

Benefits of Metformin in Reproductive-Age Women

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Metformin in Reproductive Health, Pregnancy and Gynaecological Cancer: Established and Emerging Indications

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Background

Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality that affects women of reproductive age and can be diagnosed in 5%-10% of them. It is characterized by oligo-ovulation, hyperandrogenism, and polycystic ovaries.^[1] Insulin resistance plays an important role in its etiology. The liver and skeletal muscles are resistant to the actions of insulin, so in order to maintain euglycemia, insulin is overproduced. Insulin and insulin-like growth factor (IGF), however, act as a growth factor in the ovary and stimulate its androgen synthesis. Androgens are then responsible for hirsutism, acne, and arrested follicle development as well. Over 50% of women with PCOS are overweight or obese, which further augments insulin resistance.

PCOS is not the only condition accompanied by insulin resistance. Being overweight or obese is also associated with insulin resistance. Insulin resistance, if left untreated, can ultimately result in glucose intolerance and even type 2 diabetes.

This review summarizes the known and potential benefits of metformin therapy in reproductive-age women.

Reproductive Health

The benefits of metformin have been extensively studied among infertile women diagnosed with PCOS. The lack of regular ovulation is usually the primary cause of infertility among them. Clomiphene citrate is the typical first-line drug administered to induce follicle growth. Metformin is also frequently prescribed to help ovulation, although randomized trials have not shown superior results when compared with clomiphene. A systematic review found improved ovulation rates with metformin over placebo (OR, 1.81; 95% CI, 1.13-2.93), and the combination of metformin plus clomiphene resulted in superior results over clomiphene alone (OR, 1.74; 95% CI, 1.5-2). Clomiphene and metformin also have a positive impact on pregnancy rates. Among obese women with PCOS, clomiphene is more likely to result in live birth when compared with metformin alone.

Pregnancy

Metformin could also have an important role in women with PCOS who undergo in vitro fertilization treatment, as it is associated with a significant reduction in risk for ovarian hyperstimulation syndrome (OR, 0.27; 95%CI, 0.16-0.47). Women with PCOS are at increased risk for complications during pregnancy, such as gestational diabetes, hypertensive complications, and toxemia. The use of metformin is safe in pregnancy; an increased risk for congenital anomalies has not been seen, and the drug has not been shown to affect fetal growth or postnatal development. Miscarriage rates have not been shown to be affected by metformin. The use of metformin, however, was associated with a reduction in maternal weight gain during pregnancy, a lower incidence of hypoglycemia, and a need for less insulin to manage gestational diabetes. Neonatal outcome was comparable with metformin and insulin among women with gestational diabetes. Metformin may have further beneficial actions during pregnancy, as it affects placental development and function and could also have positive effects on fetal metabolic programming.

Gynecologic Cancer

Obese women and those with insulin resistance or type 2 diabetes are more likely to be diagnosed with certain types of cancer. Preclinical studies have shown that metformin has growth static effects through the inhibition of glucose metabolic pathways in various cancer cell lines. Preliminary human studies have shown antiproliferative effects with breast and prostate cancer, especially among obese patients.

Obese women and those with diabetes and insulin resistance are also at increased risk for endometrial and ovarian cancer. Metformin has been evaluated as adjuvant therapy for ovarian and endometrial cancer, but the full benefit is still to be determined because epidemiologic studies have reported conflicting results.

Metformin has been widely used among those with insulin resistance and has been shown to have a positive impact on obesity, gestational diabetes, and cardiovascular complications. Its use may be associated with further benefits. Preliminary studies have reported a possible role in cancer care, and it also could improve the long-term outcome of children born to mothers with insulin resistance.

Viewpoint

Insulin resistance plays a role in the pathogenesis of various diseases. Obesity typically further augments insulin resistance and the two findings often accompany each other. Without proper intervention, insulin resistance could lead to type 2 diabetes, is associated with an increased cardiovascular risk, is a risk factor for certain types of cancers, and has significant reproductive consequences.^[2]

One cannot rely on medical therapy solely; the introduction of lifestyle changes, including a proper diet, regular exercise, and weight loss, has to be part of a successful treatment.

Those who do not improve with lifestyle modifications are usually placed on metformin. Metformin reduces gluconeogenesis in the liver and increases glucose uptake in the muscles and liver. It improves the lipid profile and results in weight loss.^[3] Metformin lowers glucose and IGF levels, and through this effect it may inhibit tumor growth.^[4]

While metformin has already been shown to improve ovulation and pregnancy rates, its reproductive effects in infertility care are often overestimated; hence, it is important that it not be used alone or as a first-line agent for the sake of improving reproductive function.^[5] Many would be reluctant to use it during pregnancy despite the available evidence that it is safe.^[6] In addition, little is known about its potential anticancer effects. However, information is accumulating in support for broader use of metformin for patients with insulin resistance.

Abstract

References

1. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod.* 2004;19:41-47. [Abstract](#)
2. Nagi DK, Yudkin JS. Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. A study of two ethnic groups. *Diabetes Care.* 1993;16:621-629. [Abstract](#)
3. Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation--implications for a novel treatment strategy. *Gynecol Oncol.* 2010;116:92-98. [Abstract](#)
4. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev.* 2012 May 16;5:CD003053.
5. de Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. *Hum Reprod Update.* 2011;17:495-500. [Abstract](#)
6. Lautatzis ME, Goulis DG, Vrontakis M. Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: a systematic review. *Metabolism.* 2013;62:1522-1534. [Abstract](#)

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