infertile women with hyperandrogenism, insulin resistance and PCOS as monotherapy or in combination with other ovulation induction drugs (2) and also as pre-treatment before intrauterine insemination or IVF/ICSI in women with PCOS (3-4).

However, looking in depth to the pharmacokinetics of metformin, we may see that it is associated with a reduction in aromatase activity in response to FSH (5). Insulin affects production of both androgen and estrogen; insulin therefore plays a central role in regulating the activity of theca and granulosa cells (5). By acting on the ovary and restoring normal ovarian activity, metformin positively modulates the reproductive axis (namely gonadotrophin-releasing hormone (GnRH)-LH episodic release)(6). Plasma concentrations of estradiol were significantly higher in cycles treated with FSH alone than in those treated with FSH and metformin. Thus it can be assumed that co-administration of metformin before and during gonadotrophin stimulation in the IVF/intracytoplasmic sperm injection (ICSI) cycle would result in a lower estradiol concentration than gonadotrophin alone, although this finding was not consistent in all studies (7). This would help to reduce the risk of OHSS.

But hypothesis alone is not valid without clinical trials and evidence should be based on highest quality clinical trials (the so called randomized controlled trials). Four RCTs studied the effect of metformin during ovarian hyperstimulation in IVF/ICSI in 283 women with PCOS (3, 8-10). Pooling the results of the four trials showed that metformin led to fewer cases of ovarian hyperstimulation syndrome (OHSS) (RR 0.33; 95% CI 0.13–0.80). Accordingly, Metformin is beneficial for prevention of ovarian hyperstimulation syndrome and when we consider its cheap price and safety then one should recommend it for every case undergoing IVF/ICSI program.

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The polycystic ovary syndrome (PCOS) is characterized by chronic anovulation and hyperandrogenism and affects approximately 5-10% of women of reproductive age (1-3). PCOS is the most prevalent endocrinopathy in women and by far the most common cause of anovulatory
Insulin resistance with compensatory hyperinsulinaemia is a prominent feature of the syndrome and appears to have a pathophysiologic role in the hyperandrogenism of the disorder for both lean and obese women with PCOS (5). Hyperinsulinaemia results in increased ovarian androgen biosynthesis in vivo and in vitro (6, 7) and decreased sex hormone-binding globulin (SHBG) synthesis (8). Collectively, these two actions of insulin increase circulating levels of free testosterone. Further, the increase in intraovarian androgens most likely contributes to anovulation. In this manner, hyperinsulinemia may play a causal role in the two key features of PCOS: androgen excess and chronic oligo- or anovulation.

The association of insulin resistance contributing to anovulation in PCOS has led to the promising therapy of insulin-sensitizing drugs to restore ovulation and enhance pregnancy. Of the insulin-sensitizing drugs, metformin has been the one studied most widely and has the most reassuring safety profile (9). Troglitazone (Thiazolidinedione) was withdrawn by the US Food and Drug Administration (FDA) in 1999 due to reports of liver toxicity and is no longer commercially available.

Metformin (biguanide) enhances insulin sensitivity in both the liver, where it inhibits hepatic glucose production, and the peripheral tissue, where it increases glucose uptake and utilization into muscle tissue. By increasing insulin sensitivity, metformin reduces insulin resistance, insulin secretion and hyperinsulinaemia (10).

**Metformin as first line treatment in PCOS**

The first randomized, placebo-controlled trial evaluating the use of metformin for ovulation induction in PCOS was conducted by Nestler and colleagues in 1998 (11). They randomized 61 obese women with PCOS to either metformin 500 mg or placebo three times daily for 35 days. If spontaneous ovulation did not occur, subjects were entered into the second phase of the study where they were given clomiphene 50 mg daily for 5 days while continuing to take metformin or placebo for another 30 days. During the first phase of the study, where metformin was compared with placebo, 12 of the 35 women (34%) on metformin ovulated spontaneously compared with only one of the 26 women (4%) in the placebo group (p<0.001). In the second phase of the study, 19 of 21 women (90%) on the combination of metformin and clomiphene ovulated compared with only two of 25 women (8%) who received placebo and clomiphene (p<0.001). Notably, the rate of ovulation was higher in the women who received metformin for 7 weeks than in those in the placebo group who underwent a single cycle of induction with clomiphene at the 50 mg dose (34% vs. 8%, respectively). Since then, several other studies have corroborated the above findings.

In 2003, the Cochrane Library published a systematic review of the use of metformin in PCOS (12). It included randomized controlled trials that compared insulin sensitizing drugs with placebo, no treatment, or an ovulation-induction agent such as clomiphene or gonadotropin. A total of 13 trials were included for analysis (11, 13-24). In almost all studies, metformin showed a favorable effect on ovulation rates. Metformin treatment resulted in spontaneous ovulation in 46% of women, compared with a 24% ovulation rate with placebo. Clinical pregnancy rate also increased by 2.8-fold with metformin treatment, but this was not statistically significant, probably because of the small number of subjects in these studies and the fact that pregnancy was not a defined outcome measure. One should not neglect that the majority of these studies were short-term in nature and therefore were biased against showing a beneficial effect with metformin, since recent studies suggest that it may take 3-6 months for metformin to exert an optimal improvement in ovulation in PCOS.

Recently, two double-blinded randomized controlled trials in which metformin was directly compared with CC as first-line treatment in 509 infertile women with PCOS were published (25, 26). The pooled clinical pregnancy rate after six months of treatment was significantly lower after metformin (27).

**Metformin as co-treatment in combination with CC**

Seven randomized controlled trials compared CC plus metformin with CC in 985 infertile women
with PCOS (14, 28-33). There was a significantly higher clinical pregnancy rate in the metformin plus CC group. However, there was significant heterogeneity in treatment effect across the trials.

Metformin in CC-resistant women

A randomized clinical trial in which metformin was compared with placebo in 18 infertile women with CC-resistant PCOS was reported by Ng et al. in 2001. In this small number of women there was no evidence of a difference in clinical pregnancy or live birth rate (34).

Five randomized controlled trials in which CC plus metformin was compared with CC alone in 210 infertile women with CC-resistant PCOS (35-39). Collectively, these studies showed that metformin plus CC led to a significantly higher clinical pregnancy rate than CC alone. Live birth rate was also in favor of metformin plus CC compared with the CC group.

Metformin versus laparoscopic ovarian drilling

Palomba et al. 2004 reported a randomized trial in which metformin treatment was compared with laparoscopic ovarian drilling (LOD). There was no difference in clinical pregnancy rate. Live birth rate however was higher in the metformin group (40).

In 2006, Kocak and Ustun published a randomized trial including 42 PCOS patients in which they compared LOD followed by metformin or LOD alone. There were no significant differences in clinical pregnancy rate or live birth rate between both groups (41).

Metformin and gonadotrophins

In 2003 George et al., published a randomized clinical trial where they compared metformin plus CC with gonadotrophins in 60 CC-resistant women. There was no difference in clinical pregnancy rate between the two groups. They did not report on live birthrate, multiple pregnancy rate or OHSS (42).

In four randomized controlled trials, FSH plus metformin was compared with FSH alone in 154 infertile women with PCOS (24, 25, 43, 44). The clinical pregnancy rate was significantly higher in the FSH plus metformin group compared with FSH only group. However, a difference in live birth rate could not be proven. Although metformin led to less multiple pregnancies, there was no evidence of a difference in OHSS.

Metformin use in IVF

Four trials studied the effect of metformin during ovarian hyperstimulation in IVF/ICSI in 283 women with PCOS (45-48).

In the first study, reasons for IVF treatment were not specified, patients number was (8 versus 9), the authors concluded that co-administration of metformin is therefore likely to increase the number of oocytes collected after ovarian stimulation in insulin-resistant women with PCOS but is unlikely to reduce the requirement for FSH. (45).

In the second study by Kjotrod et al. (n=37versus36), women received IVF or ICSI because of other fertility problems like tubal pathology, endometriosis or male subfertility. The results showed that pre-treatment with metformin prior to conventional IVF/ICSI in women with PCOS does not improve stimulation or clinical outcome (46).

In the third study, women with PCOS in whom conventional therapy had not lead to pregnancy, were included (n = 53 versus 55), they concluded that Metformin does not lead to any improvement in IVF/ICSI outcomes among patients with PCOS (47).

In the fourth study, reasons for IVF were failure of conventional therapy and other fertility problems, (n = 51 versus 47); 4 patients entered twice (48). the authors concluded that short-term co-treatment with metformin for patients with PCOS undergoing IVF/ICSI cycles does not improve the response to stimulation but significantly improves the pregnancy outcome and reduces the risk of OHSS. Combining the results of these trials did not show a significant difference between the women treated with metformin or placebo Live birth rate was reported in two studies (46, 48). There was no evidence of a significant difference between the two groups. Pooling the data of the two trials that reported multiple pregnancy gave no evidence of a significant difference between the two groups on multiple pregnancy rate (46, 48). OHSS was reported in all studies. When combining the
results, there was a significant reduced risk in favor of metformin (27).
There is no evidence for better live birth rates when metformin is used during ovarian hyperstimulation in IVF. This is based on two studies with a limited number of patients and with heterogeneous populations of women, as in one study a mix of women after failed ovulation induction and with other indications was included, while in the other studies only women with other fertility problems were included. In IVF addition of metformin may however, reduce the risk of OHSS.

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