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Pharmacogenomics of ovulation induction: facilitating decisions on who, when and how to treat

"Many have tried to find phenotypic factors that might influence the response to clomiphene. However, to date no model has been proposed that can reliably predict outcome in ovulation induction with clomiphene citrate."

Polycystic ovary syndrome (PCOS) is the most common form of anovulatory infertility. Estimating its prevalence is difficult due to the different criteria that are used to diagnose this syndrome. According to the NIH criteria, diagnosis is based on the presence of chronic anovulation and clinical or biochemical signs of hyperandrogenism [1]. In 2003, the Rotterdam European Society of Human Reproduction and Embryology (ESHRE)/American Society of Reproductive Medicine (ASRM)-Sponsored PCOS Consensus Workshop Group agreed to base the diagnosis on the presence of two of three possible features: clinical or biochemical hyperandrogenism, oligo- or an-ovulation, and the presence of polycystic ovaries on ultrasound examination [2]. The view of the Androgen Excess-PCOS Society Task Force is that PCOS should be defined by the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) and the exclusion of related disorders [3]. Due to this lack of consistency in phenotyping, PCOS is a heterogeneous syndrome, making tailored treatment difficult.

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Treatment of infertility in PCOS is mainly based on increasing the level of FSH exposed to the ovary either by antagonizing the effect of estrogen in the hypothalamus by clomiphene citrate or through a direct effect on the ovary with recombinant FSH. Less standardized treatment forms are insulin sensitizers (such as metformin) and aromatase inhibitors.

With clomiphene citrate, ovulation is restored in approximately 80% of treated patients, and clomiphene citrate resistance (no ovulation up to 150 mg) is seen in the other 20% [4]. Prediction of

response to clomiphene citrate is complex. Many have tried to find phenotypic factors that might influence the response to clomiphene [5–10]. However, to date no model has been proposed that can reliably predict outcome in ovulation induction with clomiphene citrate. Recently, we studied the relationship between a known polymorphism on the FSH receptor (p.N680S, rs6166) and clomiphene citrate resistance. In normal ovulatory women, this polymorphism results in different FSH levels within the normal range, pointing out a difference in sensitivity of the receptor [11]. It has been demonstrated that patients harboring the least sensitive variant (Ser/Ser) need higher doses of exogenous FSH for ovarian stimulation in ART [12–19]. In our data in women with PCOS, we could not find a difference in the FSH levels between different variants of the polymorphism, but found that the Ser/Ser variant was significantly more often present in women resistant to clomiphene citrate. This is probably caused by faulty feedback in the pituitary of PCOS patients. In women harboring the Ser/Ser-variant of the FSH receptor polymorphism, it is more difficult to overcome the FSH threshold after which follicle maturation start [20]. On the latest ESHRE congress in Amsterdam, data was presented showing that harboring the Ser/Ser variant of the FSH receptor polymorphism was significantly associated with a decreased chance of pregnancy when treated with clomiphene citrate [21]. For tamoxifen, a drug structurally much alike clomiphene citrate, pharmacogenomic data is accumulating. The same mechanisms that explain poor response to tamoxifen could be applicable for clomiphene citrate resistance (for example, *CYP2D6* polymorphism) [22] and in this way might be a source for new hypotheses in the field of ovulation induction.

If clomiphene citrate does not lead to ovulation (clomiphene resistance) or subsequent pregnancy (clomiphene failure), second-line

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treatment consists of exogenous gonadotropins. Recombinant FSH stimulates follicle recruitment and follicular growth and maturation and is prescribed in a low-dose step-up protocol, aiming at slowly surpassing the FSH-threshold by starting at a low dose of recombinant FSH and slowly increasing the dose, reducing the risk of excessive stimulation and development of multiple preovulatory follicles. Overall, low-dose regimens result in a monofollicular ovulation rate of approximately 70% and a pregnancy rate of 20% [23]. However, the precise dose in which monofollicular growth occurs varies widely among individuals and is particularly difficult in PCOS patients, who are prone to hyperstimulation. The gap in our understanding of the pharmacogenomic pathways in ovulation induction is well demonstrated by the finding that the presence of the Ser/Ser variant in treatment with recombinant FSH is associated with a 80% higher chance of pregnancy [21].

“Because ovulation induction is an emotional, costly and time consuming treatment, it is of great importance that data on pharmacogenomics will be incorporated in future research, allowing more accurate scoring and thus better patient care.”

Metformin is commonly used as a drug to induce ovulation, however, its efficacy remains controversial. Metformin probably improves ovulation in women with PCOS by reducing gluconeogenesis, improving insulin sensitivity and reducing ovarian androgen production. Similar to clomiphene and recombinant FSH, much remains unclear regarding which patient benefits the most from treatment with metformin. From recent studies it seems that metformin is most effective in insulin-resistant PCOS patients, particularly in the non-obese group [10]. Some small steps are made in order to clarify the variance in response in patients. In the field of pharmacogenomics for diabetic care, OCT1, an organic cation transporter critical for elimination of foreign

substances, was found to be highly polymorphic, contributing to variation in response to the drug in diabetic patients [24]. This might very well also be relevant for patients treated for ovulation induction. Legro *et al.* reported that a polymorphism on the *STK11* gene affected ovulation rates in women with PCOS treated with metformin [25].

In summary, data about pharmacogenomics for ovulation induction drugs is sparse. Deducing the aforementioned information to some simple recommendations for tailored treatment would lead to the following: if the patient is lean, has a low free-androgen index, has a sensitive variant of the FSH receptor polymorphism and/or is not insulin resistant, she is likely to ovulate on clomiphene citrate. Lean and insulin resistant patients are best treated with metformin, while patients with a Ser/Ser-variant of the FSH receptor polymorphism and obese patients have the most favorable outcome with recombinant FSH treatment. However, these recommendations are based on a few studies and there have been no studies in which the different treatments and influencing factors, both on a genotypic as well as on a phenotypic level, have been adequately compared in a reasonably large population.

Because ovulation induction is an emotional, costly and time consuming treatment, it is of great importance that data on pharmacogenomics will be incorporated in future research, allowing more accurate scoring and thus better patient care. In the future doctors should apply a combination of phenotypic and genetic markers as routine diagnostic tests before starting ovulation induction in order to be able to choose the most effective drug for each patient.

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