Review Article

Use of Metformin in Pregnant Women with Polycystic Ovarian Syndrome and the Need for Follow-up of their Offspring

Chidera Nneji Obiegbusi*

Department of Gynecology, Shenyang Medical College, Shenyang, Liaoning Province, China

Corresponding author:
Chidera Nneji Obiegbusi,
Department of Gynecology,
Shenyang Medical College,
Shenyang, Liaoning Province, China,
E-mail: 13072498010@163.com

Received: 20-Jun-2022,
Manuscript No. AMHSR-22-67083;
Editor assigned: 22-Jun-2022,
PreQC No. AMHSR-22-67083 (PQ);
Reviewed: 06-Jul-2022,
QC No. AMHSR-22-67083;
Revised: 22-Aug-2022,
Manuscript No: AMHSR-22-67083 (R);
Published: 29-Aug-2022,
DOI: 10.54608.annalsmedical.2022.19

Abstract

Women with Poly Cystic Ovarian Syndrome (PCOS) who become pregnant have a high risk of metabolic and endocrine disorders that predispose them to complications such as gestational diabetes, miscarriage, small for gestational age infants, and neonates with an increased risk of admission to a neonatal intensive care unit, among others. Metformin, the first line treatment for type 2 diabetes, provides an attractive therapeutic option for managing such patients due to its benefits on various metabolic aspects. Using metformin to treat women with PCOS during pregnancy has yielded favorable pregnancy outcomes. However, some recent reports associate prenatal exposure to metformin with obesity in children. Additionally, several animals' studies associate metformin use in pregnancy to sexual and fertility problems in the offspring, which highlights the need to conduct clinical studies specially designed to assess these types of undesirable outcomes in humans. In conclusion, there is a need to weigh the risks against the benefits of prescribing metformin for different patient groups. Moreover, it should be recommended to give parent counseling regarding the potential development of overweight in their children.

Keywords: Metformin; Pregnancy; Polycystic ovarian syndrome; Offspring; Long-term effect

Introduction

Poly Cystic Ovarian Syndrome (PCOS) is the most common endocrine disorder affecting women which is complicated with infertility, hyperandrogenism, insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, and adverse cardiovascular effect [1,2]. According to the 2003 Rotterdam ESHRE/ASRM consensus, PCOS diagnostic criteria should be based on the presence of at least two out of the three following findings:

- Identification of polycystic ovaries on ultrasound.
- Clinical or biochemical hyperandrogenism.
- Oligo/anovulation.

The global prevalence of PCOS is unknown due to limited data from several geographical regions but is estimated to range from 6% to 26% among women of reproductive age [3]. PCOS is a leading cause of an ovulatory infertility, accounting for more than 90% of an ovulatory women seeking treatment for infertility [4,5]. Therefore, women with PCOS have difficulty getting pregnant without medical intervention. On the other hand, the prevalence of insulin resistance among patients with PCOS is between 34.78% and 64% [6,7]. Insulin resistance is a typical characteristic of normal pregnancy due to several hormonal changes, such as elevations in human placental lactone, progesterone, and cortisol levels. However, a combination of PCOS and physiological hyperinsulinemia in pregnancy places patients at a higher risk of complications, such as an increased risk of gestational diabetes, Early Pregnancy Loss (EPL), preterm delivery, preeclampsia, and cesarean section. Moreover, their underlying medical condition predisposes them to a higher risk of fetuses and neonatal complications; small for gestational age infants, fetal intrauterine growth restriction, fetal microsomal, and neonates with an increased risk of admission to a Neonatal Intensive Care Unit (NICU) [8-11]. Metformin, an insulin sensitizer used for treating type 2 diabetes, significantly reduces the rate of miscarriage, gestational diabetes requiring insulin

How to cite this article: Obiegbusi CN. Use of Metformin in Pregnant Women with Polycystic Ovarian Syndrome and the Need for Follow-up of their Offspring. Ann Med Health Sci Res. 2022;12:1-4

treatment, and fetal growth restriction when administered during pregnancy to women with PCOS [12-16]. However, since some studies have found a correlation between prenatal exposure to metformin, and reproductive and metabolic impairment in the offspring of treated mothers, there is much concern about the metformin treatment during pregnancy. In this review, we discuss the clinical and experimental evidence showing a possible negative impact of metformin on the offspring's metabolism and fertility.

Literature Review

Metformin

Metformin (1,1-dimethylbiguanide hydrochloride) is the first line treatment for type 2 diabetes because of its benefits in glycemic profile and the reduction in cardiovascular mortality [17]. After oral administration, metformin arrives in the liver where it decreases glucose production and opposes glucagon mediated signaling, resulting in glucose lowering, improved glucose tolerance, and enhanced insulin sensitivity [18-20]. Metformin also enters the cells through organic cation transporters and exerts its actions, primarily, in the mitochondrion. It inhibits complex I, decreasing the efficiency of the electron transport chain that decreases ATP generation and the activation of AMP Activated Protein Kinase (AMPK). AMPK regulates lipogenesis, gluconeogenesis, mechanistic target of kanamycin (mTOR), and NF kappa B signaling, among others. The inhibition of mitochondrial complex I also impair the response to glucagon. In women with PCOS, metformin administration can decrease insulin resistance, promote weight loss, restore regular ovulatory cycles, decrease androgen levels, limit the likelihood of early pregnancy loss, and lower the risk of gestational diabetes These benefits are carried out through its action on several tissues, such as the liver, adipose tissue, skeletal muscle, and ovary. Regarding exertion, metformin is mainly excreted from the body through kidneys without previous metabolization by the liver. Thus, metformin is contraindicated in patients with abnormal renal function because of the risk of developing lactic acidosis, one of its most side effects. Considering side effects, metformin commonly causes gastrointestinal symptoms, such as nausea, constipation, diarrhea, abdominal pain, distended abdomen, and heartburn. These symptoms range from mild to severe but resolve spontaneously in most cases. Rarely, one-third of patients develop vitamin B_{12} deficiency following chronic metformin use and they need to receive vitamin B_{12} supplementation.

Metformin use in pregnant women with the polycystic ovarian syndrome

Obstetricians find it challenging to manage pregnant women with PCOS due to their complications and risk factors 6,8,11. However, several traits implicated in early pregnancy have demonstrated that metformin improves weight loss and insulin resistance in addition to decreasing hyperandrogenism. Based on several Randomized Control Trials (RCT), metformin is associated with a reduction of spontaneous abortions and the risk of gestational diabetes mellitus. Therefore, the use of metformin in the management of PCOS in pregnancy is increasing.

Benefits in glucose homeostasis

Compared with healthy women, patients with PCOS are more prone to have abnormal glucose intolerance during pregnancy. Since metformin's benefit to risk ratio exceeds that of other insulin sensitizers, its administration in pregnancy is the preferred treatment to control their blood glucose level a meta-analysis carried out. Reports that in five out of seven studies analyzed, metformin reduces the development of gestational diabetes mellitus in pregnant women with PCOS. Furthermore, Chrysostom et al. compared the effects of metformin treatment in a historic PCOS group with untreated patients in a small cohort study and found that the prevalence of gestational diabetes mellitus drops from 36% to 14%. On the other hand, few studies refute claims of metformin lowering the risk of gestational diabetes development. For example, during 2019, an RCT evaluated metformin use for managing PCOS in pregnant women from 3 different countries showed that metformin did not prevent gestational diabetes. Additionally, in the same study, they found that metformin may lower the risk of preterm birth and miscarriage.

Improvements in androgen levels

Androgen excess is associated with ovarian dysfunction and infertility in non-pregnant women with PCOS. In pregnancy, androgen excess is linked to low birth weight and EPL 10. Decreasing testosterone levels, therefore, will improve pregnancy outcomes. Metformin is postulated to inhibit androgen production. Various clinical studies have demonstrated that metformin limits the elevation in androgen concentration by working on the adrenal gland and the ovary. Regarding the involved mechanism, it has been suggested that metformin reduces pituitary luteinizing hormone secretion and increases the production of sex hormone binding globulin by the liver. A study examining the mechanism by which metformin reduces androgen production showed that metformin treatment decreases the androgen production in the human adrenal cortex derived cell line NCI-H295R by inhibiting the activity of microsomal enzyme catalyst, which is essential for the biosynthesis of glucocorticoid, sex steroid precursors (CYP17-lyase), and protein-coding gene, hydroxy-delta-5-steroid dehydrogenase, 3 beta and steroid delta-isomerase 2 (HSD3B2).

Improvements in gestational hypertension

Metformin decreases the risk of gestational hypertension and preeclampsia possibly through improving endothelial function and lowering the production of antigenic factors. A meta-analysis of RCTs confirmed that metformin use reduces the incidence of hypertensive disorders in pregnancy leading to a decrease in the frequency of first trimester pregnancy loss.

Teratogenicity studies of metformin treatment

Metformin is an FDA category B drug: Metformin crosses the placenta with a 36.3% placental partition coefficient and has a cord plasma concentration of 0.1-2.9 mg/L during labor. However, animal studies have shown that the administration of high doses of metformin to pregnant females does not result in carcinogenic or teratogenicity effects in their fetuses. There is limited evidence regarding metformin's safety and efficacy from research studies conducted on human beings. A previous observational 3 years cohort study investigated the occurrence of fetal abnormalities following intrauterine exposure to metformin. It showed that exposure to metformin during the first trimester is not associated with an increase in the incidence of congenital anomalies. Moreover, a systematic review and meta-analysis of first-trimester exposure to metformin and the occurrence of congenital birth defects among offspring of pregnant women with PCOS demonstrated unaltered rates of congenital defects in the metformin exposed group compared with the metformin unexposed group.

Long-term effect of prenatal exposure to metformin

Despite the clinical evidence of the benefits of metformin treatment in PCOS pregnant women and the absence of teratogenicity effects, there is still some concern about the possibility of long-term adverse consequences of this medication on infants subjected to prenatal exposure, due to some studies reporting metabolic and reproductive abnormalities.

Evidence in animals

Recent animal studies have focused on the long-term metabolic effects of prenatal exposure to metformin in the offspring. Among the positive findings, metformin was found to improve glucose tolerance and insulin secretion in male offspring, as well as glucose tolerance in old female mice. Moreover, metformin exposure in pregnancy does not lead to cardiovascular and metabolic impairment in rat offspring. On the contrary, some disadvantages of using metformin have been described in the offspring of pregnant rodents. One study found that adult mice that had experienced prenatal exposure to metformin showed significantly increased body weight in adulthood. Moreover, other studies demonstrated that metformin exposure during pregnancy is associated with the reprogramming of theca and granuloma cells in rats, due to elevated plasma estradiol levels during the estrus stage. Recently, an evaluation of the intrauterine effect of metformin on the ovaries and uteri of rat offspring illustrated that maternal exposure to metformin during pregnancy can decrease the endometrial thickness and estradiol production of their offspring. Finally, Álvarez et al. demonstrated that metformin administration in rats could limit the elevation in estradiol levels and reduce the number of antral follicles, follicular cysts, and multiple oocyte follicles in fetal ovaries, thereby preventing ovarian abnormality during adulthood. In addition, metformin is postulated to cause sexual dysfunction in rats. A study that evaluated the relationship between maternal use of metformin in pregnancy and reproductive parameters in their male offspring showed that these male offspring had sexual impairment (decreased sperm count), compared with their unexposed counterparts. More evidence was added by a similar research study showing that the in *vivo* administration of metformin to pregnant rats reduced fetal and neonatal testicular sizes of their offspring.

Evidence in humans

There are a limited number of studies on the long-term effect of intrauterine exposure to metformin and they show conflicting results regarding offspring's body weight. Besides showing that metformin is not teratogenicity found that it did not have any effect on the offspring's weight or growth in their first 18 months of extra uterine life. Similarly, another study shows that metformin exposure during fetal life did not affect children body composition and growth at 8 years of age. In contrast, a recent meta-analysis investigating the long-term effect of intrauterine exposure to metformin that followed-up children with prenatal exposure to metformin up to the age of 13 years and compared them to children without metformin exposure, documented heavier weights in children exposed to metformin. Nonetheless, that study showed that body composition, metabolic parameters, and neurophysiological development did not differ between groups. Similar results were observed in a meta-analysis conducted in which the offspring of women with PCOS or gestational diabetes mellitus followed up for 9 years showed that children exposed in utero to metformin are heavier than controls. Moreover, an RCT reported that children with prenatal exposure to metformin weighed more than their unexposed counterparts in their first year of age. Finally, an RCT that followed-up offspring to the age of 4 years documented a higher body mass index and incidence of overweight and obesity among children prenatally exposed to metformin. Regarding potential sexual and fertility problems, prepuberal testicular size in male offspring with prenatal exposure to metformin has been shown to be unaltered.

Discussion

Metformin is an oral antidiuretic drug used in the management of type 2 diabetes and has recently been adopted to treat pregnant women with PCOS because of its favorable pregnancy outcomes. Although metformin crosses the placental barrier, most reports do not suggest any significant adverse effect or teratogenicity. However, its use in pregnancy remains a controversial issue because some recent reports associate the use of this medication as a risk factor for obesity in children who were exposed to the medication during intrauterine life. In addition, several animal studies associate metformin use in pregnancy to decreased sperm count and reduced testicular size in male offspring, and reprogramming of theca and granulose cells during fetal development in females. Hence, further studies in humans regarding fertility and sexual problems in the offspring of pregnant women with PCOS treated with metformin are needed.

Conclusion

In conclusion, based on the available evidence we suggest being cautious. Healthcare providers and patients should be informed about the need to follow-up the offspring of all women with PCOS that were prenatally exposed to metformin since the long-term clinical implications of childhood overweight in those patients is still unclear. Finally, long-term clinical follow-up studies should be conducted to determine if the sexual and fertility complications found in rodents are also replicated in humans.

Acknowledgments

We are grateful to the management of the second affiliated hospital of chongqing medical university for their support in providing the necessary material for this review.

Compliance with Ethical Standards

The management approved this study in line with the regulations of the second affiliated hospital of Chongqing medical university guideline for all studies.

Declaration of Interest

None.

References

1. Practice Committee of the American Society for Reproductive Medicine. Obesity and reproduction: an educational bulletin. Fertil Steril. 2008;90:21-29.
2. Fauser BCJM. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81:19-25.
3. Rao M, Broughton KS, LeMieux MJ. Cross-sectional Study on the Knowledge and Prevalence of PCOS at a Multiethnic University. Prog Prev Med. 2020;5:0028.
4. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex conditions with psychological, reproductive and metabolic manifestations those impacts on health across the lifespan. BMC Med. 2010;8:41.
5. Giviziez CR, Sanchez EGM, Approbato MS, Maia MCS, Fleury EAB, Sasaki RSA. Obesity and anovulatory infertility: A review. JBRA Assist Reprod. 2016;20:240.
6. Boomsma CM, Eijkemans MJC, Hughes EG, Visser GHA, Fauser BCJM, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update. 2006;12:673-683.
7. Tabassum R, Imtiaz F, Sharafat S, Shukar-ud-din S, Nusrat U. Prevalence and clinical profile of insulin resistance in young women of poly cystic ovary syndrome: A study from Pakistan. Pakistan J. 2013;29:593-596.
8. Palomba S, De Wilde MA, Falbo A, Koster MPH, La Sala GB, Fauser BCJM. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update. 2015;21:575-592.
9. Sir-Petermann T, Hitchsfeld C, Maliqueo M. Birth weight in offspring of mothers with polycystic ovarian syndrome. Hum Reprod. 2005;20:2122-2126.
10. Boomsma CM, Fauser BCJM, Macklon NS. Pregnancy complications in women with polycystic ovary syndrome. Semin Reprod Med. 2008;26:72-84.
11. Qin JZ, Pang LH, Li MJ, Fan XJ, Huang RD, Chen HY. Obstetric complications in women with polycystic ovary syndrome: a systematic review and meta-analysis. Reprod Biol Endocrinol. 2013;11:56.
12. Ghazeeri GS, Nassar AH, Younes Z, Awwad JT. Pregnancy outcomes and the effect of metformin treatment in women with polycystic ovary syndrome: an overview. Acta Obstet Gynecol Scand. 2012;91:658-678.
13. Nawaz FH, Khalid R, Naru T, Rizvi J. Does continuous use of metformin throughout pregnancy improve pregnancy outcomes in women with polycystic ovarian syndrome? J Obstet Gynaecol Res. 2008;34:832-837.
14. Lovvik TS, Carlsen SM, Salvesen O. Use of metformin to treat pregnant women with polycystic ovary syndrome (PregMet2): a randomised, double-blind, placebo-controlled trial. lancet Diabetes Endocrinol. 2019;7:256-266.
15. Crisosto N, Echiburu B, Maliqueo M. Improvement of hyperandrogenism and hyperinsulinemia during pregnancy in women with polycystic ovary syndrome: possible effect in the ovarian follicular mass of their daughters. Fertil Steril. 2012;97:218-224.
16. Vanky E, Stridsklev S, Heimstad R. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. J Clin Endocrinol Metab. 2010;95:448-455.
17. Davies MJ, D Alessio DA, Fradkin J. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41:2669-2701.
18. Jorquera G, Echiburu B, Crisosto N, Sotomayor Zarate R, Maliqueo M, Cruz G. Metformin during Pregnancy: Effects on Offspring Development and Metabolic Function. Front Pharmacol. 2020;11:653.
19. Pernicova I, Korbonits M. Metformin-mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinal. 2014;10:143-156.
20. Sam S, Ehrmann DA. Metformin therapy for the reproductive and metabolic consequences of polycystic ovary syndrome. Diabetologia. 2017;60:1656-1661.