

CONTEMPORARY REVIEW ARTICLE

# Use of Metformin in Clomiphene Citrate (CC) Resistant Polycystic Ovary Syndrome (PCOS)

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**Abstract:** Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting between 4% and 8% of reproductive aged women. Although the symptoms and signs of PCOS are very heterogeneous, the syndrome usually presents with any combination of the following, menstrual irregularities (usually oligomenorrhea or amenorrhea), signs of hyperandrogenism (hirsutism, acne, alopecia) a characteristic appearance of the ovaries on ultrasound examination and an endocrine disturbance often involving high serum concentrations of LH and androgens.

There is a well established association between PCOS, insulin resistance and hyperinsulinemia. Insulin resistance is a pivotal defect in PCOS probably counts as one of the most important advances in the battle to control the disorder. This metabolic abnormality leads to a compensatory increase in circulating insulin and this elevated insulin level directly stimulates the ovary to produce excess androgens. It also decreases hepatic sex hormone binding globulin (SHBG), so increasing biologically available free testosterone concentration in the circulation. This metabolic derangement leads to oligomenorrhea and anovulation.

Different insulin sensitizers are used to revert the hyperinsulinemic condition. Metformin is top of them, which proved to enhance ovulation in insulin resistant PCOS when used with different ovulation inducing agents. Metformin reduces insulin resistance of peripheral tissue and allows muscle and adipose cells to take in glucose at normal insulin levels. It inhibits hepatic glucose production, decreases intestinal absorption and promotes glucose uptake, utilization by peripheral tissues at the postreceptor level. In this way it reduces insulin level and subsequently androgen level. It is easily available, safe and no teratogenic or adverse fetal outcome were reported by any researcher. It can be used safely in clomiphene resistant PCOS patients.

**Keywords:** Resistant PCOS, metformin, clomiphene citrate, anovulation, early pregnancy loss.

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting between 4 and 8% of reproductive aged

women.<sup>1</sup> Although the prevalence may be as high as 30% in women with secondary amenorrhea, 75% in women with oligomenorrhea and 90% in women with hirsutism.<sup>2</sup> About 20% of couples seeking fertility treatment are anovulatory and 85-90% of those have PCOS.<sup>3</sup> Although the symptoms and signs of PCOS are very heterogeneous, the syndrome usually presents with any combination of the following menstrual irregularities (usually oligomenorrhea or amenorrhea), signs of hyperandrogenism (hirsutism, acne, alopecia) a characteristic appearance of the ovaries on ultrasound examination and an endocrine disturbance often involving high serum concentrations of LH and androgens.

There is a well established association between PCOS, insulin resistance and hyperinsulinemia. Insulin resistance is a pivotal defect in PCOS probably counts as one of the most important advances in the battle to control the disorder. This metabolic abnormality leads to a compensatory increase in circulating insulin and this elevated insulin level directly stimulates the ovary to produce excess androgens.<sup>4,5</sup> It also decreases hepatic sex hormone binding globulin (SHBG),<sup>6</sup> so increasing biologically available free testosterone concentration in the circulation.<sup>7,8</sup>

This metabolic derangement leads to oligomenorrhea and anovulation. The antiestrogen clomiphene citrate (CC) is widely accepted a first line drug for ovulation induction in PCOS. Almost 50-80% of anovulatory patients ovulate and 40-50% conceive on CC at dose of 50-150 mg/day.<sup>9,10</sup> However, in spite of administering high doses of CC, some patients may fail to ovulate, thus they are considered as CC resistant. The recommended maximum dose is 150 mg/day as there is no clear evidence of efficacy at higher doses and this is in accordance

with FDA recommendations of 750 mg/treatment cycle.<sup>11</sup> CC resistance is associated with insulin resistance. As insulin resistance turns out to be one of the primary cause of anovulation in PCOS, we would expect drugs that reverse insulin resistance to also relieve hyperandrogenism, restore normal menses and help eliminate the infertility associated with PCOS. At the top of that list of pharmaceutical agents is metformin, which was developed in 1957 to treat type 2 diabetes. Metformin reduces insulin resistance of peripheral tissue and allows muscle and adipose cells to take in glucose at normal insulin levels. It inhibits hepatic glucose production,<sup>12</sup> decreases intestinal absorption and promotes glucose uptake, utilization by peripheral tissues at the post receptor level.<sup>13</sup> Metformin increases the number of insulin receptors but not insulin concentration and therefore does not cause hypoglycemia in normoglycemic patients. The sum total of these actions is a decrease in insulin levels and as a consequence a lowering of circulating total and free androgen levels with a resulting improvement of the clinical sequel of hyperandrogenism. Once androgen falls ovarian response to CC or other stimulating agents increases. So by reducing insulin levels by insulin sensitizer CC resistance reverts.

### **BASIS OF HYPERINSULINEMIA AND INSULIN RESISTANCE IN PCOS**

According to Acien and colleagues<sup>14</sup> there are at least 3 types of disorders associated with PCOS:

1. Simple hyperinsulinemic, nonhyperandrogenic obesity.
2. Typical PCOS probably with hyperactivity of steroidogenic enzymes but without hyperinsulinemia.
3. Insulin resistant PCOS resulting from anomalies in the genes involved in the secretion and action of insulin.

Insulin resistance is defined as a state in which greater than normal amounts of insulin are required to produce a quantitatively normal response. Since an initial report in 1980 of the association between PCOS and hyperinsulinemia it has become apparent that women with PCOS are both insulin resistance and hyperinsulinemic in relation to weight matched control.<sup>15,16</sup> Insulin resistance in PCOS is due to a post-binding defect in signaling and is associated with constitutive serine phosphorylation of the insulin receptor (IR). Hyperinsulinemia plays a role in the etiopathogenesis of hyperandrogenism in women with PCOS by increasing ovarian androgen production and decreasing the serum sex hormone binding globulin (SHBG) concentration.<sup>17-19</sup> Hyperinsulinemia is proposed to stimulate p450c, 17-alpha activity in PCOS.<sup>20</sup> Cytochrome p450c, 17-alpha is a bifunctional enzyme that has both 17-alpha

hydroxylase and 17, 20-lyase activity and is key in the biosynthesis of ovarian androgens.

Hyperinsulinemia can result from any one of or a combination of the following reasons:

- a. Increased insulin production by beta cells.
- b. Insulin resistance in target cells or impaired hepatic insulin clearance.

Abnormalities in insulin secretion have been reported in studies of women with PCOS with and without a family history of type 2 diabetes mellitus are partly due to increased basal insulin secretion.<sup>21</sup> This disproportionate beta cell effect is dependant on the insulin gene and its regulatory site.

### **RELATION BETWEEN HYPERINSULINEMIA, HYPERANDROGENISM AND ANOVULATION**

Insulin and insulin like growth factor-1 (IGF-1) receptors are found in the ovary.<sup>22</sup> Androgen production is stimulated by insulin in ovarian theca and stromal cell cultures from hyperandrogenic and normal women<sup>18</sup> and reduction of serum androgen with short-term suppression of serum insulin with diazoxide in some patients<sup>5</sup> indicates a role for insulin in the pathophysiology of PCOS. Plasma insulin correlates with androgen levels and hyperinsulinemia may itself induce high androgen production in both the ovary<sup>23,24</sup> and the adrenal glands.<sup>25</sup> *In vitro* studies have shown that the direct ovarian effects of insulin is to increase androgen precursors from theca cells<sup>26</sup> and aromatization in granulosa cells.<sup>27</sup> In a study on rat it was found that rat treated with insulin follicular structure was completely damaged and stromal dominance was observed. So insulin may directly play a role in follicular arrest in addition to elevating levels of androgens in the microenvironment. Besides increasing ovarian androgen production hyperinsulinemia decreases SHBG level, which further stimulates hyperandrogenism.<sup>5,18,19</sup> However, it is not insulin resistance but the elevation of circulating insulin that stimulates ovarian androgen production and suppress SHBG. When insulin release is inhibited by diazoxide androgen and SHBG levels returns to normal.<sup>5</sup>

Insulin is responsible for glucose uptake by cells and thereby maintains blood glucose level. In PCOS there is decreased insulin clearance. This may be directly related to hyperinsulinemia, which decreases the number of hepatic receptors for insulin or secondary to hyperandrogenicity, which also decreases hepatic insulin clearance.<sup>28</sup> Insulin resistance can exist when cellular response does not occur following exposure to insulin. The causes for such abnormal cellular response to insulin are impaired insulin receptor binding due to receptor

defect or autoantibodies to insulin receptor as a defect in insulin signaling which is mediated through a tyrosine kinase receptor causing activation of a number of phosphorylation-dephosphorylation steps. Due to this postreceptor signaling defect there is decreased response to insulin. As insulin cannot work properly blood glucose level raised which stimulates the beta cells of pancreas to produce more insulin until blood sugar level falls. As a result insulin level rose, which causes increased secretion of androgen both by adrenal gland and ovaries. Excess androgen itself suppresses SHBG which in turn increases the free level of androgens. Thus, a vicious cycle established and hyperandrogenemia results. This excess androgen is responsible for impaired folliculogenesis and anovulation.

### **INSULIN SENSITIZING AGENTS TO REVERT THE SITUATION**

At least five different modalities have been used to lower insulin levels in PCOS. These include weight loss, diazoxide, metformin, thiazolidinediones (pioglitazone, rosiglitazone, troglitazone is no longer available for use) and D-chiroinositol. Among all drugs metformin is the most comprehensively evaluated drug. Both metformin and the thiazolidinediones effect reductions in insulin levels but they do so by fundamentally different mechanism. None of the insulin sensitizing drugs have Food and Drug Administration (FDA) approval for use in PCOS. Nonetheless the scientific evidence supporting their salutary effects in PCOS is substantial and progressively mounting and their use for this purpose by clinicians is already established. Although troglitazone is effective in resulting ovulation in PCOS due to need of liver transplantation and death from hepatic failure it is withdrawn from the market.<sup>29</sup> Much published data assessing rosiglitazone and pioglitazone and D-chiroinositol in PCOS are not available. Moreover, D-chiroinositol is not yet commercially available.

### **Metformin**

Metformin is a biguanide antihyperglycemic that is approved for the management of type 2 diabetes mellitus. The mechanism by which metformin enhance insulin sensitivity are not fully characterized. At a molecular level, metformin may increase the activity of the enzyme adenosine monophosphate-activated protein kinase.<sup>30</sup> Metformin appears to suppress hepatic glucose output, decreased intestinal absorption of glucose, increased insulin mediated glucose utilization in peripheral tissues and has an antilipolytic effect on fatty acid concentration reducing gluconeogenesis.<sup>31</sup> It does not produce hypoglycemia in either normal subjects or patients with type 2 diabetes. It is rapidly absorbed from the small intestine and without metabolism

largely excreted in the urine. It is available in a generic form as 500 mg, 850 mg and 1000 mg tablets. The target dose of metformin is in the range of 1500 to 2550 mg.<sup>32</sup> Metformin is given with meals to reduce the gastrointestinal side effects. The most common side effects of metformin are diarrhea, nausea, vomiting, flatulence, indigestion and abdominal discomfort. The gastrointestinal side effects may be caused by high intestinal metformin concentration that cause build-up of lactic acid in the bowel.<sup>33</sup> A rare problem caused by metformin is lactic acidosis, which is fatal in as many as 30-50% of cases.<sup>34</sup> Chances of lactic acidosis is increased when patients have renal insufficiency. So it should not be prescribed if serum creatinine level is greater than 1 mg/dl. Liver disease, congestive heart failure and previous history of lactic acidosis are other contraindications of metformin therapy. Metformin should be temporarily suspended for all major surgical procedures that involve restriction of fluid intake. In 10% of cases of lactic acidosis due to metformin have occurred in patients after the intravenous administration of iodinated contrast agents.<sup>35</sup> So most authorities recommend that metformin should be discontinued 48 hours before any radiologic procedure that involves intravenous administration of iodinated contrast material. Though some authorities believe that it is safe to give contrast media to person taking metformin as long as renal function is known to be normal.<sup>36</sup>

### *Evidences of use of Metformin in PCOS*

Number of questions are concerned regarding the use of metformin in PCOS are: Can metformin induce ovulation in PCOS with or without insulin resistance? Can it increase sensitivity of ovaries of insulin resistant PCOS patients to other ovulation inducing agents? Can metformin reduce the chance of abortion and development of gestational diabetes mellitus in PCOS patients?

The first study was done by Velazquez et al<sup>37</sup> to test the hypothesis that androgen reduction follows from reduction of insulin by metformin. Metformin was administered to 26 women with PCOS at a dose of 500 mg thrice daily for 8 weeks and resulted in a significant reduction in total testosterone, free testosterone, free androgen index as well as a significant rise in SHBG in comparison with pretreatment levels. Subjects of this study lost weight, which was a likely contributor to the reduction in insulin secretion. As a result the effect of metformin upon insulin secretion could not be clearly separated from that of weight loss.

To isolate the confounding effects of weight reduction on both insulin secretion and androgen levels Ehrmann D et al<sup>38</sup> treated 14 obese non diabetic PCOS women with metformin

for a 3 months period during which body weight was maintained and compared their ability to respond to oral and intravenous glucose challenges before and after treatment. They found that both the glucose and insulin response to a oral glucose challenge and the profound insulin resistance of obese women with PCOS were not improved by metformin. These findings were in contrast to those of Nestler and Jakubowicz<sup>20</sup> who found in a study of similar design that the area under the serum insulin curve decreased by 53% after oral glucose administration and was associated with a reduction in both the basal and luprolide stimulated serum 17-hydroxyprogesterone concentration.

Acbay and Gundogdu<sup>39</sup> reported that insulin resistance and associated metabolic and hormonal abnormalities did not improve in patients with PCOS who were given metformin for 10 weeks. BMI did not change during the therapy so these patients did not have the beneficial effect of weight loss. However, some studies showed good results with metformin therapy in women with PCOS. One randomized placebo controlled trial showed that metformin therapy administered for 4-8 weeks resulted in decreased levels of insulin, 17-OHP and free testosterone levels and increased SHBG levels without changing in BMI.<sup>20</sup> In another placebo controlled study metformin improved hyperinsulinemia and reduced androgen levels in non obese women with PCOS within 4-6 weeks.<sup>40</sup> No changes were noted in control group. Improvement in ovulatory rate with metformin have been reported by different authors.<sup>41-44</sup> On the contrary another study with 12 weeks metformin therapy did not found any improvement of adrenal androgen secretion, menstrual cyclicity and hirsutism.<sup>45</sup> In other 8 trials on no obese PCOS metformin decreased BMI in 4 and did not reduce in 3 trials. The positive result in reducing androgen level in both the cases indicates that metformin not only acts through weight loss but also stimulates resolution of the symptoms by itself. Why metformin is successful in some studies and not in others is a concern, however, obesity, variation in the dose, genetic background and duration of therapy may be major factors in patient response.

#### *Metformin versus Clomiphene Citrate for Induction of Ovulation*

Metformin is not an ovulation inducing drug. It is a drug that effects metabolism and acts indirectly to cause ovulation by reducing the circulating concentration of insulin. On the other hand CC is specifically a fertility drug that acts directly to induce ovulation by blocking negative feedback on the hypothalamic pituitary axis. To compare the effects of two drugs in ovulation a head to head trial of metformin and CC is required. But no such study has been reported to evaluate the effects of metformin

in PCOS in comparison to CC. In a multicenter study by Nestler *et al* ovulation rate by metformin was 34% and by CC was 8% approved metformin treatment to be more efficacious.<sup>46</sup> But RS Legro *et al* found no superior effects over CC.<sup>47</sup> A recent meta-analysis of 17 rigorously conducted studies with 1639 subjects shows improvement of menstrual cyclicity and ovulation rate with metformin.<sup>48</sup> CC is first acting drug with chance of multiple pregnancy, but metformin takes time to make the women ovulatory resulting in a singleton pregnancy. The ESHRE/ASRM consensus group recommended to use metformin for those patients who are not in a hurry for pregnancy and to use first acting CC to those who desire pregnancy immediately and for them time is of the essence.<sup>49</sup>

#### *Addition of Metformin to Clomiphene Citrate for Ovulation Induction*

Metformin has been used as an adjuvant agent for ovulation induction in women with PCOS. When metformin used alone 40% patients resumed regular cycles and ovulation<sup>50</sup> and addition of CC in no responders increased ovulation rate to 67%. In another study 28.2% ovulation rate and 4.2% pregnancy rate were achieved with CC in PCOS.<sup>51</sup> But when metformin was added both ovulation and pregnancy rates were increased to 57.9% and 65.2% respectively. The combination of metformin and CC seems to be synergistic. But the ESHRE/ASRM consensus report states that addition of metformin to CC as primary therapy for induction of ovulation has no beneficial effect.<sup>49</sup> On the other hand meta-analysis conducted after the consensus paper, which includes the studies cited in the consensus paper as well as the well-designed studies reported that these addition of metformin to CC significantly increased both the ovulation rate and pregnancy rate in women with PCOS. Another positive effect of adding metformin is reduced multiple pregnancy rates.

#### *Pretreatment with Metformin before Ovulation Induction with Clomiphene Citrate*

For women who have no immediate desire for pregnancy consideration should be given to pretreatment with metformin before adding clomiphene as appropriate.<sup>46</sup> This approach offers two advantages. Firstly, pretreatment with metformin for 2 or more months may increase the ovarian sensitivity to CC and may be associated with higher rates of ovulation and live birth. Secondly, obese PCOS are less responsive to CC and develop many pregnancy related complications like pre-eclampsia, diabetes mellitus.<sup>10</sup> Metformin facilitates weight loss and pretreatment for several months can reduce those

complications.<sup>52-57</sup> Different studies showed positive effect of pretreatment with metformin. A multicenter randomized double-blind placebo controlled trial<sup>44</sup> was conducted in CC resistant PCOS patients. Metformin 500 mg thrice daily or placebo alone was administered for 7 weeks and then metformin or placebo was continued in the anovulatory women, while clomiphene treatment was began at 50 mg. With ovulation the dose was not changed but with anovulation it was increased by 50 mg for the next cycle. Significant improvements in ovulation and pregnancy rates were observed in the women treated with metformin. In the metformin group 75% ovulated in comparison to 27% in placebo group. Pregnancy rate was also higher 58% in the metformin group, whereas only 13% conceived in the placebo group. Another trial<sup>58</sup> compared metformin with placebo before induction with CC. They used 850 mg metformin twice daily during the first cycle and then added 100 mg CC for the subsequent cycle. In addition to a significant decrease in total testosterone, LH level, LH/FSH ratio, insulin resistance and mean BMI in the study group the ovulation rate was significantly higher in the study group than in the control group (77 vs 14%). The pregnancy rate did not differ significantly but the total number of pregnancies in the metformin group was significantly higher.

#### *Metformin as Adjuvant to Gonadotropin Ovulation Induction in CC Resistant PCOS*

Much randomized, double blind, placebo controlled trial of an insulin sensitizing drug as an adjuvant to gonadotropin ovulation induction has not yet been reported. One study evaluated the effects of metformin along with FSH in CC resistant PCOS patients. They randomized the patients to receive either no treatment or metformin 1500 mg daily for one month prior to ovulation induction.<sup>59</sup> Number of follicles >15 mm on the day of hCG administration was significantly lower in women treated with metformin compared with untreated group (mean 2.5 vs 4.5 follicles respectively). Due to over stimulation hCG was not withheld in any cycle in women treated with metformin compared with 6 cycles withheld in untreated group. Yarali and colleagues<sup>60</sup> did not observe any improvement in either insulin sensitivity or ovarian response in CC resistant PCOS patients when pretreated with metformin 850 mg twice daily and then induced with recombinant FSH. Although insulin sensitivity did not change during 6 week metformin treatment an increase in spontaneous ovulation rate was observed.<sup>61</sup> Overall ovulation rates and pregnancy rates were higher in the metformin group (94 vs 75% and 31.3 vs 6.3%). This study showed that metformin administration during ovarian stimulation led to higher overall ovulation and pregnancy rates

when given to CC resistant PCOS. But other authors have not observed beneficial effects of the drug despite a treatment period of 10-12 weeks.<sup>38,39,60</sup>

#### *Metformin for In Vitro Fertilization in PCOS*

An abstract of ASRM in 1990 showed that metformin treatment increased the number of mature oocytes retrieved from women with PCOS undergoing gonadotropin stimulated *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI).<sup>62</sup> Metformin treatment 500 mg twice daily from day 1 of the cycle prior to GnRH suppression significantly increased the number of mature oocytes, fertilization rates and number of embryo produced. Stadtmauer and coworker<sup>62</sup> reported improvement in IVF and pregnancy rates in CC-resistant PCOS patients pretreated with metformin. They administered 1000-1500 mg metformin daily for 1 cycle before induction with gonadotropins. Fertilization and clinical pregnancy rates were higher in patients who received metformin. The author observed better response when metformin was used in combination with rFSH. These studies supports the use of metformin as an adjuvant treatment in CC resistant PCOS.

#### *Metformin and Early Pregnancy Loss in PCOS*

Women with PCOS are at increased risk of first trimester abortion due to high LH. First trimester abortion are reported to be 30-50% in women with PCOS,<sup>63-67</sup> which is three-fold higher than the rate of 10-15% reported for normal women.<sup>68,69</sup> In other way 36-82% of women with recurrent early pregnancy loss are reported to have PCOS.<sup>66,69-71</sup> Hyperinsulinemia has been implicated as an independent risk factor for early pregnancy loss.<sup>72</sup> Glueck et al found a very low rate of first trimester spontaneous abortion in patients receiving metformin during pregnancy.<sup>73</sup> Metformin reduces plasminogen activator inhibitor (PAI). PAI has a positive association with worse pregnancy outcome.<sup>74</sup>

#### *Metformin and Prevention of Gestational Diabetes Mellitus in PCOS*

Obesity, hyperinsulinemia and insulin resistance of PCOS are risk factors for developing gestational diabetes.<sup>2,4,37,41-43,46,74-81</sup> When metformin is used in resistant PCOS as adjuvant of ovulation inducing agent it reduces blood glucose level, so there is less chance of pancreatic beta cell exhaustion and development of gestational diabetes mellitus (GDM). Glueck et al found GDM in 31% of patients who did not take metformin vs 3% of patients who took it.<sup>82</sup> It represents a 10-fold reduction of GDM in PCOS patients who took

metformin compared with women who did not take it. In another study Glueck et al found GDM in 7% and 30% of patients with and without metformin respectively.<sup>83</sup> Begum MR et al<sup>84</sup> found that GDM was higher in CC resistant PCOS patients who did not continue metformin throughout pregnancy compared with patients of same category who continued it (30 vs 3.44%). Pregnancy increases requirements for insulin secretion. This along with insulin resistance increases demand on pancreatic beta cells.<sup>85-92</sup> Metformin reduces the demand on pancreatic beta cells and effects maintained throughout pregnancy and may have contributed to reduce the development of GDM.

### SAFETY ISSUE

Metformin for several reasons is the currently preferred insulin-sensitizing drug for the treatment of infertility in PCOS. The majority of ovulation studies were conducted with metformin so the weight of scientific evidence is greater for that drug. In addition metformin is easily available worldwide with well delineated side effects and toxicities. Among commercially available insulin sensitizing drugs only metformin has a reassuring safety profile for use during pregnancy. Metformin is classified as a category B drug, which means that no teratogenic effects have been demonstrated in animal models. No teratogenic effects or adverse foetal outcome were reported by any author.<sup>82-84, 93-95</sup>

### CONCLUSION

Superiority to reduce hyperinsulinemia in PCOS, hence enhancing ovulation and safety of metformin was proved by many researchers. Metformin can be used safely in PCOS patients who are not responsive to CC. It can eliminate laparoscopic ovarian drilling which is invasive and risky procedure. Its adjuvant use may reduce the cost of gonadotropins and risk of multiple pregnancies. Thus, before going for laparoscopic ovarian drilling and FSH administration in CC resistant PCOS patients it is a better recommended option of treatment.

### RECOMMENDATIONS

- In women with PCOS for whom pregnancy is a goal at a more distant time and patients are young then initial treatment with metformin combined with diet and exercise is an option to induce ovulation.
- In women with PCOS where rapid result is desired and patients are relatively elder with long infertility clomiphene citrate should be the first line agent.

- If patient is not responsive to CC or CC resistant then metformin can be used 6-8 weeks prior to readministration of CC and continued till pregnancy. Metformin can be started along with CC stimulation where previous response was nearly ovulatory.
- In spite of addition of maximum dose of metformin and CC if patient does not ovulate FSH is to be added according to response of previous cycle. This combination therapy reduces the dose of FSH and chance of hyperstimulation.

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