PRECONCEPTION METABOLIC OPTIMIZATION AND PHARMACOLOGICAL SEQUENCING IN WOMEN WITH POLYCYSTIC OVARY SYNDROME: FROM INSULIN SENSITIZATION TO OVULATION INDUCTION

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ABSTRACT. Polycystic ovary syndrome (PCOS) is characterized by complex interactions among insulin resistance, hyperinsulinemia, adiposity, hyperandrogenism, disturbed folliculogenesis, and chronic anovulation. These abnormalities may coexist in different combinations, creating heterogeneous metabolic and reproductive phenotypes. In women planning pregnancy, therapeutic success may therefore depend not only on direct ovulation induction but also on preconception correction of adverse metabolic factors.

Objective. To evaluate the rationale for a staged pharmacological strategy in women with PCOS, integrating preconception metabolic optimization with subsequent ovulation induction according to the dominant metabolic–reproductive phenotype.

Materials and Methods. A focused narrative analysis of contemporary evidence concerning insulin resistance, obesity, hyperandrogenism, ovulatory dysfunction, and pharmacological treatment of PCOS was performed. Particular attention was given to metformin, glucagon-like peptide-1 receptor agonists, letrozole, clomiphene citrate, and gonadotropins. Therapeutic strategies were evaluated according to their effects on metabolic risk, body weight, insulin sensitivity, ovulation, fertility outcomes, and reproductive safety.

Results and Discussion. Current evidence supports a phenotype-oriented rather than uniform therapeutic approach. In women with marked insulin resistance, central adiposity, dyslipidemia, or impaired glucose regulation, preconception metabolic optimization may represent an important first step before active fertility treatment. Metformin remains the most established insulin-sensitizing drug and may improve fasting glucose, insulin resistance, menstrual cyclicity, and selected endocrine parameters. Its principal role, however, is metabolic rather than direct ovulation induction.

GLP-1 receptor agonists represent an emerging option for women with PCOS and excess body weight. Their major benefit is clinically significant weight reduction and improvement of metabolic risk. Nevertheless, their use requires careful reproductive planning because pregnancy safety data remain limited, and they should not be considered established fertility drugs.

When the primary therapeutic goal is restoration of ovulation, letrozole remains the preferred first-line pharmacological strategy in women with anovulatory infertility and no additional infertility factors. By inhibiting aromatase and reducing estrogen-mediated negative feedback, letrozole promotes endogenous follicle-stimulating hormone secretion and dominant follicle development. Clomiphene citrate remains an effective alternative, while combination of clomiphene with metformin may be useful in selected women with a more pronounced metabolic phenotype.

A clinically rational sequence may therefore include initial correction of metabolic abnormalities in women with obesity or insulin resistance, followed by ovulation induction when pregnancy is actively

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planned. This strategy should not be applied rigidly, because delayed fertility treatment may be undesirable in older reproductive-age women. Age, ovarian reserve, metabolic severity, previous treatment response, and reproductive priorities should therefore determine the timing and sequence of therapy.

Conclusion. Preconception management of PCOS should integrate metabolic and reproductive goals. Metformin is best positioned as a metabolic modifier, GLP-1 receptor agonists as weight-centred therapy in appropriately selected women, and letrozole as the preferred first-line agent for anovulatory infertility. A staged pharmacological strategy based on metabolic phenotype, reproductive intention, and age may provide a more individualized approach than treatment based solely on ovarian morphology. Future prospective studies should determine whether preconception improvement of insulin resistance and body weight translates into higher ovulation, pregnancy, and live-birth rates.

Keywords: polycystic ovary syndrome, preconception care, insulin resistance, metformin, GLP-1 receptor agonists, letrozole, ovulation induction, infertility, pharmacological sequencing.

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