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Journal of Endocrinology, Diabetes & Obesity

Mini Review

Effect of Metformin on Reproduction–A Mini Review

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Abstract

About 10% of European couples are suffering infertility problems. The underlying cause is evenly distributed. In the female polycystic ovaries, often associated with anovulatory cycles, contribute to a high extend of underlying problems. Despite the anovulation many of these have an underlying insulin resistance and increased risk of ovarian hyperstimulation syndrome when ovarian hyperstimulation is performed. Last but not least, when conception is achieved the prevalence of recurrent abortion, as well as increased gestational complications are increased in women with polycystic ovaries and /or insulin resistence. Therefore the Off-label use of the anti-diabetic drug metformin has been tested as a treatment option in combination with different reproductive procedures. Last, but not least, since many advantages could be noted in women with PCOS under the metformin therapy, the range of application has been widened. This review will shed some light on the different potential implication of Off-label metformin therapy in reproductive medicine.

Special Issue on

Antidiabetic Drug-Metformin

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Submitted: 25 March 2014

Accepted: 26 May 2014

Published: 28 May 2014

ISSN: 2333-6692

Keywords

- Metformin
- In vitro fertilization
- Assisted reproduction
- Insulin resistance
- Polycystic ovarian syndrome

ABBREVIATIONS

PCOS: Polycystic Ovary Syndrome; OHSS: Ovarian Hyperstimulation Syndrome

INTRODUCTION

Metformin (1, 1-dimethylbiguanide hydrochloride) is a biguanide with actions in different tissues,mainly improving insulin sensitivity [1,2]. A decrease in endogenous glucose production by the liver followed by a reduction of hyperinsulinemia has been demonstrated [3], as well as direct changes in tyrosine kinase activity of the insulin receptor in the peripheral target tissues sensitive to insulin [4]. The use of Metformin has a wide range of implication in reproductive medicine, including restoration of the menstrual cycle with follicular development, changes in endometrial biology, co-application during ovarian hyperstimulation, potential implication during pregnancy, as well as potential effects on sperm quality, all of which will be discussed in detail in this article.

Metformin effect on ovulation induction

Particularly anovulatory, hyperinsulinemic women with PCOS are successfully treated off-label with metformin [5]. This has been proven in many studies showing a restoration of follicular development, which is thought to be due to a reduction peripheral androgen levels, followed by spontaneous ovulation thus increasing fertilization rates in women with PCOS [6-9]. Furthermore, in obese women with polycystic ovary syndrome, the use of metformin in addition to regular exercise does not only facilitate the weight control, but also contributes to the reduction of hyperandrogenemia, supporting the restoration of menstrual regularity [3].When metformin therapy is used to establish ovulatory cycles in women with PCOS, monofollicular development is typically seen, therefore reducing the risk of multiple gestations [7,10]. However, while several studies suggest a benefit of metformin treatment in anovulatory women trying to conceive this is still highly controversial [11].

Metformin and *in vitro* fertilization parameters/ outcome

The effect of metformin in PCOS women undergoing gonadotrophin stimulation for ovarian induction or *in vitro* fertilization has been previously studied [12,13]. Against the underlying hypothesis these groups did not show higher ovulation, nor pregnancy rates. Nevertheless, it is important to observe that metformin therapy during/prior to in vitro fertilisation reduces the risk of ovarian hyperstimulation syndrome (OHSS), a common feature in women with PCOS. The Cochrane analysis by Tso found a similar effect in reduction of OHSS while pregnancy rates and live birth rate were not improved, therefore making ovarian stimulation a safer procedure. Similarly, a systemic review of randomized control trials of PCOS women undergoing in vitro fertilisation with or without metformin treatment by

Palomba came to the same conclusion, that metformin did not improve the overall pregnancy rate or live birth rate. However, ovarian hyperstimulation syndrome as well as the miscarriage rate were significantly reduced and the implantation rate increased in the metformin group [14]. In a previous work of the same research group, Palomba suggested that pre-/cotreatment with high doses of metformin during *in vitro* fertilisation cycles lead to a prolongation of stimulation time needed and therefore higher overall gonadotropin doses used, followed by a reduced number of dominant follicles at the time of ovulation induction, suggesting an influence of metformin on the oocyte maturation process [15].

In an intention to treat analysis of Kjortrod, higher clinical pregnancy rates and live birth rates were noted in PCOS women with normal body mass index (BMI) with pretreatment of metformin for 12 weeks prior to *in vitro* fertilisation which could be contributed to higher conception rates during the time until IVF treatment was started, as pregnancy rates and live birth rates were identical in the IVF treatment groups in accordance to the above statement [16]. While metformin therapy is considered to be an easy, safe and low-cost drug [16], Legro still advises gynecologists to be careful with metformin treatment for women with PCOS undergoing IVF until more convincing evidence is available [17].

There is also a possibility that live birth rates might improve in embryo transfer cycles, when embryos were electively cryopreserved due to ovarian hyperstimulation during metformin treated in vitro fertilisation cycles compared to controls [18].

While metformin is typically used in women with PCOS, it has been looked at its effect on other patient groups. Particularly women with polycystic ovaries without any further signs of the polycystic ovary syndrome (menstrual cycle abnormalities or hyperandrogenism) were studied, as these women react to gondadotropin stimulation in a similar fashion as PCOS patients with an increased risk of ovarian hyperstimulation syndrome. However, no beneficial effect of metformin could be noted concerning the frequency of ovarian hyperstimulation neither regarding pregnancy nor life birth rate in this subpopulation [19].

Jinno examined a low dose metformin treatment in women, who experience repeated unsuccessful in vitro fertilisation cycles independent of a PCOS feature. When 500mg metformin per day was administered prior to IVF in women with a discrimination score above 0,667 higher pregnancy rates were achieved compared to control or women with a discrimination score below 0,667, suggesting a potential benefit by insulin reduction in this particular subgroup of women. The discriminant score was calculated from 9 parameters obtained before administration of metformin (age, body mass index, number of previous failed IVF/ICSI attempts, fasting plasma glucose (FPG), fasting insulin resistance index (FIRI, fasting glucose x fasting insulin/25), HOMA-R, SBP, and the hepatic enzymes ALP, and γ-GTP) [20].

In addition to this, Manno and Tomei (2014) suggest in a retrospective analysis, that metformin might reduce the risk of premature luteinisation of endometrial tissue, a factor that negatively affects embryo implantation rates. This beneficial effect seems to be independent of the underlying reason for infertility and needs to be further elucidated [21].

Metformin therapy during pregnancy

Recently, Tang. revised a meta-analysis on the effect of metformin on women with PCOS [11]. Live birth rates were not different when metformin alone was compared to metformin plus comiphene citrate (CC), but higher pregnancy rates were noted, when metformin alone was compared to placebo and when the combination of metformin with CC was compared to CC alone. Particularly a subgroup analysis showed that non-obese PCOS patients had better clinical pregnancy rates (metformin compared to placebo). However, heterogeneity was too high in the analysis of live births in non-obese women for the results to be pooled for analysis [11]. Miscarriage and multiple pregnancy rates were similar between the obese and non-obese patient groups.

Hyperinsulinemia, often associated with obesity and hyperandrogenemia, as well as secondary changes within the blood clotting system are thought to be responsible for fetal growth restriction and increased risk of fetal abortions in women with PCOS [22]. Even elevated plasma testosterone levels found independent of the PCOS phenotype seem to be associated with recurrent miscarriages [23]. Since the hyperinsulinemia, as well as the elevated androgen serum levels are believed to impair endometrial function during the implantation window, the improve pregnancy outcome under metformin therapy, particularly in women with a history of early pregnancy loss, can be explained by it's positive influence on the insulin resistance and hyperinsulinemia, as well as on the normalisation of the hyperandrogenemia [24].

Women with PCOS are particularly prawn to develop gestational diabetes. While many women with PCOS become pregnant while taking metformin off-label to improve pregnancy rates (see above), the treatment is mostly stopped, when pregnancy is established. In order to find out, if continuation of the metformin medication might improve pregnancy outcome for the mother, Khattab. studied the continuation of metformin throughout pregnancy in comparison with the cessation of the medication after conception was achieved [16]. A significant benefit with a reduced incidence of gestational diabetes and preeclampsia was found in the continuous treatment group, suggestion its benefit during pregnancy. It is important to notice that PCOS women with preconceptional insulin resistance experienced fewer miscarriages and other gestational diseases [including gestational hypertension and gestational diabetes, as well as preterm deliveries] when metformin was continued throughout pregnancy in a low maintenance dose after the first trimester [25].

Metformin effect on fertilisation

While the endometrium as well as the overall insulin sensitivity seems to benefit from metformin treatment, bovine studies using metformin either during the *in vitro* embryo production or on the *in vitro* fertilisation process showed a negative metformin effect on the cleavage capacity of oocytes after insemination most likely through changes in the AMPK pathway [26].

Bertoldo (2014), on the other hand, found a higher fertilization rate and number of normal zygote development when frozen mouse sperm was used which was cryopreserved in the presence

of low concentrations of metformin [27].

Metformin therapy influences endometrial perfusion

In a small study (n = 20 in each group), Kazerooni have demonstrated that in women with clomiphene citrate (CC) resistance, short term co-treatment with 500 mg metformin three times a day could improve endometrial thickness (9.69±1.96 vs. 7.24±1.41, $p < 0.001$, metformin plus CC vs. placebo plus CC), cervical score (9.16±1.08 vs. 7.15±1.06, $p < 0.001$) and increase the number of patients with a mature follicle on day 14 (16 (88.9%) vs 4 (21.05%))[28].

In addition, endometrial parameters are changed by the application of metformin in PCOS women. Not only the endometrial thickness is improved, but the endometrial blood flow is also increased and thought to support adequate implantation and pregnancy development [10].

Similarly, Mohsen demonstrated a significant increase in the endometrial thickness, endometrial volume, and endometrial and subendometrial vascularity indices (vascularization index, flow index, vascularization flow index) after 6 months of metformin treatment in PCOS women. However, the resistance index and the pulsatility index of the uterine artery in both periovulatory and midluteal phases remained unchanged [29].

Effect of metformin on the molecular changes of the endometrium

While several in vitro studies have suggested a direct effect of metformin on the gene expression as well as the decidualization capacity of endometrial stromal cells [30,31], an *in vivo* study of Dafopoulos demonstrated that administration of 850 mg metformin twice a day in healthy women lead to a change of the expression of corticotropin-releasing hormone (CRH) and urocortin within the endometrial tissue during the window of implantation [32]. Furthermore, endometrial samples taken from women with PCOS and insulin resistance taking metformin for at least 3 month compared to untreated women showed different GLUT4 gene and protein expression. In this study, the metformin therapy led to an increased GLUT4 expression, demonstrating its effect on the insulin-signalling pathway within endometrial tissue [33]. Similar effects could be noted *in vitro*, where testosterone pretreated endometrial epithelial cells demonstrated a reduction of GLUT-4, as well as insulin receptor substrate-1 expression, which could be restored by the addition of metformin [34], while insulin pretreated endometrial stromal cells demonstrated elevated GLUT-4 expression which could be attenuated by metformin treatment [35,36]. *In vitro* studies have shown that insulin induced androgen production in theca cells is ameliorated by metformin [37] and that endometrial epithelial cells are more sensitive to insulin in an hyperandrogenic state when metformin is present [34].

Metformin as a treatment option in gynaecological diseases

Newer gynaecological indications for off-label metformin therapy include treatment of endometrial hyperplasia [38] as well as endometrial carcinoma [39] (see chapter about metformin and cancer therapy).

Side-effects: Metformin was also associated with increased gastrointestinal symptoms such as nausea and diarrhea [11].

CONCLUSION

While many options of off-label metformin treatment are discussed above, including ovulation induction as well as reduction of pregnancy complications and OHSS during in vitro fertilization, larger studies are still needed to determine the benefit of this therapy in different patient groups.

ACKNOWLEDGEMENT

Edison Capp is scholarship recipient from CNPq and participates as Guest Professor at the Excellence Initiative from Heidelberg University.

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Cite this article

Germeyer A, Capp E (2014) Effect of Metformin on Reproduction–A Mini Review. J Endocrinol Diabetes Obes 2(2): 1037.