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REVIEW ARTICLE

Metformin and Pregnancy Outcomes: Evidence Gaps and Unanswered Questions

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Abstract: ***Background*:** Metformin is sometimes used as an alternative to insulin in gestational diabetes mellitus (GDM). It is also used to achieve ovulation in polycystic ovary syndrome (PCOS). Pre-natal exposure to metformin results from its continuation after a successful ovulation in women with PCOS, its maintenance in women with pre-gestational diabetes or the installation of metformin in GDM. Little is known about the potential consequences of metformin exposure on pregnancy outcomes and offspring development. The aim of this review is to summarize the metformin effects on pregnancy outcomes and offspring development. Gaps in the available evidence and unanswered questions are also discussed.

***Methods*:** A comprehensive literature search was carried out to identify eligible studies from MEDLINE/PubMed, EMBASE and SCIELO databases through 1995 first semester.

***Results*:** Several factors limit the effect of metformin on embryos. In contrast, placental transport of metformin is effective allowing for a higher fetal exposure; the impact of this finding remains unclear. It seems that the interruption of metformin after a pregnancy diagnosis in women with PCOS is not associated with a higher miscarriage risk and it continuation does not seem to impair the maternal metabolic prognosis or prevent emerging GDM.

***Conclusions*:** It seems to have no sense to prolong the use of metformin after a pregnancy diagnosis in women with PCOS. Patients with GDM may be treated with metformin under on judicious basis, and a careful attachment to clinical guidelines and regulations is recommended. The long-term effects of pre-natal exposure to metformin on the offspring remain uncertain

Keywords: Metformin, gestational diabetes mellitus, polycystic ovary syndrome, pregnancy outcomes.

1. INTRODUCTION

Metformin is a biguanide agent (1,1-dimethylbuguanide) used as first line therapy for the treatment of type 2 diabetes [1]. It has also recommended as an alternative to insulin in the treatment of gestational diabetes mellitus (GDM) [2]. GDM is a frequent entity that may affect pregnant women. It is usually defined as a type of diabetes that starts or is first recognized during pregnancy. Its prevalence varies according to the applied diagnostic criteria, ethnicity, personal and family antecedent and other factors. According to the United States Centers for Disease Control and Prevention (US CDC) data, it might affect close to 10% of all pregnancies [3]; some other Countries report up to 15% prevalence rates [4]. GDM accounts for 85-90% of all cases of diabetes in pregnancy [4]. In addition, metformin is frequently used to achieve ovulation in women with polycystic ovary syndrome (PCOS). PCOS, that affects 5-10% of women at childbearing age, is a treatable cause of infertility by affecting ovulation in several ways. When pregnancy is achieved, women with PCOS display a higher risk of adverse pregnancy outcomes, pre-term birth, GDM and pregnancy associated hypertension and pre-eclampsia [5]. Infant mortality seems to be also elevated [5].

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In practice, pre-natal exposure to metformin may result from (i) the continuation of the metformin treatment after a successful ovulation in women with PCOS, (ii) the maintenance of an oral treatment in women with pre-gestational type 2 diabetes mellitus or (iii) the installation of metformin as part of the treatment of GDM after diagnosis. Metformin crosses the placental barrier and achieves fetus concentrations close to those observed in mothers [6]. Even when its potential effects on embryos seem to be very limited, metformin may act on the placenta and fetuses inducing a series of intracellular and metabolic effects. As suggested from *in vitro* and animal studies, metformin may also induce some epigenetic effects that could affect the metabolic phenotype of the offspring [7]. Nevertheless, little is known in this area and the relevance of these findings in human being is still to be clarified.

Even when a significant number of studies have been conducted on women with PCOS exposed to metformin evaluating pregnancy outcomes and potential changes in children phenotype, many relevant questions persist still unanswered. Similarly, the recommendation of metformin for GDM treatment, as well as its benefits and risks on the mother and children, remains a matter of strong debate far yet of being elucidated. The impact of discontinuing metformin in women with PCOS after a diagnosis of pregnancy (including risk of miscarriage, emerging GDM and/or pre-eclampsia) as well as the effects of metformin exposure throughout pregnancy on the offspring phenotype and growing pattern in patients with PCOS or GDM are examples of valid questions to be addressed and answered in order to shed some more light on this challenging topic in this area of practical endocrinology.

The aim of this review is to summarize the available knowledge about the effects of metformin exposure on pregnancy outcomes and offspring phenotype and growth, as well as the potential practical derivations of these findings in clinical endocrinology. In addition, some key gaps in the available evidence as well as some unanswered questions in this field will be also pointed out and discussed.

2. METFORMIN AND ITS MECHANISMS OF ACTION

Metformin clinical effects on glucose metabolism in patients with type 2 diabetes are well known. However, the molecular mechanisms of action of metformin are not entirely understood. By reducing the mitochondrial electron transport in the liver, metformin activity is associated with an inhibition of gluconeogenesis and lipogenesis that results in blood glucose reduction (with a very low incidence of hypoglycemia and no drug-induced increase in body weight) as well as some favorable changes in the lipid profile [8]. Nevertheless, the effects of metformin are not confined to the liver. Some anti-inflammatory effects (associated with changes in cytokine concentrations as well as a reduction in the differentiation of monocytes into macrophages) have been described and some hemorheological actions (probably linked to this anti-inflammatory profile) have been identified [8]. Metformin-induced modification on the intestinal microflora, with an increase in the *Akkermansia* population and a reduction in *Intestinibacter spp* contribute at least in part to the systemic metabolic and anti-inflammatory effects of the drug [8]. Direct and indirect effects of metformin facilitating the intestinal secretion of Glucagon-Like Peptide-1 (GLP-1) are also associated with at least a part of the metabolic and pleiotropic benefits associated with the use of the drug.

The use of metformin in other insulin resistance states (for instance, PCOS) proved more controversial. Insulin sensitizers, selective estrogen receptor modulators and aromatase inhibitors are commonly used for ovulation induction in patients with PCOS [9]. Metformin alone increases the ovulation rate in women with PCOS when compared with placebo [10]. Several mechanisms have been postulated to explain this effect on ovulation. The benefits and risks of keeping metformin after a successful ovulation resulting in pregnancy will merit for a deeper discussion in the following sections.

Despite being the most widely used drug in the treatment of type 2 diabetes mellitus, the mechanisms of action of metformin are poorly known. Metformin inhibits the mitochondrial complex I activity at mitochondria, reducing the ratio of ATP to AMP concentration (Fig. **1**) [11]. It has been proposed that this effect results in an increased AMP kinase (AMPK)-Thr172 phosphorylation. The activity of this enzyme is enhanced and a down-regulation of key gluconeogenic enzymes is observed. Metformin also inhibits the activities of acetyl-CoA carboxylase 1 (ACC1) and ACC2, modulating lipid homeostasis [11-13]. This increase in the AMPK activity results in an inhibition of the mTOR pathway which is associated with a decrease in protein synthesis and cell proliferation as well as apoptosis, autophagy and cell cycle modulation [8]. Some non-AMPK-dependent mechanisms of metformin have also been proposed [8]. The relevance of these mechanisms to explain the clinical benefits of metformin is a matter of strong debate. It has been suggested that the previously described mechanisms cannot explain some of the key clinical effects of the drug [14]. Many other alternative pathways have been explored. For instance, it has been proposed that by inducing mitochondrial dysfunction, the biguanide phenformin triggers a loss of RagC from the cell nuclei that, in turn, results in an inhibition of the nuclear pore complex (NPC), a critical step in mTORC1 activation [14]**.** Nuclear effects of metformin (including some epigenetic changes) may play an important role in the clinical response to the drug. Many of these non-canonical mechanisms of metformin action are still under scrutiny.

Some more complex effects are potentially associated with a direct or indirect inhibitory action of metformin on the mTORC pathway. As an example, it has been demonstrated that metformin can modulate and normalize the autophagy rate and flow in several tissues in patients with type 2 diabetes, as well as induce some noticeable changes in the apoptosis rate (not only by down-regulating the mTORC pathway but also by reducing the reactive oxygen species production at several steps) (Fig. **1**) [15].

Other indirect effects of metformin have also been described. Vitamin B12 deficiency is informed in patients receiving metformin with some frequency. Reductions in

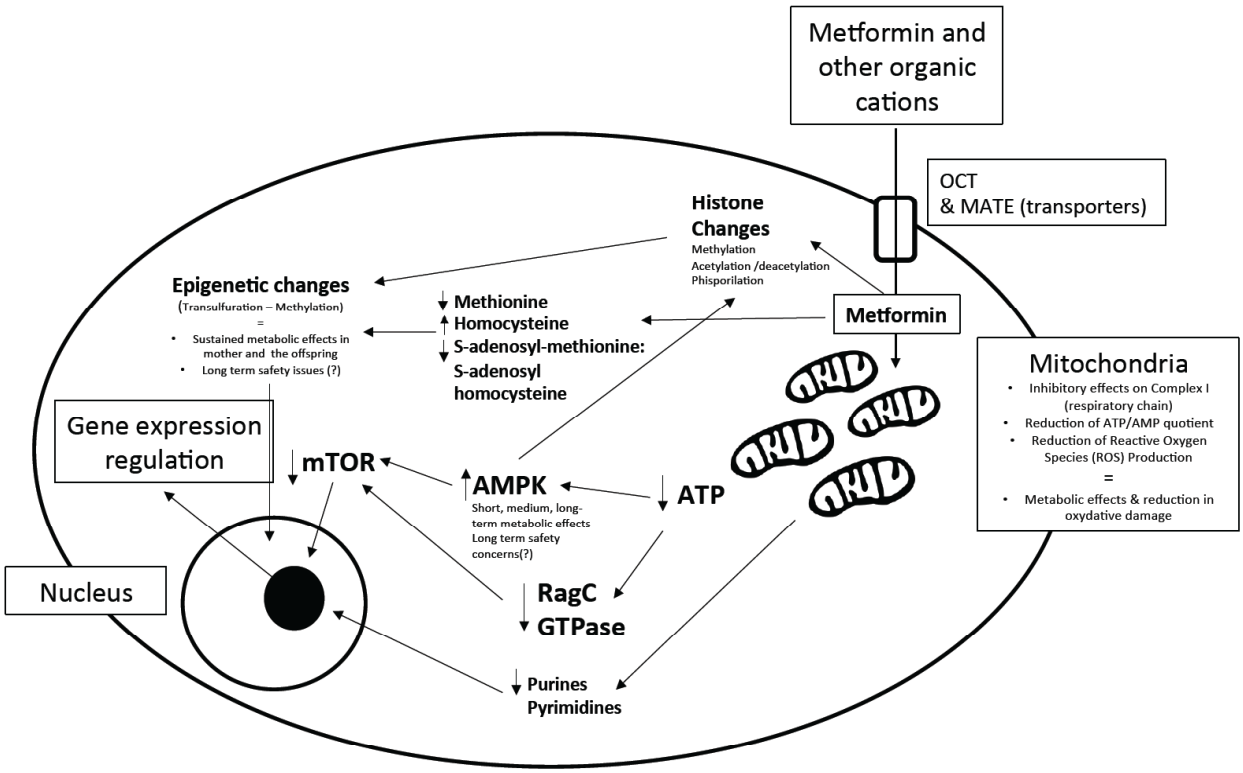

Fig. (1). Molecular mechanism of action of metformin.

blood red cell folate concentrations have also been informed and serum concentrations of homocysteine have been reported elevated [16]. Several studies reported Vitamin B12 and folate changes in pregnant women under metformin treatment [7]. Decreased folate and Vitamin B12 levels might potentially have some impact on the mothers and also on the development of the offspring. Nevertheless, it seems that these reductions in concentrations might have some clinical relevance only in women at severe risk of deficiency [7]. The potential relevance of these findings on pregnancy outcomes and the offspring is not clear.

3. TRANSPLACENTAL TRANSPORT AND EFFECTS ON EMBRYOS AND FETUSES

Metformin passes across the placental barrier [17]. Studies in pregnant women reported that umbilical cord serum concentrations of metformin at delivery are at least comparable to maternal concentrations of the drug [18]. Due to its hydrophilic nature, metformin exists as a cationic species at physiological pH with low lipid solubility. From the pharmacokinetics standpoint, metformin has an oral bioavailability close to 50%, with a negligible binding to plasma proteins and a predominant urinary excretion as unmodified drug: the renal clearance of metformin is increased by a third in the two last trimesters of pregnancy when compared with postpartum reflecting the changes in glomerular filtration rate and renal blood flow registered along these periods [7]. Concentrations in breast milk are very low to be considered relevant in practice [7].

Metformin transmembrane passage is mostly transporter dependent. The Organic Cation Transporter- 3 (OCT-3) seems to play a significant role in the transplacental transport of metformin [18]. Human placentas mainly express OCT3/Oct3 mRNA with minimal or null transcription of other cation transporters OCT1/2 and MATE1/2 at the basal membrane in the placental barrier [18]. OCT-3 expression is directly, positively associated with gestational age.

Even when transmembrane passage of metformin is facilitated by OCTs, experiences in mice suggest that OCT-3 and MATE 1 expression in embryos is extremely low making the drug access to the intracellular environment very difficult [2]. In contrast, fetuses are exposed to higher concentrations of metformin that penetrates much easier inside the cytoplasmic compartment [6].

Placental exposure to metformin is highly variable, depending on several conditions including the health status and the pregnancy stage. In addition, and even when metformin seems not to concentrate into the placental tissues, potential effects of the drug on the placenta have been described and were also linked to placental functional and structural alterations. As previously mentioned, a significant part of the metformin effects rely on its activity in the mitochondrial respiratory chain. Placental mitochondrial dysfunction seems to be linked with several pregnancy-associated disorders. For instance, preeclampsia is associated with alterations in the placental perfusion as well as with an increased production of reactive oxygen species [19]. Mitochondrial fission, fusion, and alterations in the mitochondrial content have been demonstrated in placental tissues from women with preeclampsia [19]. Mitochondrial complexes I, III, and IV seem to be decreased in preeclampsia [20]. Some of these changes are associated

with epigenetic patterns [20]. Metformin modifies the mitochondrial physiology by inhibiting the Complex I activity at the respiratory chain; moreover, reactive oxygen species production at this step is also reduced. The oxidative damage is decreased and some mechanisms linked to cell death are down-regulated [21]. Metformin might protect the mitochondria from oxidative damage. Maternal diabetes and maternal obesity have also been linked to mitochondrial structural and functional alterations [19]. Metformin reduces endothelial dysfunction, the concentration of circulating markers of vascular dysfunction and ROS production by mitochondria [20]. It has been hypothesized that metformin might have some beneficial effect on placental function and circulation in women with several metabolic alterations [19]. Nevertheless, the impact of these effects on relevant clinical outcomes is a matter of debate [6]. In a small randomized placebo-controlled clinical trial carried out in pregnant women with PCOS, Doppler ultrasound examinations of the uterine arteries suggested that metformin treatment in pregnancy was associated with a reduction in uterine artery impedance between 12 and 19 weeks of gestation [22]. In another small randomized trial, a sample of pregnant women was divided into three groups receiving metformin 2000 mg or aspirin 80 mg daily, or no intervention until the end of pregnancy: metformin and low dose aspirin reduced uterine artery impedance at week 20 [23]. These results suggest that metformin might improve the uteroplacental circulation in pregnant women with PCOS. A more recent study failed in demonstrating any immediate effect on the uterine artery pulsatility index in pregnant women with PCOS other than some reduction in blood flow after a meal [24]. Whether these circulatory effects on the placenta may have some impact on the pre-eclampsia rates in women with PCOS and/or GDM remains unclear. No definitive conclusions can be extracted from this limited number of small studies and further research on this field is granted.

As mentioned before, the effects of metformin on embryos are likely minor, if any. Firstly, because the exposure of embryos tissues to metformin seems to be minimal due to a quite limited transport through OCTs. Secondly, because some metabolic particularities of embryos physiology might impose some limits to the effects of metformin. For instance, the dependency on mitochondrial aerobic respiration increases with gestational time, reaching their maximal intensity by the second and third trimesters of gestation. As a critical step in metformin mechanism of action involving a certain degree of mitochondrial respiratory chain inhibition, a relevant part of the metformin effects may be limited in embryos when compared with fetuses [25]. In summary, relevant direct effects on embryos seem unlikely; in contrast, some effects on fetuses are biologically plausible even when their demonstration and consequences in human beings are not conclusive.

4. METFORMIN IN WOMEN WITH PCOS: EFFECTS ON PREGNANCY OUTCOMES AND OFFSPRING GROWTH AND DEVELOPMENT

The PregMet study [26] was a prospective, randomized, placebo controlled, multicenter trial in pregnant women with PCOS aimed to determine the preventive effects of metformin exposure from first trimester to delivery on pregnancy complications. The primary endpoints for this study were prevalence of preeclampsia, preterm delivery, emerging GDM and a composite of the diagnoses. No significant differences between metformin and placebo were detected in terms of pregnancy or newborn associated main outcomes [26]. Nevertheless, head size of the metformin treated group newborns was larger when compared with the placebo results. In a post hoc analysis of ultrasound data on this study population, metformin exposed offspring had larger heads at week 32 (bi-parietal diameter 86.1mm versus 85.2 mm, $p= 0.03$) and at birth (head circumference 35.6 cm vs. 35.1 cm, $p < 0.01$). Nevertheless, these differences were only observed in offspring of overweight or obese mothers [27]. A follow-up of children of mothers who participated in "The Metformin Treatment of Pregnant Women with Polycystic Ovary Syndrome study" or the PregMet study found that children exposed to metformin had higher Body Mass Index (BMI) ($p <0.01$), with a higher prevalence of overweight/obesity at 4 years of age, with an Odds Ratio (OR) of 2.17 (95% Confidence Interval: 1.04 to 4.61), $p=0.038$ [28]. A limited proportion of the original population was available for follow-up. The rate of smokers was lower among the mothers of the followed-up children when compared with the non-followed subset. These aspects may impose certain limitations in the interpretation of these results. Authors suggested that an intracellular catabolic process may result from the inhibitory effect of metformin on complex I of the respiratory chain and the consequent reduction in the ATP: AMP quotient -in some way, similar to starvation [29]. This process initiates, in turn, several signaling cascades able to induce several epigenetic changes finally affecting postnatal life (in the way proposed by the so called "Barker hypothesis") [29]. This programming effect might explain the differences in weight. Similar explanations have been also proposed by other authors [30]. Nevertheless, the evidence results inconclusive. The lack of consistency with other studies is manifest. Postnatal growth of children exposed to metformin during pregnancy of mothers with PCOS did not differ from reference at the age of 18 months in a non-randomized clinical study [31]. Feng *et al* published a meta-analysis aimed to evaluate the efficacy of metformin on pregnancy-related PCOS [32]. This meta-analysis included five studies (two randomized trials; 3 non-randomized ones) with 502 PCOS patients exposed to metformin throughout pregnancy and 427 controls who used metformin just to get conception were included. The PregMet study results were included into this systematic review. A lower rate of emerging miscarriage as well as of prematurity was observed in the exposed group, with a pooled relative risk reduction of 68% for miscarriage and 60% for premature birth. No difference was detected in the rate of emerging GDM and pre-eclampsia [32]. Nevertheless, other meta-analyses failed in demonstrating a clear result on miscarriage risk (as described below).

In a large monocentric prospective cohort study on the safety of metformin treatment in the first trimester of pregnancy (336 exposed pregnancies and 1011 matched controls), no increase in the risk of congenital malformations was observed [33]. The exposed cohort included pregnancies with metformin exposure for PCO (56.8%), diabetes (25.9%) and 'insulin resistance' (14.9%) [33]. The pattern of birth

defects among the exposed cohort and those recorded retrospectively in an adverse drug reaction database did not differ. Neither the proportion of major birth defects (adjusted OR 0.58, 95% CI 0.3–1.3) nor of abortions (adjusted Hazard Ratio [HR]: 0.95, 95% CI 0.6–1.5) was increased among the exposed pregnancies [33].

It has been suggested that metformin use in women with PCOS could be associated with an increase in pregnancy rates or live-birth proportion when compared with placebo. Taking into consideration the available evidence from randomized clinical trials and meta-analyses comparing metformin vs placebo, there is insufficient data to suggest that metformin may elevate live-birth rates [10]. Nevertheless, in combination with clomiphene citrate, metformin seems to improve ovulation and pregnancy rates without improving live-birth when compared with clomiphene alone [10].

As mentioned before, it has also been suggested that metformin might have a potential beneficial effect in reducing miscarriage risks along the pregnancy. In addition, the potential risk of stopping metformin after the diagnosis of pregnancy may be a matter of concern. Nevertheless, several limitations affect the quality of the evidence in this field. Several meta-analyses found no increase in the risk of miscarriage when metformin was stopped [10]. Stopping metformin does not seem to be associated with an increased risk of miscarriage in women with PCOS. Nevertheless, the available information is limited in terms of quality and quantity, and further research in this area is granted.

Finally, metformin does not seem to modify the future metabolic profile in women with PCOS after 7.7 years of follow-up [34]. Similarly, metformin does not seem to prevent the development of GDM in women with pre-gestational insulin resistance [35]. Statistical power and some methodological issues may affect the validity of these conclusions and more research is needed in both areas.

5. METFORMIN IN GDM

Metformin effects on pregnancy outcomes were also explored in women with GDM. Several randomized clinical trials compared the use of metformin vs. insulin in the treatment of GDM. In the 'Metformin in Gestational diabetes' (MiG) trial, women with GDM were randomized to receive either metformin (plus insulin if needed) or insulin [36]. A 46.3% of the women at the metformin arm required insulin supplementation to improve glycemic control. Pregnancy outcomes did not differ between the groups. Nevertheless, an increased rate of preterm birth (12.1% vs. 7.6%, p=0.04) was observed among the metformin exposed pregnancies. To note, this difference was attributed to a higher proportion of spontaneous, non- iatrogenic, preterm births. The effect of chance on these results could not be excluded. No increase into the complications rate was observed among the preterm birth subset. On the other hand, neonates of pregnant women exposed to metformin exhibited significantly lower rates of severe hypoglycemia (3.3% vs. 8.1%) (severe hypoglycemia defined as <1.6 mmol of glucose per liter [28.8 mg per deciliter]) when compared with insulin [36].

Some offspring of women enrolled in the MiG trial were followed up as part of the MiG TOFU study comparing body composition and some metabolic outcomes at 7–9 years of age in those children exposed to metformin (plus/minus insulin) during pregnancy with the those of mothers treated with insulin (without metformin) [37]. Both groups had a similar total and abdominal body fat proportion and metabolic measures at 7–9 years. Nevertheless, metformin-exposed children were larger at 9 years [37]. Some weaknesses in the study design and follow-up should be noticed. The follow-up rate was relatively low; in addition, the population included in this follow-up study seems to differ in many aspects from the original MiG trial one. The open label design imposes additional limits to the validity of the study. Pubertal status was determined through a parental questionnaire (instead of a physician's examination) and the adjustment for confounding factors was limited by the power of the sample. In consequence, even when interesting, it is very difficult to sustain a definitive conclusion from the results of this study [37]. In another randomized study, metformin exposure from pregnancies with GDM resulted in heavier children at 18 months of age. Nevertheless, it was found that the growth of the metformin-exposed offspring was quite proportional. Those children were taller than controls [38]. Niromanesh *et al*. also compared women with GDM treated with metformin vs. insulin between the weeks 20 and 34 of pregnancy in a randomized clinical trial [39]. No difference in neonatal and obstetric outcomes was found, but the proportion of neonates with a body weight above the 90^{th} percentile was lower in the metformin treated group [39]. In another comparative randomized clinical trial, Mesdaghinia *et al*. found no difference in birth weight, Apgar test or neonatal hypoglycemia rates between both arms; in contrast, the incidence of neonatal jaundice was higher among the children of mothers in the insulin arm [40]. In another randomized study, Ainuddin *et al*., compared treatment with metformin alone, metformin plus insulin and insulin alone in women with GDM. The results found, less maternal weight gain a lower risk of pre-eclampsia and neonatal complications among metformin treated subjects, with a lower weight at birth when compared with insulin [41]. As a general finding for all the previously described trials, the need for supplemental insulin to optimize the glycemic control was higher in the metformin arms.

Several meta-analyses of randomized clinical trials comparing metformin vs insulin in patients with GDM revealed no relevant differences in terms of maternal outcomes, with a lower maternal weight gain in those patients treated with metformin [7]. Su and Wang published a meta-analysis of six randomized clinical trials including 1420 women concluding that metformin use in gestational diabetes was not significantly associated with any major adverse maternal or neonatal outcomes [42]. As seen in other reports, less weight gain was observed in mothers receiving metformin as well as a lower rate of neonatal hypoglycemia was also demonstrated. Nevertheless, a higher rate of premature birth was informed for the metformin exposed arms [42].

CONCLUSION

The use of metformin to treat some of the clinical features associated with PCOS results in highly heterogeneous responses. While a moderate benefit is generally recognized within the area of the body composition

and weight maintenance, no clear beneficial effects have been described in the management of hirsutism, alopecia, acne, menses regulation and live birth rate [43]. Benefits on glucose intolerance are also accepted, but its long-term implications remain uncertain. Outcomes of metformin therapy of type 2 diabetes are well established with a large body of clinical evidence in favor, being a first line drug for treatment of these patients as established at several guidelines and consensus reports [44]. In the field of GDM, the use of metformin to control maternal glucose excursions is considered acceptable for several regulatory bodies and agencies across the World, always associated with appropriate lifestyle changes [2]. Nevertheless, many medical associations remark that insulin should be considered as the first-line agent to consider for managing GDM [2]. Long-term safety data are scarce and relatively week, and many unanswered questions remain open.

Even taking into consideration the limited amount of good quality evidence available in this field of knowledge, some conclusions can be drafted from the information previously discussed:

1. The impact of the potential effects of metformin on the embryos seems to be limited by several pharmacokinetic and pharmacodynamic factors such as the low or null expression rate of OCT transporters and a lower dependency of embryonal tissues on mitochondrial respiration.
2. In contrast, placental transport of metformin is effective, allowing for a higher fetal exposure to the drug; nevertheless, the clinical impact of this higher exposure rate is difficult to estimate in human beings.
3. Effects of metformin on the placenta are plausible; some effects on placental circulation have been informed. Nevertheless, the potential benefits of these placental actions on pregnancy associated complications (such as pre-eclampsia, for instance) are not elucidated.
4. Even when the available information in this area is very limited, it seems that the interruption of metformin after a pregnancy diagnosis in women with PCOS is not associated with a higher risk of miscarriage.
5. The use of metformin in pregnant women with PCOS does not seem to impair their metabolic prognosis or prevent emerging GDM.
6. Beneficial effects on pregnancy outcomes with metformin are uncertain.
7. Taking all the previous items into consideration, even when the probability of major effects on the embryos is apparently very low, it seems to have no sense to prolong the use of metformin after a pregnancy diagnosis in women with PCOS. As emerging GDM is more frequent in patients with PCOS, the importance of the screening for GDM should be emphasized in these women. Even when the utility of persisting on metformin during the first trimester of pregnancy is probably low, it seems unlikely to face major risks for the embryos within this period.
8. The risk / benefit profile of remaining on metformin treatment along the second and third trimesters persists still unclear for this PCOS patients.
9. Patients with GDM may be treated with metformin on judicious basis, and a careful attachment to clinical guidelines and regulations is recommended. The long-term effects of pre-natal exposure to metformin on the offspring remain uncertain.
10. Several unanswered questions may be extracted from the list of conclusions presented above. Much more research is needed to clarify many relevant topics at almost all the items listed before. The availability of an effective oral drug to manage GDM should be always considered as a highly valuable resource. Nevertheless, the quality of the available information in the field of the potential long-term effects of metformin exposure on the offspring growth and development imposes a call for a careful judgment and a highly individualized approach as well as for a more active research in this important area of endocrinology.

DECLARATION OF FINANCIAL/OTHER RELATIONSHIP

The authors have indicated that they have no conflicts of interest regarding the content of this article and have received no payment in the preparation of this manuscript.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Bailey CJ. Metformin: historial overview. Diabetologia 2017; 60: 1566-76.
[2] Lindsay RS, Loeken MR. Metformin use in pregnancy: promises and uncertainties. Diabetologia 2017; 60: 1612-9.
[3] DeSisto CL, Kim SY, Sharma AJ. Prevalence Estimates of Gestational Diabetes Mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007-2010. Prev Chronic Dis 2014; 11: E104.
[4] International Diabetes Federation (IDF). Diabetes Atlas. 7th Edition 2015. http://www.diabetesatlas.org/ (Accessed Oct 10, 2018).
[5] Lazaridou S, Dinas K, Tziomalos K. Prevalence, pathogenesis and management of prediabetes and type 2 diabetes mellitus in patients with polycystic ovary syndrome. Hormones (Athens) 2017; 16: 373-80.
[6] Barbour LA, Scifres C, Valent AM, Friedman JE, Buchanan TA, Coustan D, *et al*. A cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. Am J Obstet Gynecol 2018; 219: 367-72.

[7] Priya G, Kalra S. Metformin in the management of diabetes during pregnancy and lactation. Drugs Context; 7: 1-22.
[8] Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia 2017; 60: 1577-85.
[9] Tanbo T, Mellembakken J, Bjercke S, Ring E, Åbyholm T, Fedorcsak P. Ovulation induction in polycystic ovary syndrome. Acta Obstet Gynecol Scand 2018; 97: 1162-7.
[10] Practice Committee of the American Society for Reproductive Medicine. Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline. Fertil Steril 2017; 108: 426-41.
[11] Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 2000; 348: 607-14.
[12] Cao, J. Meng S, Chang E, Beckwith-Fickas K, Xiong L, Cole RN *et al.* Low concentrations of metformin suppress glucose production in hepatocytes through AMP-activated protein kinase (AMPK). J Biol Chem 2014; 289: 20435-46.
[13] Fullerton MD, Galic S, Marcinko K, Sikkema S, Pulinilkunnil T, Chen ZP, *et al*. Single phosphorylation sites in Acc1 and Acc2 regulate lipid homeostasis and the insulin-sensitizing effects of metformin. Nat Med 2013: 19: 1649-54.
[14] Gough NR. Placing the nuclear pore in the metformin mechanism of action. Sci Signal 2017; 10. pii: eaam6836. doi: 10.1126/ scisignal.aam6836.
[15] Gonzalez CD, Lee MS, Marchetti P, Pietropaolo M, Towns R, Vaccaro MI, *et al*. The emerging role of autophagy in the pathophysiology of diabetes mellitus. Autophagy 2011; 7: 2-11.
[16] Luciano-Mateo F, Hernandez-Aguilera A, Cabre N, Camps J, Fernandez-Arroyo S, Lopez-Miranda J, *et al.* Nutrients in energy and one-carbon metabolism: learning from metformin users. Nutrients 2017; 9: 1-19.
[17] Nanovskaya TN, Nekhayeva IA, Patrikeeva SL, Hankins GD, Ahmed MS. Transfer of metformin across the dually perfused human placental lobule. Am J Obstet Gynecol 2006; 195: 1081-5.
[18] Lee N, Hebert MF, Wagner DJ, Easterling TR, Liang CJ, Rice K, *et al.* Organic Cation Transporter 3 Facilitates Fetal Exposure to Metformin during Pregnancy. Mol Pharmacol 2018; 94: 1125-31.
[19] Holland O, Dekker Nitert M, Gallo LA, Vejzovic M, Fisher JJ,Perkins AV. Placental mitochondrial function and structure in gestational disorders. Placenta 2017; 54: 2-9.
[20] Romero R, Erez O, Hüttemann M, Maymon E, Panaitescu B, Conde-Agudelo A, Pacora P, *et al.* Metformin, the aspirin of the 21st century: its role in gestational diabetes mellitus, prevention of preeclampsia and cancer, and the promotion of longevity. Am J Obstet Gynecol 2017; 217: 282-302.
[21] Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 2000; 348: 607-14.
[22] Salvesen KA, Vanky E, Carlsen S. M. Metformin treatment in pregnant women with polycystic ovary syndrome - is reduced complication rate mediated by changes in the uteroplacental circulation? Ultrasound Obstet Gynecol 2007; 29: 433-7.
[23] Jamal A, Milani F, Al-Yasin A. Evaluation of the effect of metformin and aspirin on utero placental circulation of pregnant women with PCOS. Iran J Reprod Med 2012; 10: 265-70.
[24] Stridsklev S, Salvesen Ø, Salvesen KÅ, Carlsen SM, Vanky E. Uterine Artery Doppler in Pregnancy: Women with PCOS Compared to Healthy Controls. Int J Endocrinol 2018: 2604064. doi: 10.1155/2018/2604064
[25] Cassina M, Donà M, Di Gianantonio E, Litta P, Clementi M. First-trimester exposure to metformin and risk of birth defects: a systematic review and meta-analysis. Hum Reprod Update 2014; 20: 656-69.
[26] Vanky E, Stridsklev S, Heimstad R, Romundstad P, Skogøy K, Kleggetveit O, *et al.* Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. J Clin Endocrinol Metab 2010; 95: E448-55.
[27] Hjorth-Hansen A, Salvesen Ø, Engen Hanem LG, Eggebø T, Salvesen KÅ, Vanky E, *et al.* Fetal Growth and birth anthropometrics in metformin-exposed offspring born to mothers with PCOS. J Clin Endocrinol Metab 2018; 103: 740-7.
[28] Hanem LGE, Stridsklev S, Júlíusson PB, Salvesen Ø, Roelants M, Carlsen SM, *et al.* Metformin use in PCOS pregnancies increases the risk of offspring overweight at 4 years of age: Follow-up of two RCTs. J Clin Endocrinol Metab 2018; 103: 1612-21.
[29] Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. Cell Metab 2014; 20: 953-66.
[30] Sinclair KD, Lea RG, Rees WD, Young LE. The developmental origins of health and disease: current theories and epigenetic mechanisms. Soc Reprod Fertil Suppl 2007; 64: 425-43.
[31] Glueck CJ, Goldenberg N, Pranikoff J, Loftspring M, Sieve L, Wang P. Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. Hum Reprod 2004; 19: 1323-30.
[32] Feng L, Lin XF, Wan ZH, Hu D, Du YK. Efficacy of metformin on pregnancy complications in women with polycystic ovary syndrome: a meta-analysis. Gynecol Endocrinol 2015; 31): 833-9.
[33] Scherneck S, Schlinke N, Beck E, Grupe K, Weber-Schoendorfer C, Schaefer C. Pregnancy outcome after first-trimester exposure to metformin: A prospective cohort study. Reproductive Toxicology 2018; 81: 79-83.
[34] Underdal MO, Stridsklev S, Oppen IH, Høgetveit K, Andersen MS, Vanky E. Does metformin treatment during pregnancy modify the future metabolic profile in women with PCOS?. J Clin Endocrinol Metab 2018; 103: 2408-13.
[35] Valdez E, Sepulveda-Martinez A, Candia P, Abusada N, Orellana R, Manukian B, *et al.* Metformin as a prophylactic treatment of gestational diabetes in pregnant patients with pregestational insulin resistance: A randomized study. J Obstet Gynaecol Res 2018; 44: 81-6.
[36] Rowan JA, Hague WM, Gao W, Battin MR, Moore MP; MiG Trial investigators. metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008; 358: 2003-15.
[37] Rowan JA, Rush EC, Plank LD, Lu J, Obolonkin V, Coat S, *et al*. Metformin in gestational diabetes: the offspring follow-up (MiG TOFU): body composition and metabolic outcomes at 7-9 years of age. BMJ Open Diabetes Res Care 2018; 6:e000456. doi: 10.1136/bmjdrc-2017-000456.
[38] Ijas H, Vaarasmaki M, Saarela T, Keravuo R, Raudaskoski T. A follow-up of a randomised study of metformin and insulin in gestational diabetes mellitus: growth and development of the children at the age of 18 months. BJOG 2015; 122: 994-1000.
[39] Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. Diabetes Res Clin Pract 2012; 98: 422-9.
[40] Mesdaghinia E, Samimi M, Homaei Z, Saberi F, Moosavi SGA, Yaribakht M. Comparison of newborn outcomes in women with gestational diabetes mellitus treated with metformin or insulin: a randomised blinded trial. Int J Prev Med 2013; 4: 327-33.
[41] Ainuddin J, Karim N, Hasan AA, Naqvi SA. Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country: a randomized control trial. Diabetes Res Clin Pract 2015; 107: 290-9.
[42] Su DF, Wang XY. Metformin vs insulin in the management of gestational diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2014; 104: 353-7.
[43] Sam S, Ehrmann DA. Metformin therapy for the reproductive and metabolic consequences of polycystic ovary syndrome. Diabetologia 2017; 60: 1656-61.
[44] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, *et al.* 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: 2669-701.

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