogen signaling pathway. However, they do so by reducing the concentration of estrogen rather than inhibiting estrogen receptors. This decrease in estrogen leads to the up-regulation of the hypothalamic pituitary ovarian axis. That leads to increase in GnRH levels, triggering increase in LH and FSH levels [27]. In contrast to CC, which down-regulates estrogen receptors, aromatase inhibitors have a reduced inhibitory effect and thus do not reduce endometrial thickness, making this treatment modality an attractive alternative [28, 31, 32].

Mitwally et al. studied 12 anovulatory women with PCOS comparing letrozole with CC and found that the mean endometrial thickness of patients using letrozole was 0.81 cm. This was significantly thicker than the mean in those undergoing CC treatment (0.62 cm). In effect, this supports the

theory of estrogen down-regulation and demonstrates that the depletion of receptors adversely affects endometrial growth [28]. Also, in the meta-analysis by Polyzos et al., CC was linked to negative impact on endometrial thickness. They concluded that CC with its antiestrogenic effect on cervical mucus and endometrial thickness is linked to a reduced rate of implantation, resulting in the lower pregnancy rates observed in patients treated with CC. Women undergoing treatment with aromatase inhibitors, however, were found to have significantly greater endometrial thickness and consequently higher pregnancy rates [67-69].

Those in favor of aromatase inhibitors argue that it is superior to CC because they are relatively inexpensive and are easily administered and monitored. In addition, aromatase inhibitors have a much shorter half-life (40 to 45 h) than CC. This means that they are more rapidly cleared from the body and are usually not present at the time of fertilization and embryogenesis [28, 70-73]. Despite their apparent advantages, there is a great deal of conflicting data on their effectiveness when compared with other forms of treatment. In the meta-analysis of randomized trials by Polyzos et al., pregnancy and delivery rates were significantly higher and in favor of aromatase inhibitors over CC [74]. Mitwally et al. found similar results. In their study, ovulation with CC occurred in 44.4% of women with none achieving a pregnancy. However, after 1 treatment cycle of letrozole, ovulation was induced in 75% and pregnancy occurred in 25%, suggesting greater success with the aromatase inhibitor [28]. In contrast, a study of 438 anovulatory women with PCOS found no difference in pregnancy rates between those taking letrozole and CC; the rate of miscarriage was similar as well [75]. Polyzos et al. concluded that the most recent data suggest no obvious benefit in terms of ovulatory and pregnancy outcomes for aromatase inhibitors over CC [74].

Comparisons are also being made between aromatase inhibitors to find the most effective modality. Al-Omari et al. compared letrozole and anastrozole and found that the mean endometrial thickness and ovulation rates were significantly higher in those treated with letrozole as opposed to anastrozole. The pregnancy rate was also higher, 18.8 vs. 9.7%, although not significantly so [76]. With so many conflicting opinions, aromatase inhibitors must continue to be investigated for better understanding of their capabilities and effects.

Gonadotropins for ovulation induction

There are many studies which compare the effectiveness of both urinary FSH (uFSH) and recombinant FSH (rFSH) in PCOS. Gerli et al. found

no statistically significant differences between the two in terms of development of follicles as well as rates of pregnancy and delivery. There seems to currently be a consensus that the only major difference is uFSH is more cost effective than rFSH [77, 78]. One study similarly found no major differences in pregnancy rates, however those using rFSH required a lower dose to achieve the necessary FSH threshold than uFSH [78, 79]. Using a lower dose is beneficial because of the relationship between gonadotropins and Ovarian Hyperstimulation Syndrome (OHSS). It has been seen that the risk of OHSS increases as the total dose increases therefore limiting the dose is imperative.

It has been determined that finding a dose threshold can be vital in choosing how much to use during the therapy [78]. A dose threshold is the minimum treatment amount that will initiate optimal follicle growth. Two treatment protocols that are being practiced include step-up and step-down protocols which differ in their starting doses as well as maintenance doses. These protocols are intended to mimic the normal FSH/LH levels that are seen during ovulation and to have ovulation of one follicle. Both methods begin at the start of natural or induced bleeding. In the step-down method, the starting dose is most often 150 IU. The follicles are then closely monitored while the patient is given doses that continually decrease by 37.5 IU every week until a dominant follicle is apparent. A dose of hCG is then given in order to induce ovulation. The step-up method usually begins with a dose of 75 IU followed by an increase by 37.5 IU weekly. The restriction with this method is that there is a maximum limit of 225 IU because of the high incidence of OHSS. This approach has been thought to be more ideal in order to avoid multifollicular growth which can lead to multiple pregnancies as well as OHSS [78]. A study conducted by Balasch et al. (2000), compared a step-up protocol with two different initial doses of rFSH, 37.5 IU and 50 IU, in women who failed to ovulate or achieve pregnancy using CC. Doses were then increased by their initial given dose until an ovarian response was achieved. They found that there were no statistically significant differences in outcomes and that 37.5 IU is sufficient enough to induce follicular growth. However, this dose may lead to a longer treatment window [80]. This specific step-up method has shown to produce a single follicle ovulation rate of about 70% with low rates of disadvantages such as multiple pregnancies and OHSS [81].

Comparing all of the different gonadotropin treatment options can be difficult when trying to decide what is best for a patient. However, many studies have shown that all of these methods are

equally effective. This treatment overall is found to have a pregnancy rate of as high as 90% in women that have gone through six cycles [81]. Gonadotropin treatment can be adversely effected by many factors associated with women diagnosed with PCOS such as BMI, age, and response to clomiphene citrate [78, 82]. If ovulation induction is not achieved by this method, the last line of therapy is considered, laparoscopic ovarian drilling.

Assisted reproduction in polycystic ovary syndrome

Assisted reproductive techniques (ART) such as classic *in-vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) can be utilized in women with PCOS who fail to conceive spontaneously during the various ovulation induction treatments. As soon as a woman with PCOS successfully ovulated during treatment, she is advised to initiate timed intercourse to achieve spontaneous pregnancy. If a woman fails to conceive after 6 months of ovulation induction, intra-uterine insemination (IUI) may be attempted while continuing ovulation management. Subsequently, when a pregnancy is not achieved after 4 ovulatory cycles using IUI, IVF is the next step. It is very difficult during IVF treatment to control the number of mature eggs that will ovulate in women with polycystic ovaries, so multiple pregnancies and OHSS are major risks involved in the IVF treatment [83]. Thus the outcome of ART in women with PCOS seems to be similar to that of women with other types of infertility and undergoing IVF, so its use is beneficial, doubling the rate of pregnancy in women with PCOS from 25 to 40-50% [83].

Heijnen et al. conducted a meta-analysis that evaluated the outcomes of conventional IVF in women with PCOS. They found that woman with and without PCOS obtained similar pregnancy rates, 37.4 vs. 32%, and also similar live birth rates. Urman et al. (2004) reported that women with polycystic ovaries tend to have a greater response to gonadotropins during stimulation in IVF, and therefore these women produce more follicles and oocytes leading to a higher retrieval rate [84]. This was observed in Heijnen's study as well. However, the higher oocyte retrieval rate was countered by lower rates of fertilization. In a recent literature report, there was no significant difference in the dosage of gonadotropins between the women with PCOS and those without PCOS. However, the duration of stimulation was significantly longer in the women with PCOS [85]. Another study similarly found no significant difference in pregnancy rates between PCOS and non-PCOS women undergoing IVF. However, much of their data is conflicting. Oocyte recovery rates were reported to be

comparable, and additionally, there was no significant difference in the incidence of OHSS in the women with PCOS [86]. Thus, even though, women with PCOS who utilize IVF are at an increased risk for cycle cancellation [85-87], ART have proved to be effective in this group.

Clomiphene, metformin, and aromatase inhibitors may offer additional benefits to women with PCOS during IVF treatment. Many believe that the use of CC in IVF is not warranted due to its adverse effects on the endometrium, which many result in negative treatment outcomes. However, a proposed advantage of combining CC with human-menopausal gonadotropin is that CC supports the luteal phase in these women, and there is a lesser need for the administration of human menopausal gonadotropin (HMG) and high doses of progesterone during the luteal phase [88]. A study by Dickey et al. corroborates this idea; clinical pregnancy and birth rates were higher in the women receiving CC with HMG than in those receiving human menopausal gonadotropin alone [89].

High levels of insulin, stemming from insulin resistance and compensatory hyperinsulinemia, can adversely affect a woman's sensitivity to FSH, so insulin suppression through the co-administration of metformin with FSH during IVF has been investigated. In a meta-analysis of metformin co-administration during IVF, Costello et al. concluded that metformin had no significant impact on the pregnancy rate but that there was a trend toward improved pregnancy rates, 28% with metformin and 10% without, which may warrant further studies with larger sample sizes [90]. Another meta-analysis also found no significant difference in the pregnancy rates, number of oocytes retrieved or the live birth rates [91] after administration of metformin with gonadotropin induction ovulation regimen. In comparison, Tang et al. found an improvement in pregnancy rates, 38.5% for the metformin group and 16.3% for the controls [92]. At this point, the most beneficial aspect of metformin co-administration during IVF in women with PCOS seems to be a reduction in the incidence of OHSS, with one study even noting a reduction of 80% [91, 92].

Aromatase inhibitors are beginning to be studied in combination with gonadotropins during assisted reproductive techniques as well. In a study of controlled ovarian hyperstimulation and IUI with 28 women with PCOS, Mitwally et al. compared the use of FSH alone to FSH in combination with letrozole. They discovered that those treated with both had significantly less cancellations of IUI. These cancellations occur when there is an inadequate response to ovarian treatment. The combination of both treatments also leads to a similar and sometimes higher pregnancy rate than treatment

with FSH alone. Additionally, with the use of aromatase inhibitors, less than 50% dose of FSH used in FSH-only treatment was required to produce a similar number of follicles. This reduction in dose is beneficial because FSH is associated with severe OHSS and multiple gestations, with usage of high doses. By reducing the dosage of FSH, aromatase inhibitors effectively improves the adverse outcomes of this procedure [93].

Laparoscopic ovarian drilling: a surgical option

Laparoscopic ovarian drilling may be beneficial for patients with PCOS for ovulation induction. High levels of LH correlate with a reduction in oocyte and embryo quality and subsequent miscarriage. Laparoscopic ovarian drilling is effective because it reduces the elevated LH levels. Many believe that the use of laparoscopic ovarian drilling prior to ART increases the rate of successful outcomes because of this reduction in LH levels [84, 94-96]. According to a study conducted by Colacurrier et al. (1997), women who underwent the procedure prior to IVF had higher pregnancy rates than those who did not. Tozer et al. had similar findings such as higher pregnancy rates and lower miscarriage rates, but the differences were not statistically significant [97].

Surgery is considered the last line of therapy for treating women with PCOS. It is ideal for women who are both clomiphene resistant and unable to respond to FSH therapy. Dating back to 1935, ovarian wedge resection, the removal of one-half to three-quarters of each ovary was the first surgical technique performed by Stein and Leventhal [98, 99]. Although there was a promising resumption of the menstrual cycle, many complications of concern were noted. A loss of an excessive amount of ovarian tissue was observed which can lead to premature ovarian failure since it affects the vascular supply to the ovary. More controversial was the formations of ovarian adhesions with the potential to cause infertility [98]. These factors lead to the abandoning of this procedure for treating PCOS.

A new minimally invasive technique known as laparoscopic ovarian drilling (LOD) was developed as a replacement for ovarian wedge resection. It is equally effective and it carries a lower risk of post-surgical adhesions as compared to ovarian wedge resection. This procedure utilizes a monopolar/bipolar electrode or a laser to create 2-4 mm punctures in each ovary [98, 99]. There are many types of lasers that can be considered for use; however the potassium titanyl phosphate and carbon dioxide lasers are the most precise at focusing their energy reducing the thermal damage on the ovaries. Neodymium-yttrium-aluminum is another type of laser which can be used. It can

diffuse its energy over a larger area, having an effect on the ovary even at a slight distance so that it is only necessary to use the laser in a non-contact mode [3]. The number of punctures that should be made per ovary is quite controversial. A study conducted by Malkawi and Qublan tested the difference in outcomes between ovaries that were punctured with an insulated needle 5 vs. 10 times. They found no significant differences between the groups in terms of ovulation and pregnancy rates. Both numbers did however produce a significant reduction in luteinizing hormone (LH) levels, LH:FSH ratio, as well as androgen concentrations signifying that LOD is effective [100]. This study has been reviewed by many others which agree that fewer punctures are preferred.

The exact mechanism of LOD is unknown, however there are many hypotheses. One possibility is that the process of LOD destroys thecal and stromal tissue resulting in a significant decrease in androgen production. Since androgens are aromatized to estrogens, this limits the production of estrogens as well. This decrease in estrogen levels is believed to restore the hypothalamic-pituitary ovarian feedback mechanism, thus increasing gonadotropin production, specifically FSH which stimulates the growth and development of follicles, a necessary process for ovulation to occur. Another hypothesis is that the procedure increases the blood flow to the ovary which increases the transport of gonadotropins to the follicles thus improving ovulation. A final proposed mechanism is that the decrease in LH levels may directly correlate to the decrease in androgen levels as well as an increase in FSH levels [99, 100].

The overall outcome of LOD has been compared to the use of gonadotropins as treatment for PCOS. It has been found that both result in similar ovulation and pregnancy rates. However, an advantage of LOD is that there is no increased risk of developing ovarian hyperstimulation syndrome (OHSS). Also, a decrease in hyperandrogenemia is observed which is beneficial because an over-production of androgens can be detrimental to ovulatory outcomes. The one time LOD treatment is relatively inexpensive compared to the constant use of gonadotropin medications. The major disadvantage of this procedure is the formation of adhesions which can adversely affect fertilization [3, 98]. However, it has been found that using a laser instead of an electrode may reduce the risk of these adhesions. The adhesions may block the tubes in which the ovum passes through inhibiting it from reaching its site of fertilization. Although, LOD is considered the last line of therapy, it provides a promising treatment of PCOS.

Ovarian hyperstimulation syndrome: complication of ovulation induction

Ovarian hyperstimulation syndrome (OHSS) is a condition characterized by ovarian enlargement and has varying degrees of severity. Mild OHSS is described as clinically benign with minimal ovarian enlargement, typically less than 5 cm. Often, in the absence of pregnancy, it may resolve spontaneously. This mild form can cause women to experience abdominal bloating, pelvic discomfort, and nausea. But in moderate OHSS with greater ovarian enlargement and more serious symptoms which needs to be managed in a hospital such as, vomiting, abdominal distension, and ascites, the accumulation of fluid in the peritoneal cavity. This generally occurs in about 5% of patients. In severe OHSS ovarian enlargement is greater than 10 cm. Women tend to suffer from tense abdominal ascites with or without pleural effusion. This form can cause respiratory distress, oliguria, hemoconcentration, and thrombosis. However, less than 1% of women develop the severe form [101-103].

Ovarian hyperstimulation syndrome occurs in roughly 30% or more of the women undergoing ovarian hyperstimulation with gonadotropins [104]. Ovarian hyperstimulation syndrome occurs more readily in women undergoing treatment with injectable gonadotropins. Women with PCOS are at a greater risk for OHSS because their ovaries are more sensitive to FSH stimulation [105, 106]. Although they have decreased aromatase activity, it is easily stimulated by external FSH injections. This is because their high androgen concentration increases estrogen concentration which stimulates FSH receptors. So these women respond to FSH administration with multiple follicular development and consequently OHSS. This sensitivity to FSH puts them at greater risk for OHSS during IVF. Moderate to severe OHSS will occur in roughly 10.5% women with PCOS undergoing IVF treatment [101, 103, 106, 107]. This concludes that these women have an odds ratio of 6.8 for developing OHSS. The best way to treat and prevent OHSS from occurring is recognizing the high risk patients, like women with PCOS, administering lower doses of treatment drugs and increasing the frequency with which these women are monitored [107].

Conclusions

Because PCOS is an important cause of female infertility, its diagnosis can cause distress and concern about a woman's reproductive future. Fortunately, treatments for ovulation induction are being investigated in order to assist these women in correcting their menstrual cycle and managing the infertility. Lifestyle modifications are by far the most cost-effective form of treatment and should

be suggested prior to any sort of pharmaceutical treatment in women who are overweight and obese. If this fails, drug therapy with CC, metformin, other insulin sensitizing agents, and gonadotropins can be used. Surgery is a last resort. Aromatase inhibitors, at this point, are under investigation and require larger, more powerful studies before they can truly be assessed.

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