DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

REVIEW

Metformin in the management of diabetes during pregnancy and lactation

Gagan Priya MD, DM[1], Sanjay Kalra MD, DM[2]

[1]Department of Endocrinology, Fortis Hospital, Mohali, India; [2]Department of Endocrinology, Bharti Hospital, Karnal, India

Abstract

This review explores the current place of metformin in the management of gestational diabetes (GDM) and type 2 diabetes during pregnancy and lactation. The rationale and basic pharmacology of metformin usage in pregnancy is discussed along with the evidence from observational and randomized controlled trials in women with GDM or overt diabetes. There seems to be adequate evidence of efficacy and short-term safety of metformin in relation to maternal and neonatal outcomes in GDM, with possible benefits related to lower maternal weight gain and lower risk of neonatal hypoglycemia and macrosomia. Additionally, metformin offers the advantages of oral administration, convenience, less cost and greater acceptability. Metformin may, therefore, be considered in milder forms of GDM where glycemic goals are not attained by lifestyle modification. However, failure rate is likely to be higher in those with an earlier diagnosis of GDM, higher blood glucose, higher body mass index (BMI) or previous history of GDM, and insulin remains the cornerstone of pharmacological treatment in such cases. The use of metformin in type 2 diabetes has been assessed in observational and small randomized trials. Metformin monotherapy in women with overt diabetes is highly unlikely to achieve glycemic targets. Hence, the use should be restricted as adjunct to insulin and may be considered in women with high insulin dose requirements or rapid weight gain. There is clearly a need for more clinical trials to assess the effect of combined insulin plus metformin therapy in pregnancy with type 2 diabetes. Additionally, there is a paucity of data on long-term effects in offspring exposed to metformin *in utero*. It is imperative to further explore its impact on offspring as metformin has significant transplacental transfer and has the potential to impact the programming of the epigenome. Therefore, caution must be exercised when prescribing metformin in pregnant women. More research is clearly needed before metformin can be considered as standard of care in the management of diabetes during pregnancy.

Keywords: diabetes, epigenetic programming, gestational diabetes, metformin, oral antidiabetic agents, pregnancy, type 2 diabetes.

Citation

Priya G, Kalra S. Metformin in the management of diabetes during pregnancy and lactation. Drugs in Context 2018; 7: 212523. DOI: 10.7573/dic.212523

Introduction

The prevalence of pre-existing diabetes among pregnant women is increasing. Additionally, a substantial number of women may be detected to have hyperglycemia during routine screening in pregnancy. Longitudinal studies suggest that even mild degree of hyperglycemia during pregnancy is associated with the risk of adverse maternal, fetal and neonatal outcomes [1,2]. Intensive glycemic control with lifestyle modification, self-monitoring of blood glucose (SMBG) and pharmacological therapy reduces this risk [3]. Insulin is considered as the pharmacological therapy of choice during pregnancy for both pre-existing and gestational diabetes (GDM). Oral antidiabetic agents, particularly glyburide (glibenclamide) and metformin, have been evaluated for their efficacy and safety. The earliest reports of the use of metformin during pregnancy were from South Africa in early 1980s, by Coetzee and colleagues, in women with pre-existing non-insulin-dependent diabetes and GDM [4–6]. Kelley and colleagues recently reviewed the current treatment strategies for women with GDM [7]. Since then, there have been several observational and randomized controlled trials comparing metformin with insulin and glyburide. Most of these studies suggest that metformin does not increase maternal or short-term fetal adverse outcomes and may reduce maternal weight gain during pregnancy and that it has lower risk of neonatal hypoglycemia and large for gestational age (LGA) babies. However, metformin freely crosses the placenta and its use during pregnancy can lead to significant fetal exposure. Due to its propensity to cause cellular energy depletion and affect one-carbon (1-C) metabolism, concerns have been raised about the long-term effects of prenatal metformin exposure on fetal programming and long-term health of exposed offspring.

In this review, we focus on the rationale, clinical evidence, concerns and unresolved issues with regard to the use of metformin in the management of diabetes during pregnancy and lactation. A detailed search of MEDLINE, EMBASE and Cochrane databases was undertaken to include all relevant research.

Rationale for metformin in gestational and pre-existing diabetes during pregnancy

Metformin increases insulin sensitivity, reduces hepatic glucogeneogenesis and enhances peripheral glucose uptake, resulting in lowering of blood glucose with minimal risk of hypoglycemia and weight gain [8]. Metformin is, therefore, considered as the first-line drug in the management of type 2 diabetes (T2D) with excellent data of its efficacy, tolerability and safety in nonpregnant individuals. With the rising prevalence of T2D, decreasing age at onset of the disease and rising maternal age at pregnancy [9], a significant number of pregnant women have pre-existing T2D [10]. They are often obese and have high rates of maternal morbidity, including pregnancy-induced hypertension (PIH), preeclampsia and Caesarian delivery [11]. Infants of diabetic mothers have higher rates of LGA and macrosomia and an increased perinatal morbidity and mortality [12]. Further, maternal weight gain in excess of the Institute of Medicine (IOM) recommendations has been associated with a higher risk of adverse fetal and maternal outcomes [13]. While insulin is usually required for adequate glycemic control in these women, metformin has the potential to improve maternal glycemic control with less maternal weight gain and a reduction in insulin dose requirement. On the other hand, discontinuation of metformin may result in perturbations in glycemic control and significant rise in insulin dose, especially in the latter half of pregnancy when there is a further physiological decline in insulin sensitivity.

During pregnancy, there occurs a physiological increase in secretion of several counter-regulatory hormones, including cortisol, growth hormone (GH), human placental lactogen (hPL), progesterone and prolactin. This results in a state of insulin resistance starting in midpregnancy. In most women, the rise in insulin resistance is compensated by an increase in insulin secretion and most women remain normoglycemic due to adequate β-cell compensation. GDM develops if β-cell function is decreased or fails to compensate for the rise in insulin resistance [14]. Metformin, therefore, seems to be a logical treatment for GDM.

Pharmacokinetic considerations of metformin in pregnancy and lactation

Metformin is a hydrophilic and positively charged biguanide, and hence it requires transporter proteins to cross cell membranes [8]. The predominant proteins involved in metformin transport include organic cation transporters (OCT), plasma membrane monoamine transporters (PMAT) and multidrug and toxic compound extrusion protein (MATE). Gut, hepatocytes, renal tubular epithelial cells and reproductive tissues readily internalize metformin [15]. OCT3 and PMAT regulate the gastrointestinal absorption of metformin and OCT1 is responsible for transport to the interstitial fluid. OCT1, OCT3 and MATE are expressed on the basolateral membrane of hepatocytes. OCT2 regulates uptake by renal epithelial cells and MATE1 and 2 regulate excretion into urine.

Placental tissue expresses several OCTs, including OCT2, and metformin has been shown to freely cross the placenta. Several other transporters are also expressed in the human syncytiotrophoblast, including P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP 1) and breast cancer resistance protein (BCRP). The transport of metformin across the placenta is regulated by these proteins and seems to be bidirectional. Fetal concentrations of metformin can reach at least 50 percent of maternal concentration. Metformin concentrations in umbilical cord plasma at the time of delivery were found to range between nondetectable (<5 ng/dL) and 1263 ng/mL [16]. Importantly, metformin is not retained in the placenta and fetal-to-maternal transfer of metformin was found to be significantly higher than maternal-to-fetal transfer in dually perfused human placenta [17,18]. Moreover, metformin does not seem to affect placental uptake and transport of glucose [19].

The renal clearance of metformin is significantly increased (by 29%) in mid and late pregnancy compared with postpartum, parallel to increased renal plasma flow and glomerular filtration during pregnancy [16,20]. Hence, patients may require higher doses of metformin for adequate glycemic efficacy. Metformin doses ranging from 500 to 2500 mg/day have been used to treat women with GDM and the impact of doses exceeding 2500 mg/day on maternal, fetal and neonatal safety has not been determined.

Metformin is excreted into breast milk, but the amount is clinically insignificant. Eyal and colleagues estimated that the daily intake of metformin transferred via breast milk to the infant was 0.13–1.28 mg. Studies have estimated that the relative infant dose is 0.5–0.65% of mother's weight-adjusted dose [20,21]. There was no effect of metformin intake in lactating mothers on blood glucose in three infants after 4 hours of breastfeeding [21].

Clinical experience with use of metformin in GDM

There was significant apprehension surrounding the use of metformin during pregnancy due to concerns about fetal exposure, as it freely crossed the placenta and could affect fetal health. There were early concerns that because

metformin could increase the risk of lactic acidosis and the fetal environment is relatively hypoxic, metformin may have a negative impact on both maternal and fetal health. For these reasons, metformin was not considered an optimal choice during pregnancy and early evidence was limited to observational and small non-randomized studies. Interest in the role of metformin in GDM gained momentum following the publication of the Metformin in Gestational Diabetes (MiG) trial in 2008. The MiG trial was a randomized multicenter open-label trial comparing metformin *versus* insulin in 751 women diagnosed with GDM between 20 and 33 weeks of gestation [22]. The glycemic control was comparable to insulin group but 46.3% patients on metformin required supplemental insulin, indicating a high failure rate. Maternal weight gain (from enrollment to 36–37 weeks of gestation) was lower with metformin than insulin (0.4±2.9 *versus* 2.0±3.3 kg, $p<0.001$). In a questionnaire, a significantly large number of women responded that they would opt for metformin again (76%) than insulin (27%) in a subsequent pregnancy, suggesting greater patient acceptability. There was no difference in the primary composite outcome (a composite of neonatal complications including respiratory distress, need for phototherapy, birth trauma, low Apgar score or prematurity) between metformin group (32.0%) and insulin group (32.2%). Birth weight was similar (3372±572 g in metformin group *versus* 3413±569 g in insulin group, $p=0.033$), but the incidence of neonatal hypoglycemia was significantly lower with metformin (3.3 *versus* 8.1%, $p=0.008$). The incidence of preterm births (< 37 weeks of gestation) was, however, higher with metformin than insulin (12.1 *versus* 7.6%, $p=0.04$), though prematurity was not associated with an increased complication risk.

Over the past decade, several retrospective, prospective and randomized studies have been published that compared maternal and fetal outcomes in GDM women treated with metformin and insulin or glyburide. These are summarized in Tables 1 and 2. Several meta-analyses have compared the outcomes from randomized controlled trials (RCTs), as detailed in Table 3. Glycemic control with metformin was similar to insulin or glyburide, but a variable percentage of

Table 1. Retrospective and prospective cohort studies of metformin use in GDM.

Author, country, year published	Study design	Key outcomes
Retrospective cohort studies		
Tertti et al., Turkey, 2008 [23]	173 women with GDM. Comparison groups: metformin, insulin.	No difference in maternal outcomes, birth weight, macrosomia at gestational age at delivery. 18% metformin users needed supplemental insulin. Lesser incidence of neonatal hypoglycemia with metformin.
Silva et al., Brazil, 2017 [24]	705 women with GDM. Comparison groups: metformin, insulin, combined metformin plus insulin.	Metformin group – less risk of newborns with SGA (adjusted OR 0.25) and higher chance of newborns with appropriate for gestational age (adjusted OR 2.10). Insulin group – lower risk of preterm birth (adjusted OR 0.13). Insulin plus metformin group – higher chance of newborns with LGA (adjusted OR 3.56) and lower risk of preterm birth.
Prospective case-control studies		
Balani et al., UK, 2009 [25]	127 women with GDM treated with metformin. 100 women who remained exclusively on metformin were compared with 100 matched women treated with insulin.	Greater maternal weight gain with insulin (2.72±0.4 *versus* 0.94±0.3 kg, $p<0.001$). No difference in PIH, preeclampsia, induction of labor, rate of Caesarian section or macrosomia. Improved neonatal morbidity with metformin – lower rates of prematurity (0 *versus* 10%, $p<0.01$), neonatal jaundice (8 *versus* 30%, $p<0.01$) and NICU admissions (6 *versus* 19%, $p<0.01$).
Balani et al., UK, 2012 [26]	Metformin (n=286) or metformin plus insulin (n=38). Compared with 175 women on lifestyle modification alone.	Metformin use associated with: a) Lower risk of LGA or SGA b) Higher rate of induced labor or planned Caesarian c) Lower mean birth weight d) Greater need of phototherapy for neonatal jaundice

GDM, gestational diabetes; LGA, large for gestational age; NICU, neonatal intensive care unit; OR, odds ratio; PIH, pregnancy-induced hypertension; SGA, small for gestational age.

Table 2. Randomized controlled trials comparing metformin with insulin or glyburide in women with gestational diabetes.

Author, country, year published	Trial design	Key outcomes
Moore et al., USA, 2007 [27]	63 women with GDM; Metformin *versus* insulin	No difference in maternal or fetal outcomes. No patient on metformin required insulin. Trial was underpowered.
Rowan et al., Australia & New Zealand, 2008 [22]	751 women with GDM at 20–33 weeks of gestation; metformin *versus* insulin	46.3% metformin users required supplemental insulin. No difference in primary composite outcome (composite of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score <7 or prematurity) – RR 0.99, 95% CI: 0.80–1.23. No difference in secondary outcomes (neonatal anthropometry, maternal glycemic control, PIH and postpartum glucose tolerance). Better patient acceptability.
Silva et al., Brazil, 2010 [28]	72 women with GDM; metformin (n=40) *versus* glyburide (n=32)	Less maternal weight gain with metformin (7.6 *versus* 10.3 kg, p=0.02). Similar fasting and postprandial glucose, birth weight, LGA and neonatal hypoglycemia. Similar rates of treatment failure with need for insulin.
Moore et al., USA, 2010 [29]	149 GDM women; metformin (n=75) *versus* glyburide (n=74)	34.7% in metformin group and 16.2% in glyburide group required insulin. Higher failure rate of metformin.
Ijas et al., Finland, 2011 [30]	100 GDM women; metformin *versus* insulin	No differences in LGA, birth weight, mean cord artery pH or neonatal morbidity. Higher rates of Caesarian section with metformin (RR 1.9, 95% CI: 0.99–3.71). 32% women in metformin group required supplemental insulin. When compared to those who did not need insulin, these women had the following: 1. Higher BMI (36 *versus* 30 kg/m^2, p=0.002). 2. Higher fasting glucose (6.1 *versus* 5.0 mmol/l, p=0.001). 3. Earlier need for medical treatment for GDM (26 *versus* 31 weeks of gestation, p=0.002).
Niromanesh et al., Iran, 2012 [31]	160 women with GDM between 20 and 34 weeks; metformin *versus* insulin	Similar fasting and postprandial glucose. No difference in neonatal and obstetric complications. 14% required supplemental insulin. Less maternal weight gain with metformin (p<0.001). Less risk of birth weight > 90th centile (RR 0.5, 95% CI: 0.3–0.9, p=0.012) with metformin.
Silva et al., Brazil, 2012 [32]	200 GDM women; metformin [104] *versus* glyburide [96]	Lower maternal weight gain with metformin (7.78 *versus* 9.84, p=0.04). Lower birth weight (3193 *versus* 3387 kg, p=0.01) and ponderal index (2.87 *versus* 2.96, p=0.05) with metformin. Greater neonatal hypoglycemia with glyburide. No difference in Caesarian sections, gestational age at delivery, LGA, neonatal hypoglycemia, NICU admissions or perinatal death.
Mesdaghinia et al., Iran, 2013 [33]	200 GDM women at 24–34 weeks; metformin *versus* insulin	22% in metformin group required supplemental insulin. No difference in glycemic control, PIH, route of delivery. No difference in birth weight, dystocia, Apgar score, hypoglycemia and still birth.

Table 2. (*Continued*)

Author, country, year published	Trial design	Key outcomes
		Higher maternal weight gain, preterm labor and end of pregnancy HbA1c in insulin group. Higher incidence of neonatal jaundice, respiratory distress and NICU admission in insulin group.
Spaulonci et al., Brazil, 2013 [34]	94 women with GDM; metformin *versus* insulin	Less maternal weight gain (p=0.02) and lower frequency of neonatal hypoglycemia (p=0.032) with metformin. 26% metformin users required supplemental insulin. Predictors of need for insulin were early gestational age at GDM diagnosis and higher mean pre-treatment glucose.
Tertti et al., Finland, 2013 [35]	217 GDM patients; metformin *versus* insulin	No difference in birth weight, neonatal or maternal outcomes. 20.9% required supplemental insulin. Factors predicting need for insulin – older age (p=0.04), earlier gestational age at diagnosis (p=0.01) and higher baseline serum fructosamine concentration.
Ruholamin et al., Iran, 2014 [36]	109 GDM women; metformin *versus* insulin	Similar glycemic control and other maternal outcomes, including preterm delivery. No difference in neonatal outcomes (hypoglycemia, birth weight, Apgar score, hyperbilirubinemia).
George et al., India, 2015 [37]	159 South Indian women with GDM; metformin *versus* glyburide	Primary outcome (composite of macrosomia, hypoglycemia, need for phototherapy, respiratory distress, stillbirth or neonatal death and birth trauma): 35% in glyburide group and 18.9% in metformin group. Higher rate of neonatal hypoglycemia with glyburide (12.5%) *versus* none with metformin. No difference in birth weight, glycemic control, PIH, preterm birth, mode of delivery or complications of delivery.
Ainuddin et al., Pakistan, 2015 [38]	150 women with GDM; metformin *versus* insulin	42.7% in metformin group required supplemental insulin. Less maternal weight gain with metformin (9.8±1.5 kg) than insulin (12.5±1.1 kg). Less risk of preeclampsia with metformin. Lower mean birth weight (3.4±0.4 *versus* 3.7±0.5 kg, p<0.01) and less neonatal morbidity with metformin.
Ashoush et al., Egypt, 2016 [39]	Women with GDM at 26–32 weeks. Metformin (n=47) *versus* insulin (n=48)	23.4% metformin users needed supplemental insulin. Metformin associated with less maternal weight gain (p<0.001) and lower fasting glucose during first and last 2 weeks of treatment (p=0.014 and 0.008, respectively). Fetal and maternal outcomes similar.
Nachum et al., Israel, 2017 [40]	53 patients on glyburide and 51 patients on metformin	Similar glycemic control. Failure rate 34% with glyburide, 29% with metformin. Obstetric and neonatal outcomes comparable.
Arshad et al., Pakistan, 2017 [41]	71 GDM women; metformin *versus* insulin	Metformin associated with lower birth weight. Higher HbA1c at term and more Caesarian sections with insulin. More babies born after 38 weeks with insulin.

GDM, gestational diabetes; HbA1c, hemoglobin A1c; LGA, large for gestational age; NICU, neonatal intensive care unit; pH, potential hydrogen; PIH, pregnancy-induced hypertension; RR, relative risk.

Table 3. Summary of published meta-analysis comparing metformin with insulin or glyburide in GDM.

Author, year	Comparison groups, patient number	Maternal outcomes	Fetal outcomes
Gui et al., 2013 [42]	5 RCTs, 1270 participants; metformin *versus* insulin	Lower maternal weight gain (p=0.003), lower incidence of PIH (OR 0.52, 95% CI: 0.30–0.90), lower gestational age (p=0.02) at delivery with metformin.	Higher incidence of preterm birth with metformin (OR 1.74, 95% CI: 1.13–2.68).
Poolsup, 2014 [43]	13 RCTs, 2151 patients; oral antidiabetics *versus* insulin	Significantly lower PPG with metformin. Decreased risk of gestational hypertension with metformin.	Significant increase in preterm births with metformin. Higher risk of macrosomia and neonatal hypoglycemia with glyburide.
Su et al., 2014 [44]	6 RCTs, 1420 subjects; metformin *versus* insulin	No increase in adverse maternal outcomes. Less maternal weight gain with metformin.	Less incidence of neonatal hypoglycemia and higher incidence of premature birth with metformin.
Jiang et al., 2015 [45]	18 RCTs, network meta-analysis. Metformin, insulin, glyburide and acarbose	No difference in glycemic control. Compared to insulin, metformin was associated with lower maternal weight gain, shorter gestational age and greater premature birth. Compared to glyburide, metformin was associated with less maternal weight gain.	Metformin was associated with shorter gestational age compared to insulin. Metformin was associated with lower neonatal birth weight, less risk of macrosomia and less risk of neonatal hypoglycemia than glyburide.
Kitwitee et al., 2015 [46]	8 RCTs, 1712 women with GDM; metformin *versus* Insulin	Similar glycemic control and maternal outcomes. 14–46% required additional insulin. Pooled risk for PIH lower with metformin (RR 0.62, 95% CI: 0.38–1.02, p=0.06). Lower maternal weight gain with metformin (SMD –0.52, 95% CI: –0.78 to –0.26, p<0.01). Lower average gestational age at delivery with metformin (SMD –0.13, 95% CI: –0.23 to –0.03, p<0.01). Nonsignificant increase in preterm deliveries (RR 1.34, 95% CI: 0.73–2.46) with metformin.	Lower incidence of neonatal hypoglycemia (RR 0.74, 95% CI: 0.58–0.93, p=0.01) and NICU admissions (RR 0.76, 95% CI: 0.59–0.97, p=0.03) with metformin. 98% probability that metformin was superior to insulin for these two neonatal complications. Incidence of LGA babies lower with metformin (RR 0.79; 95% CI: 0.63–1.01, p=0.06).
Li et al., 2015 [47]	11 RCTs; metformin *versus* insulin	No difference in glycemic control or incidence of preeclampsia. Less risk of PIH (RR 0.53, 95% CI: 0.31–0.90, p=0.02) with metformin. Less maternal weight gain (MD –1.28, 95% CI: –1.54 to –1.01, p<0.0001) with metformin. Lower gestational age at delivery (MD 0.94, 95% CI: –0.21 to –0.01, p=0.03) with metformin.	Lower birth weight (MD –44.35, 95% CI: –85.79 to –2.90, p=0.04) with metformin. Lower incidence of hypoglycemia (RR 0.69, 95% CI: 0.55–0.87, p<0.001) with metformin. Lower rates of NICU admission (RR 0.82, 95% CI: 0.67–0.99) with metformin.

Table 3. ***(Continued)***

Author, year	Comparison groups, patient number	Maternal outcomes	Fetal outcomes
Amin et al., 2015 [48]	3 RCTs, 508 patients; glyburide *versus* metformin	No difference in rates of Caesarian section. Significant decrease in fasting glucose with glyburide (MD –2.4 mg/dL, 95% CI: –4.60 to –0.21, p=0.03).	Increased risk of macrosomia and LGA with glyburide (RR 1.94, 95% CI: 1.03–3.66, p=0.04). Nonsignificant increase in risk of neonatal hypoglycemia (RR 1.92, 95% CI: 0.31–12.02) with glyburide. No difference in preterm births or neonatal birth weight.
Balsells et al., 2015 [49]	15 RCTs, 2509 subjects; two compared metformin with glyburide (349 subjects). six compared metformin with insulin (1362 subjects).	Metformin *versus* insulin: less maternal weight gain (–1.14 kg, 95% CI: –2.22 to –0.06). Lower postprandial glucose (MD –0.14 mmol/l, 95% CI: –0.22 to –0.05). Lower incidence of PIH (RR 0.53, 95% CI: 0.31–0.90). Less gestational age at delivery (MD –0.16 weeks, 95% CI: –0.30 to –0.02). Treatment failure with metformin 33.8%. Metformin *versus* glyburide: less maternal weight gain (MD –2.06 kg, 95% CI: –3.98 to –0.14). Treatment failure higher with metformin (26.8 *versus* 23.5%).	Metformin *versus* insulin: less risk of neonatal hypoglycemia (RR 0.78, 95% CI: 0.60–1.01). Higher preterm births (RR 1.50, 95% CI: 1.04–2.16). Metformin *versus* glyburide: lower birth weight (MD –209 g, 95% CI: –314 to –104), less risk of macrosomia (RR 0.33, 95% CI: 0.13–0.81) and LGA (RR 0.44, 95% CI: 0.21–0.92).
Singh et al., 2015 [50]	7 RCTs, 1514 women; metformin *versus* insulin	No difference in glycemic control. Less maternal weight gain with metformin in four studies. Higher preterm births with metformin in one study. No difference in other maternal outcomes.	No difference in neonatal outcomes.
Zhu et al., 2016 [51]	8 RCTs, 1712 GDM women; metformin (n=853) *versus* insulin (n=859)	No difference in glycemic control; 15–46% required insulin. No increased risk of prematurity. Metformin – reduced risk of PIH and less maternal weight gain.	Reduced risk of neonatal hypoglycemia and NICU admissions. No difference in other neonatal outcomes.
Liang et al., 2017 [52]	32 RCTs, network meta-analysis. Metformin, insulin, glyburide, metformin plus glyburide, acarbose and placebo	Metformin had lower maternal weight gain than insulin. Ranking results – metformin had lowest incidence of PIH but lower gestational age at delivery.	Metformin had lower incidence of neonatal hypoglycemia compared to insulin or glyburide. Metformin had lower birth weight and lower incidence of macrosomia and LGA compared to glyburide. Ranking – metformin had lower birth weight and lowest incidence of macrosomia, LGA, RDS.

(Continued)

Table 3. (*Continued*)

Author, year	Comparison groups, patient number	Maternal outcomes	Fetal outcomes
Brown et al., 2017 [53]	11 RCTs comparing oral antidiabetics with placebo or other oral antidiabetics. Trials including insulin were excluded.	Metformin *versus* glyburide: no difference in maternal outcomes.	Metformin *versus* glyburide: decrease in death or serious morbidity composite. No difference in risk of LGA or neonatal hypoglycemia or perinatal mortality. Overall data insufficient to recommend one oral antidiabetic over another.
Brown et al., 2017 [54]	53 studies, 7381 participants. Insulin compared to oral antidiabetics.	Insulin associated with increased risk of hypertensive disorders of pregnancy compared to OADs. No difference in rates of preeclampsia or Caesarian section.	No difference in risk of LGA, perinatal mortality or serious morbidity, neonatal hypoglycemia or neonatal adiposity. Low quality evidence of no difference in neurosensory outcomes in offspring.
Feng et al., 2017 [55]	RCTs comparing insulin and metformin.	No difference in gestational age and Caesarian section. Lower maternal weight gain and HbA1c at 36–37 weeks with metformin. Lower rates of gestational hypertension with metformin.	No difference in neonatal respiratory distress and preterm birth or other neonatal outcomes.
Farrar et al., 2017 [56]	Metformin *versus* insulin – 11 trials. Metformin *versus* glyburide – 3 trials. Analysis not possible due to paucity of data.	Lower risk of preeclampsia, PIH, induction of labor and instrumental delivery with metformin compared to insulin.	Lower risk of LGA, macrosomia, NICU admissions, neonatal hypoglycemia with metformin compared to insulin. Lower risk of LGA with metformin compared to glyburide.
Butalia et al., 2017 [57]	16 studies, 2165 participants; metformin *versus* insulin.	Lower risk of PIH with metformin, RR 0.56; 95% CI: 0.37–0.85. Lower maternal weight gain with metformin, MD –2.07; 95% CI: –2.88 to –1.27. Metformin did not increase preterm delivery, RR 1.18; 95% CI: 0.67–2.07. No difference in rates of Caesarian section.	Lower risk of neonatal hypoglycemia with metformin, RR 0.63; 95% CI: 0.45–0.87. Lower risk of LGA with metformin, RR 0.80; 95% CI: 0.64–0.99. No difference in perinatal mortality or SGA.

GDM, gestational diabetes; LGA, large for gestational age; NICU, neonatal intensive care unit; OAD, oral antidiabetic drugs; OR, odds ratio; PIH, pregnancy-induced hypertension; PPG, postprandial plasma glucose; RCTs, randomized controlled trials; RDS, respiratory distress syndrome; RR, relative risk; SGA, small for gestational age; SMD, standardized mean difference.

women required supplemental insulin to achieve and maintain glycemic targets. This could have resulted from differences in population studied and inclusion of women with pre-existing diabetes in some studies.

Which GDM candidates are unlikely to respond to metformin?

Several studies have assessed the factors that predicted a poor response to oral antidiabetics, including metformin. In MiG trial, subgroup analysis of women who required supplemental insulin *versus* those who did not revealed that they were more obese (BMI 33.6±8.6 *versus* 31.1±7.8 kg/m^2) and had higher baseline fasting blood glucose (95.4±14.4 *versus* 109.8±19.8 mg/dL) [22]. In a recent retrospective multicenter cohort study, Gante and colleagues assessed 388 GDM women who were prescribed metformin; 135 required supplemental insulin. Predictors of poor response included higher age (odds ratio [OR] 1.08, 95% CI: 1.03–1.13; p=0.003), higher prepregnancy BMI (OR 1.06, 95% CI: 1.02–1.10; p=0.003) and earlier treatment

(OR 0.89, 95% CI: 0.85–0.94; $p<0.001$) [58]. The factors that predicted the need for supplemental insulin in GDM women treated with metformin in various studies include the following:

1. Higher fasting glucose at diagnosis [22,39,42,59,60]
2. Early detection of GDM [34,35,58,60,61]
3. Past history of GDM [60]
4. Older age at diagnosis [35,58]
5. Higher baseline HbA1c or serum fructosamine concentration [35]
6. Elevated BMI [22,39,58,60]

Effect of metformin on maternal outcomes

Most trials comparing metformin with insulin do not report an increase in adverse maternal outcomes with metformin, as detailed in Tables 1 and 2. This has been replicated in most meta-analyses (Table 3). In several studies, metformin use was rather beneficial and associated with lower maternal weight gain and lower risk of PIH. Additional advantages with metformin include a lower risk of maternal hypoglycemia than insulin or glyburide, lower cost of therapy and less need for intensive SMBG. However, some studies reported an increase in preterm deliveries with metformin, but this effect has not been replicated in other studies. In fact, two meta-analyses of studies where metformin was continued throughout pregnancy in women with polycystic ovary syndrome (PCOS) reported a lower risk of early pregnancy losses and preterm deliveries with metformin [62,63]. Moreover, Butalia and colleagues [57] and Farrar and colleagues [56] did not demonstrate any increase in rates of preterm deliveries with metformin in recent meta-analyses.

Effect of metformin on fetal outcomes

The effect of metformin on short-term fetal outcomes has been largely favorable (Tables 1, 2 and 3). Metformin use was associated with lower mean birth weight and lower incidence of macrosomia and LGA babies in several studies. Another significant benefit with metformin is a lower risk of neonatal hypoglycemia, including severe neonatal hypoglycemia, seen in both cohort studies and randomized trials. In addition, the rate of neonatal intensive care unit (NICU) admissions also appears to be lower for metformin than insulin. However, the rate of prematurity has been shown to be higher in some but not all studies.

In a recent Cochrane meta-analysis comparing metformin *versus* glyburide (11 studies), metformin was associated with decrease in composite of neonatal death or serious morbidity, while glyburide was associated with greater maternal weight gain, increased risk of neonatal hypoglycemia, higher birth weight and greater incidence of macrosomia [53]. In the network meta-analysis by Farrar and colleagues, metformin had the highest probability of being the most effective treatment in reducing the risk of neonatal hypoglycemia (probability of benefit 96.3%), macrosomia (94.0%), LGA (92.8%), preeclampsia (84.0%) and admission to NICU (61.2%) [56]. In another network meta-analysis of 32 RCTs, metformin was ranked better than insulin or glyburide due to lowest incidence of macrosomia, PIH, LGA and respiratory distress, but the incidence of preterm birth was reported to be highest. Metformin was superior to glyburide and insulin in obese GDM women [52].

Clinical experience of use of metformin in T2D during pregnancy

Women with pre-existing diabetes usually require insulin for achieving adequate glycemic control. The most obvious questions are whether or not metformin should be continued during pregnancy and whether it should be added to insulin therapy. However, most trials have excluded women with pre-existing diabetes. In a retrospective analysis of 118 pregnancies, Hellmuth and colleagues reported an increase in preeclampsia and perinatal mortality among 19 women with T2D who used metformin during pregnancy compared to insulin or sulfonylureas [64]. In other observational studies, however, there was no increase in adverse pregnancy outcomes with metformin, even though they were at higher risk of poor outcomes [65–67]. A reduction in NICU admissions was seen with metformin compared to insulin [68,69].

Hickman and colleagues reported lower rates of maternal hypoglycemia in T2D women randomized to metformin *versus* insulin during pregnancy, though 43% required supplemental insulin [70]. Ibrahim and colleagues randomized 90 pregnant women with GDM or T2D between 20 and 34 weeks gestation, who had poor glycemic control at insulin daily dose ≥ 1.12 U/kg, into two groups – addition of oral metformin *versus* increase in insulin dose; 36.9% women were able to reach glycemic targets with daily metformin dose of 1500 mg and 39.2% with daily dose of 2000 mg and 23.9% of metformin users needed increase in insulin dose. Maternal and fetal outcomes were similar [71]. In another study, Ainuddin and colleagues evaluated women with T2D using metformin or insulin. Insulin was added to metformin as required; 84.9% metformin users needed add-on insulin at a mean gestational age of 26.58±3.85 weeks. Metformin use was, however, associated with less maternal weight gain, PIH, neonatal hypoglycemia and NICU stay, but more small-for-date babies [72]. They suggested that metformin may be considered as an adjunct to insulin therapy in pregnant T2D women.

A recent Cochrane meta-analysis compared metformin and insulin in three RCTs with 241 women with pre-existing diabetes or previous GDM. There was no difference in preeclampsia, perinatal mortality or LGA, but the risk of infant hypoglycemia was less with metformin (relative risk [RR] 0.34, 95% CI: 0.18–0.62). While the likelihood of Caesarian section was lower with metformin, the overall quality of evidence was rated as poor for all outcomes [73]. Further studies are

clearly needed to assess the role of combined insulin and metformin therapy. The metformin in women with type 2 diabetes in pregnancy (MiTy) trial is a multicenter trial enrolling 500 pregnant T2D women, between gestational age 6 and 22 weeks, who are on insulin, to receive metformin 1000 mg twice daily *versus* placebo [74]. The results are likely to have important implications in the management of pregnant women with T2D. Metformin is usually considered safe for use by lactating mothers but there are no studies conducted in breastfeeding mothers [75]. Growth and motor-social development were similar in 61 nursing infants and 50 formula-fed infants born to mothers taking metformin throughout pregnancy and lactation [76].

Long-term safety data of metformin use in pregnancy

Use of metformin during pregnancy can result in significant fetal exposure but the long-term effects on exposed offspring are currently unknown. Exposure to hyperglycemia *in utero* has been associated with increased risk of obesity and diabetes in adolescence and adulthood. Some have proposed that metformin may improve fetal insulin sensitivity by altering fetal programming and reduce the long-term risk of obesity and cardiometabolic risk in the offspring. The 2-year follow-up of offspring born to mothers in the MiG trial, the offspring follow-up (MiG TOFU), generated some hope. Infants exposed to metformin *in utero* had higher subscapular and biceps skinfolds compared to unexposed infants at 2 years age, while total body fat was similar and there was no increased risk of adverse outcomes [77]. This led to speculation that metformin is associated with a healthier fat distribution with less visceral and ectopic fat but there is no conclusive evidence for the same.

On the contrary, Carlsen and colleagues reported that children born to mothers treated with metformin during pregnancy were heavier at 1 year [78]. In a longitudinal study of the offspring of mothers treated with metformin for PCOS, there were no differences in height, weight or body composition at 8 years of age between those exposed to metformin and placebo. However, fasting glucose level was higher and there was a trend toward higher systolic blood pressure in the metformin-exposed group [79]. Similarly, Ijas and colleagues reported that children exposed to metformin were heavier at 12 months (10.47 *versus* 9.85 kg) and were taller and heavier at 18 months (83.9 *versus* 82.2 cm, 12.05 *versus* 11.32 kg) [80]. The effects, if any, on childhood obesity, are unlikely to manifest until after 6–9 years of age and there is a need for longer follow-up studies.

Glueck and colleagues prospectively assessed the growth and socio-motor development of newborns that were conceived on metformin and exposed to metformin through pregnancy. There were no differences in anthropometric parameters at birth or at 18 months and motor-social development scores were also comparable to Centers for Disease Control and Prevention (CDC) control population [81]. No effect was seen on neurodevelopmental outcomes in metformin-exposed children at 2 years of age in other studies [80,82]. While there do not seem to be any obvious long-term concerns with fetal exposure to metformin, longer follow-up data are clearly required.

Concerns with fetal exposure to metformin

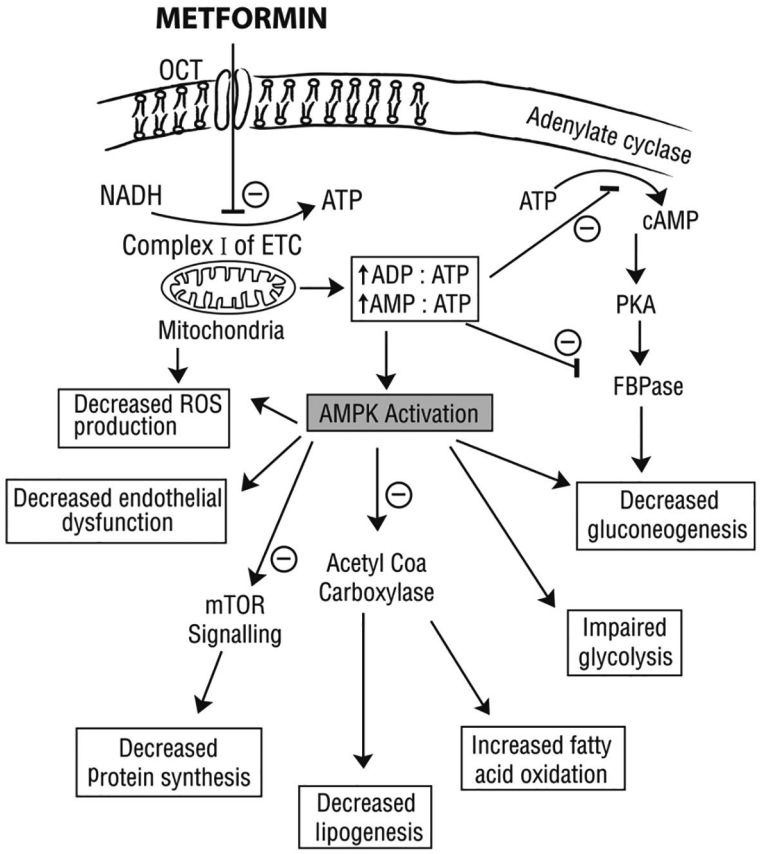
Does metformin increase the risk of embryopathy and teratogenicity?

It is important to determine if metformin has any embryopathic or teratogenic effect. This is particularly so because the predominant mechanism of action of metformin is via increase in 5'AMP-activated protein kinase (AMPK) [8]. Metformin inhibits complex I of the mitochondrial electron transport chain that couples the tricarboxylic acid (TCA) cycle to adenosine triphosphate (ATP) production. The resultant cellular energy depletion, with increased ADP:ATP and AMP:ATP ratios, leads to activation of AMPK. AMPK is a sensor of the cellular energy state and regulator of energy homeostasis [8]. AMPK mediates several metabolic effects of metformin on glucose and lipid metabolism, including increase in fatty acid beta-oxidation and insulin signaling, decrease in cholesterol, fatty acid and triglyceride biosynthesis and reduced gluconeogenic and lipogenic gene expression, as detailed in Figure 1.

It has been demonstrated that maternal hyperglycemia causes oxidative stress in the embryo and stimulates AMPK and this may drive the embryopathic effects of diabetes. AMPK activation may disrupt embryo gene expression – in particular inhibit *Pax3* (paired box 3) expression, a gene involved in neural tube closure – with resultant increased risk of neural tube defects. AMPK also induces changes in several bioactive metabolites connected to transcriptional regulators [83]. Because metformin increases AMPK activation, its effects on offspring need to be evaluated. Another important concern stems from the effect of metformin on 1-C pathways. Metformin has been demonstrated to have an antifolate effect similar to some chemotherapeutic drugs [83].

However, Lee and colleagues demonstrated that while metformin increased AMPK and inhibited *Pax3* expression in mouse embryonic stem cells *in vitro*, there was no effect on AMPK or *Pax3* in mouse embryo *in vivo*. This is possibly due to lack of expression of metformin transporters in early mouse embryos [84]. It remains to be determined if human embryo expresses metformin transporters and whether metformin affects early embryo development. In later pregnancy, metformin is freely transported across placenta, but the transport is bidirectional and there is greater transport from fetal to maternal compartment against a concentration gradient [18]. Moreover, it is uncertain if the progenitor cells of developing organs take up metformin.

Figure 1. Mechanism of action of metformin.



Metformin is transported across the cell membrane and mitochondrial membrane by organic cation transporters (OCT). Metformin inhibits the complex I of the electron transport chain in the mitochondria, leading to suppression of ATP production. The resultant increase in AMP:ATP ratio and ADP: ATP ratio causes activation of AMP-activated kinase (AMPK), which acts as the cellular energy sensor. AMPK activation leads to a switch in cell metabolism toward catabolic pathways generating energy and suppression energy consuming processes such as gluconeogenesis. Increase in AMP:ATP ratio inhibits fructose-1,6-bisphosphatase, a key enzyme involved in gluconeogenesis. Increased intracellular AMP inhibits adenylate cyclase, with decrease in cAMP production and reduced expression of gluconeogenic enzymes. AMPK activation further results in phosphorylation of acetyl-coA carboxylase and this leads to increased fatty acid oxidation and decreased lipogenesis. Additionally, AMPK activation inhibits mTOR and downstream signaling pathways with decrease in protein synthesis.

Abbreviations: ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; cAMP, cyclic AMP; ETC, electron transport chain; FBPase, fructose-1,6-bisphosphatase; mTOR, mammalian target of rapamycin; NADH, nicotinamide adenine dinucleotide; OCT, organic cation transporter; PKA, protein kinase A; ROS, reactive oxygen species.

Available animal studies suggest that metformin does not have teratogenic or carcinogenic effects even at very high doses of 600–1500 mg/kg/day [85]. A Brazilian group demonstrated that metformin had the potential to cause deoxyribonucleic acid (DNA) damage *in vitro* in cells of Chinese Hamster ovary (CHO-K1), but not *in vivo* in mice [86]. In this regard, human data are also reassuring. Metformin exposure was not associated with increased risk of congenital malformations or excess perinatal complications. Indeed, there has been widespread experience of embryo exposure to metformin, due to its use in women with PCOS in the periconceptional period and its continuation in early pregnancy. In a systematic review of nine prospective and retrospective studies, metformin use in women with PCOS or T2D in first trimester was not associated with an increased risk of birth defects [87]. In another meta-analysis of eight studies, metformin exposure in first trimester did not increase the risk of fetal malformations. The malformation rate of 1.7% in metformin group was actually significantly lower than control group, where it was 7.2% [88].

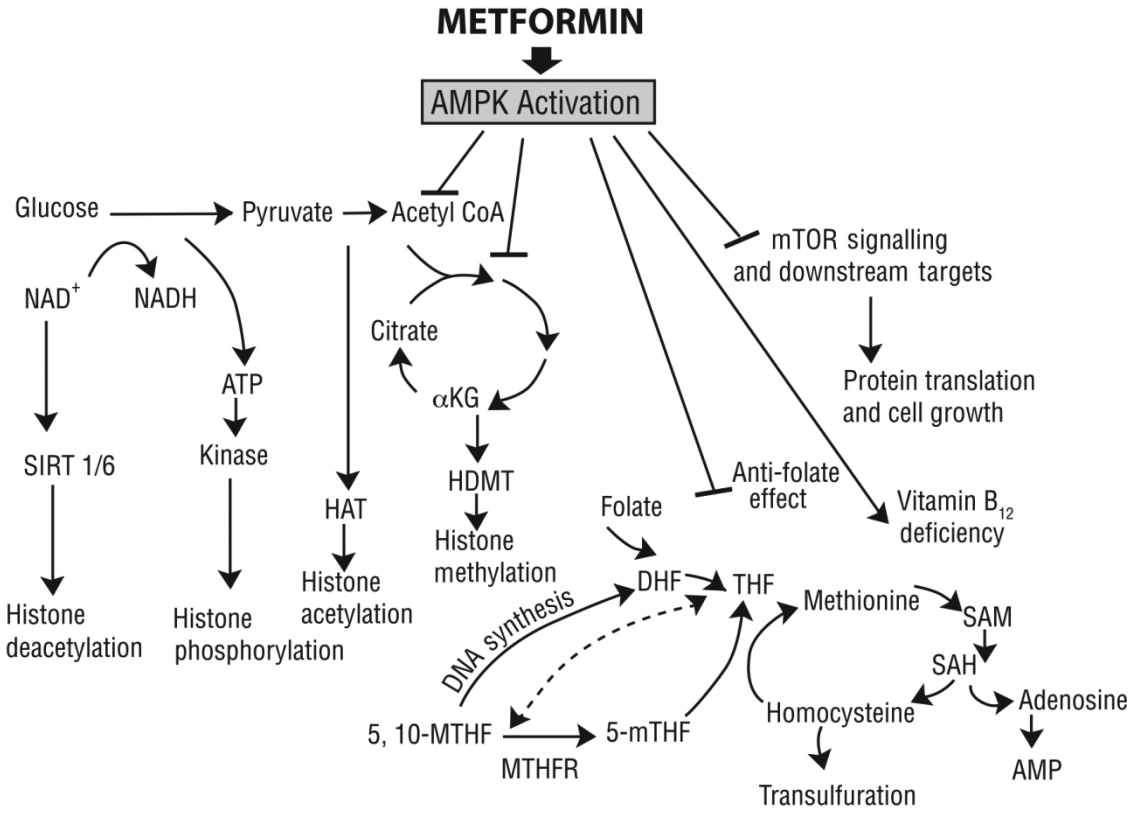
Does metformin affect epigenetics and fetal programming?

Metformin acts by modulation of mitochondrial function, causing a state of cellular nutrient restriction. Perturbations in AMPK signaling have the potential to impact programming of

the epigenome and have long-term effects. While it has been suggested from short-term follow-up of offspring exposed to metformin that fetal exposure may lead to improved metabolic health [77], there are mechanisms to suggest otherwise, and the issue is far from clear. Metformin can act via several pathways to impact developmental programming, as depicted in Figure 2:

1. Metformin impairs 1-C pathways that play a role in developmental programming. An alteration in energy and 1-C metabolism in pregnant women may increase the risk in offspring [83].
2. There is reduced availability of glycolytic and TCA cycle intermediates and depletion of glutathione stores. These are involved in histone acetylation. AMPK associates with chromatin by phosphorylating histone B2 or regulating histone deacetylases. AMPK activation increases hepatic sirtuin (SIRT1) activity, a histone deacetylase. Therefore metformin can impair histone acetylation and increase deacetylation [15].
3. AMPK regulates several key processes involved in gene expression and mammalian target of rapamycin (mTOR) induced effects on protein synthesis. AMPK also regulates transcription of several factors involved in the response to environmental stress.
4. Metformin may inhibit thiamine uptake and cause vitamin B_{12} deficiency, resulting in reduced cell supply of methyl groups. This may disrupt DNA and histone methylation [89].
5. AMPK activation increases nitric oxide synthase. While this would primarily be protective against oxidative stress, high levels of nitric oxide may lead to alterations in DNA.

Figure 2. Mechanisms by which metformin may impact epigenetic programming.



Metformin impairs glycolysis and tricarboxylic acid (TCA) cycle, resulting in reduced accumulation of glycolytic and TCA cycle intermediates, including succinate, fumarate, malate, citrate and α-ketoglutarate. Metformin can lead to epigenetic modifications through decrease in histone acetylation, histone phosphorylation and histone methylation. Metformin impairs one-carbon metabolism and has antifolate effect. It can lead to decreased availability of methyl (CH3) groups through sequential conversion of methionine to SAM, SAH and homocysteine. Additionally, metformin has been associated with vitamin B_{12} deficiency and reduce the regeneration of methionine. Metformin also inhibits mTOR and phosphorylation of its downstream targets and suppression of global protein synthesis.

Abbreviations: α-KG, α ketoglutarate; AMP, adenosine monophosphate; AMPK, AMP-activated kinase; ATP, adenosine triphosphate; DHF, dihydrofolate; HAT, histone acetylase; HDMT, histone demethyltransferase; mTOR, mammalian target of rapamycin; NAD, nicotinamide adenine dinucleotide; SAH, S-adenosyl homocysteine; SAM, S-adenosyl methionine; SIRT1, sirtuin 1; THF, tetrahydrofolate.

Therefore, it is abundantly clear that more research is needed to ascertain if metformin reprograms gene expression and, if it does, is this more favorable or detrimental to the long-term health of the offspring. In a mouse model of T2D embryopathy, Yanqing and colleagues demonstrated that metformin ameliorated insulin resistance and hyperglycemia in pregnant mice fed a high-fat diet. There was a reduction in cellular stress, apoptosis and occurrence of neural tube defects in the embryos [90]. Salomäki and colleagues demonstrated that adult mice exposed to metformin *in utero* gained more weight and mesenteric fat when fed a high-fat diet [91]. However, in another study, the same group reported the use of metformin in pregnant mice who were fed a high-fat diet. Metformin-exposed offspring gained less weight and adipose tissue and demonstrated less glucose intolerance when given a high-fat diet. Metformin also affected the expression of several genes involved in electron transport chain, particularly in the neonatal liver and adipose tissue [92]. Gregg and colleagues demonstrated that embryonic exposure to metformin prior to embryonic day 14 in pregnant mice resulted in increased number of pancreatic and duodenal homeobox 1 ($PDX1^+$) progenitors, which are precursors for pancreatic endocrine cell ontogenesis. There was also increased neurogenin 3 ($NGN3^+$) expression, which directs the undifferentiated precursor cells toward endocrine-specific differentiation, and this resulted in higher beta cell fraction at birth [93]. They proposed that metformin may confer protection from later diabetes in offspring.

Metformin and vitamin B_{12} deficiency during pregnancy?

Metformin can result in low levels of serum vitamin B_{12} and red blood cell folate [83]. Metformin can facilitate 'methylfolate trap' – the cell mistakenly interprets vitamin B_{12} deficiency as a lack of methionine and diverts folate away from DNA biosynthesis toward methylation of homocysteine to methionine. This causes a rise in cellular 5-methyl tetrahydrofolate (THF), though the cell is unable to utilize it. Deficiencies of folate and vitamin B_{12} can be detrimental to fetal growth and brain development.

In the Adelaide cohort of the MiG trial, the effects of metformin and insulin on vitamin B_{12} and homocysteine status were ascertained at randomization (20–34 weeks), 36 weeks and 6–8 weeks postpartum. Serum total vitamin B_{12} fell more between randomization and 36 weeks in metformin users. However, the bioavailable B_{12} (holotranscobalamin) was not affected [94]. This suggests that metformin is safe in pregnancy but the effect in women at risk of vitamin B_{12} deficiency or those using metformin for longer periods of time needs to be evaluated. A prospective study from Pune showed that vitamin B_{12} deficiency was very common in Indian pregnant women between 18 and 28 weeks gestation, while folate deficiency was rare [95]. Low maternal vitamin B_{12} and higher maternal erythrocyte folate concentration at 28 weeks predicted greater adiposity and insulin resistance in offspring at 6 years. Because folate supplementation in pregnancy is routinely practiced, the effect of metformin on vitamin B_{12} status and whether these women need vitamin B_{12} supplementation needs further clarification.

Does metformin affect reproductive development of offspring?

Metformin can inhibit several processes involved in protein, fatty acid and cholesterol synthesis, which are utilized by reproductive tissues for cell proliferation and the production of steroidal and peptide hormones [15]. Hence, it has the potential to affect gametogenesis and steroidogenesis in early gonadal development. In human and mouse organotypic cultures *in vitro*, metformin decreased testosterone secretion and messenger RNA (mRNA) expression of factors involved in steroid production, along with increased lactate secretion [96]. *In utero* exposure of male mice offspring to metformin was associated with reduced size of neonatal testes and reduced number of Sertoli cells, compared to controls. There was only a transient effect on Leydig cell population and testosterone content of testes, while there was no effect on germ cell number and no alterations in testicular descent [96]. Preliminary human evidence has been reassuring. Metformin-exposed offspring did not differ in male and female steroid hormone or antimullerian hormone (AMH) concentrations compared to nonexposed controls. Increase in sex hormone binding globulin (SHBG) levels has been reported in male offspring but free testosterone index was increased [15,97]. Tertti and colleagues found no difference in testicular size of prepubertal boys exposed to metformin or insulin during gestation [98]. Metformin exposure in these children began at 22 weeks. The impact of an earlier exposure during gestation is as yet unknown. The effect of metformin on gonadal development and long-term fertility, if any, merits further investigation.

Current status of metformin in clinical guidelines

Metformin is not currently approved by US Food and Drug Administration (FDA) for the management of diabetes during pregnancy and is listed as a category B drug, implying that animal studies have not demonstrated a risk to the fetus but there is lack of adequate well-controlled human studies. In Table 4, we compare the most recent recommendations from various guidelines. While International Federation of Gynecology and Obstetrics (FIGO), the UK National Institute for Health and Care Excellence (NICE), and the Endocrine Society guidelines consider insulin, glyburide, and metformin as appropriate first-line therapies for GDM [101–103], many other practice guidelines, such as the American Congress of Obstetricians and Gynecologists (ACOG), American Diabetes Association (ADA), and International Diabetes Federation (IDF), recognize that there is insufficient evidence at present to encourage

Table 4. Current guideline recommendations for use of metformin in gestational diabetes.

Guidelines	Recommendation
American Congress of Obstetricians and Gynecologists (ACOG), 2017 [99]	Insulin is first-line therapy if glycemic control is not attained with nonpharmacological treatment. Consider metformin if patient cannot take or declines insulin, but counsel about risk of placental cross-over and lack of long-term studies. Glyburide should not be used [43].
ADA Standards of Care, 2017 [100]	While metformin is associated with a lower risk of neonatal hypoglycemia and less maternal weight gain, long-term studies of oral antidiabetics are lacking and women should be informed that metformin crosses the placenta.
International Federation of Gynecology and Obstetrics (FIGO), 2015 [101]	If lifestyle modification alone fails to achieve glucose control, insulin, glyburide and metformin are safe and effective treatment options during second and third trimesters. Glyburide is inferior to both insulin and metformin, while metformin (plus insulin when required) performs slightly better than insulin. Insulin should be considered as the first-line treatment in women with GDM who are at high risk of failing on OAD therapy, including some of the following factors: 1. Diagnosis of diabetes < 20 weeks of gestation 2. Need for pharmacological therapy at <30 weeks 3. Fasting plasma glucose > 110 mg/dL 4. 1-hour postprandial glucose > 140 mg/dL 5. Pregnancy weight gain > 12 kg
UK NICE guidelines, 2015 [102]	Metformin is used if glycemic targets are not attained with lifestyle modification within 1–2 weeks and insulin is used if metformin is not tolerated or acceptable to patient. Insulin should be immediately commenced if FPG ≥ 126 mg/dL or if FPG 108–125 mg/dL and there are complications such as macrosomia or hydramnios. Glyburide is considered if patient refuses insulin and cannot tolerate metformin.
Endocrine Society, 2015 [103]	Metformin can be considered in women who decline or cannot use insulin or glyburide and are not in the first trimester. Glyburide is considered a suitable alternative to insulin in women who fail to achieve glycemic control with lifestyle modification, except for those with diagnosis before 25 weeks of gestation and FPG > 110 mg/dL.
WINGS (Women in India with GDM Strategy) guidelines, 2015 [104]	There is some evidence metformin and glyburide are safe in pregnancy. However, they cross the placenta and long-term safety data are not available. If pregnant woman is already on metformin, it may be continued during pregnancy. Metformin may be used if insulin is not available, not practical or refused by the woman.
International Diabetes Federation, 2009 [105]	If glucose targets are not met within 1–2 weeks of lifestyle modification, start glucose-lowering medication. Insulin is the treatment of choice but there is now adequate evidence to consider the use of metformin and glyburide in women who have been informed of the possible risks. Combination therapy has not been specifically studied.

FPG, fasting plasma glucose; GDM, gestational diabetes; OAD, oral antidiabetic drugs.

routine use of metformin in GDM over insulin [99,100,105]. In a recent consensus-based guideline from India, the use of oral antidiabetics was not recommended for glycemic management during pregnancy (Evidence Level A) [106]. Thus, there exists significant discord among guidelines with regard to the role of metformin and other oral antidiabetic agents in pregnancy with diabetes and there is a need to reach a uniform consensus in the light of recent evidence to avoid confusion.

Judicious use of metformin in pregnancy

Intensive insulin therapy is associated with higher cost, need for multiple daily injections and more frequent SMBG, greater time investment by health-care providers and more frequent visits to the clinic. Oral route of administration, low cost, need for less intensive monitoring, easy dose titration and a low risk of hypoglycemia make metformin an attractive option for the management of milder cases of GDM [107]. This is further supported by clinical evidence of more favorable outcomes such as lower maternal weight gain, lower risk of PIH, lower risk of neonatal hypoglycemia, NICU admissions and macrosomia seen in trials comparing metformin with insulin or glyburide. The benefits, however, need to be weighed against the possible increased risk of preterm delivery, though this has not been demonstrated in recent meta-analyses and might be a chance effect. While there is mostly a beneficial effect on immediate pregnancy outcomes in mother and newborn, there is clearly a

lack of long-term safety data in offspring exposed to metformin and further studies are required. In Table 5, we summarize the pros and cons of using metformin *versus* insulin in GDM. Metformin can have a significant failure rate in GDM and there is a need to identify which women are more likely to require insulin. A diagnosis of GDM at an earlier gestation, higher fasting glucose, higher maternal BMI, past history of GDM and older age of mother predict the need for supplemental insulin. Metformin may not be a suitable choice in these cases and insulin should be considered as first-line therapy. The role of metformin in T2D with pregnancy is less clear at the moment, but can be considered in women with high insulin dose requirements and rapid weight gain, as has been noted in a recent review [108]. However, there is lack of sufficient evidence for this practice.

While metformin can be continued in women with T2D during lactation, most women with GDM do not require pharmacological treatment after delivery. Hence, metformin can be discontinued and a glucose tolerance test repeated after 6 weeks.

In Table 6, we enlist the relative indications and contraindications for use of metformin in GDM. Metformin can be initiated in divided doses of 500 mg twice a day and

Table 5. Pros and cons of use of metformin for the management of gestational diabetes.

	Pros	Cons
Mechanism of action	Reduces insulin resistance, the main pathophysiology in GDM	May fail to achieve adequate glycemic control in presence of insulinopenia
Pharmacokinetics	Oral route of administration Easy dose titration	Increased renal clearance – need for higher doses Significant placental transfer – exposure of fetus Gastrointestinal intolerance
Efficacy	Glycemic control comparable to insulin or glyburide Low risk of maternal hypoglycemia	Failure rate in 14–46% women, who require supplemental insulin Slow onset of action – time lag in presence of significant hyperglycemia
Social and other considerations	Better patient acceptability Less cost Less need for self-monitoring of blood glucose	Not approved for use in pregnancy – category B, use is off-label Discordant views among leading guidelines
Maternal outcomes	No adverse maternal outcomes Less risk of hypoglycemia Lower maternal weight gain Less risk of pregnancy-induced hypertension	Slightly lower gestational age at delivery
Short-term fetal outcomes	No increased risk of teratogenicity in fetuses exposed in first trimester No increased risk of perinatal complications Reduced neonatal hypoglycemia Reduced NICU admissions Lower birth weight, reduced risk of LGA and macrosomia	Increased risk of preterm birth (inconsistent results)
Long-term effects of exposure of fetus	No evidence of growth or motor-social development abnormalities May result in more favorable distribution of adipose tissue in offspring (insufficient evidence)	Insufficient data of long-term effects of exposure *in utero* Concerns about impact on fetal programming Reduced testosterone secretion and Sertoli cell number in mice exposed *in utero* – significance in humans unknown
Lactation	Negligible secretion in breast milk	Insufficient trial evidence

GDM, gestational diabetes; LGA, large for gestational age; NICU, neonatal intensive care unit.

Table 6. Judicious use of metformin in the management of gestational diabetes.

Relative indications	Contraindications
As monotherapy: • GDM not responding to medical nutrition therapy and exercise, if FPG < 110 mg/dL • Poor compliance or refusal to use insulin • Lack of skills and/or resources for self-management of diabetes with insulin **Add-on to insulin therapy**: • High insulin dose requirements • Excess maternal weight gain	**Medical status**: Diagnosis in early gestation Elevated BMI with significant hyperglycemia Gastrointestinal intolerance Previous adverse reaction or allergy to metformin Renal or hepatic dysfunction **Metabolic status:** Significant hyperglycemia (FPG ≥110 mg/dL) Ketosis or ketonuria **Obstetric status:** History of major congenital anomaly in previous pregnancy Presence of hydramnios Maternal distress Fetal distress

BMI, body mass index; FPG, fasting plasma glucose.

the dose up-titrated at weekly intervals to 2500 mg per day in divided doses. Therapy should be guided by SMBG records, and in case glycemic targets are not achieved in 1–2 weeks, insulin should be added. In case there is any evidence of polyhydramnios, macrosomia, fetal growth restriction, maternal or fetal distress, the patient should be immediately switched to insulin.

Future research

There remain several unanswered questions regarding the efficacy and safety of metformin in women with GDM or pre-existing diabetes. There is a need for more animal and human studies to ascertain the effect of metformin on the developing embryo and fetus and potential long-term implications.

1. Studies to define which category of patients are more likely to respond to metformin and who may need supplemental insulin.
2. Studies to assess the effect of metformin as add-on to other pharmacological therapies such as insulin, especially in women with pre-existing diabetes.
3. Studies to assess the efficacy and safety of metformin during lactation.
4. Effect of early metformin exposure on fetal development and reproductive health of offspring.
5. Effect of metformin on fetal programming and long-term outcomes in exposed offspring.
6. Effect of metformin on vitamin B_{12} and folate status in pregnant mothers and associated effects on offspring health.

Conclusion

Metformin is an effective and well-tolerated glucose lowering agent with a well-defined mechanism of action. Current animal and human data indicate that metformin is safe and effective in the management of GDM and may improve immediate pregnancy outcomes. While there is assurance that it does not have teratogenic potential and there is some evidence of long-term effects in offspring exposed to metformin *in utero*, there is a need to further assess its role in fetal programming. Metformin may be considered as monotherapy in mild GDM, where it may result in less maternal weight gain, lower risk of PIH, lower risk of neonatal hypoglycemia and lower incidence of macrosomia. However, caution is needed due to its potential to cause significant fetal exposure and lack of long-term safety data related to fetal exposure.

Contributions: Both authors contributed to the writing of this manuscript.

Disclosure and potential conflicts of interest: The authors declare no conflicts of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at http://www.drugsincontext.com/wp-content/uploads/2018/05/dic.212523-COI.pdf

Article URL: http://www.drugsincontext.com/metformin-in-the-management-of-diabetes-during-pregnancy-and-lactation

Correspondence: Gagan Priya, Department of Endocrinology, Fortis Hospital, Sector 62, Mohali – 160059, India. gpriya77@gmail.com

Provenance: invited; externally peer reviewed.

Submitted: 3 December 2017; **Peer review comments to author:** 9 March 2018; **Revised manuscript received:** 21 May 2018; **Accepted:** 22 May 2018; **Publication date:** 15 June 2018.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252772009.

For all manuscript and submissions enquiries, contact the Editorial office dic.editorial@bioexcelpublishing.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008 May 8;358:1991–2002. https://doi.org/10.1056/NEJMoa0707943
2. Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S, Dunne F, Lawlor DA. Hyperglycemia and risk of adverse perinatal outcomes: systematic review and meta-analysis. BMJ. 2016 Sep 13;354:i4694. https://doi.org/10.1136/bmj.i4694
3. Falavigna M, Schmidt MI, Trujillo J, Alves LF, Wendland ER, Torloni MR, Colagiuri S, Duncan BB. Effectiveness of gestational diabetes treatment: a systematic review with quality of evidence assessment. Diabetes Res Clin Pract. 2012 Dec;98(3):396–405. https://doi.org/10.1016/j.diabres.2012.09.002
4. Coetzee EJ, Jackson WP. Oral hypoglycemic in the first trimester and fetal outcome. S Afr Med J. 1984 Apr 21;65(16):635–7. PubMed PMID: 24431611.
5. Coetzee EJ, Jackson WP. The management of non-insulin-dependent diabetes during pregnancy. Diabetes Res Clin Pract. 1985–1986 Feb;1(5):281–7. PubMed PMID: 3939118.
6. Coetzee EJ, Jackson WP. Metformin in management of pregnant insulin-independent diabetics. Diabetologia. 1979 Apr;16(4):241–5. PubMed PMID: 428695.
7. Kelley KW, Carroll DG, Meyer A. A review of current treatment strategies for gestational diabetes mellitus. Drugs Context. 2015;4:212282. https://doi.org/10.7573/dic.212282. PubMed Central PMCID: PMC4509429.
8. Rena G, Hardie DG, Ewan RP. The mechanism of action of metformin. Diabetologia. 2017;60(9):1577–85. https://doi.org/10.1007/s00125-017-4342-z
9. Mathews TJ, Hamilton BE. Mean age of mothers is on the rise: United States, 2000–2014. NCHS Data Brief Jan. 2016; No 232. Available at: https://www.cdc.gov/nchs/data/databriefs/db232.pdf
10. Feig DS, Palda VA. Type 2 diabetes in pregnancy: a growing concern. Lancet. 2002 May;359(9318):1690–2. https://doi.org/10.1016/S0140-6736(02)08599-9
11. Abell SK, Nankervis A, Khan KS, Teede HJ. Type 1 and type 2 diabetes preconception and in pregnancy: health impacts, influence of obesity and lifestyle, and principles of management. Semin Reprod Med. 2016 Mar;34(2):110–20. https://doi.org/10.1055/s-0035-1571196
12. Padmanabhan S, Zen M, Lee V, Cheung NW. Pre-existing diabetes in pregnancy. Minerva Endocrinol. 2016 Mar;41(1):122–37. PubMed PMID: 26878562.
13. Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, Li N, Hu G, Corrado F, Rode L, Kim YJ, Haugen M, Song WO, Kim MH, Bogaerts A, Devlieger R, Chund JH, Teede HJ. Association of gestational weight gain with maternal and infant outcomes: a systematic review and meta-analysis. JAMA. 2017 Jun;317(21):2207–25. https://doi.org/10.1001/jama.2017.3635
14. World Health Organization. Diagnostic criteria and classification of hyperglycemia first detected in pregnancy. WHO 2013, Reference number: WHO/NMH/MND/13.2.
15. Bertoldo MJ, Faure M, Dupont J, Froment P. Impact of metformin on reproductive tissues: an overview from gametogenesis to gestation. Ann Transl Med. 2014;2(6):55–67. https://doi.org/10.3978/j.issn.2305-5839.2014.06.04
16. Hughes RC, Gardiner SJ, Begg EJ, Zhang M. Effect of pregnancy on the pharmacokinetics of metformin. Diabet Med. 2006 Mar;23(3):323–6. https://doi.org/10.1111/j.1464-5491.2005.01769.x
17. Tertti K, Ekblad U, Heikkinen T, Rahi M, Ronnemaa T, Laine K. The role of organic cation transporters (OCTs) in the transfer of metformin in the dually perfused human placenta. Eur J Pharm Sci. 2010 Jan;39(1–3):76–81. https://doi.org/10.1016/j.ejps.2009.10.014

18. Kovo M, Kogman N, Ovadia O, Nakash I, Golan A, Hoffman A. Carrier-mediated transport of metformin across the human placenta determined by using the ex vivo perfusion of the placental cotyledon model. Prenat Diagn. 2008 Jun;28(6):544–8. https://doi.org/10.1002/pd.2026
19. Charles B, Norris R, Xiao X, Hague W. Population pharmacokinetics of metformin in late pregnancy. Ther Drug Monit. 2006 Feb;28(1):67–72. PubMed PMID: 16418696.
20. Eyal S, Easterling TR, Carr D, Umans JG, Miodovnik M, Hankins GD, Clark SM, Risler L, Wang J, Kelly EJ, Shen DD, Herbert MF. Pharmacokinetics of metformin during pregnancy. Drug Metab Dispos. 2010 May;38(5):833–40. https://doi.org/10.1124/dmd.109.031245
21. Briggs GG, Ambrose PJ, Nageotte MP, Padilla G, Wan S. Excretion of metformin into breast milk and the effect on nursing infants. Obstet Gynecol. 2005 Jun;105(6):1437–41. https://doi.org/10.1097/01.AOG.0000163249.65810.5b
22. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP for the MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. May 2008;358:2003–15. https://doi.org/10.1056/NEJMoa0707193
23. Tertti K, Ekblad U, Vahlberg T, Ronnemaa T. Comparison of metformin and insulin in the treatment of gestational diabetes: a retrospective, case-control study. Rev Diabet Stud. 2008 Summer;5(2):95–101. https://doi.org/10.1900/RDS.2008.5.95
24. Silva AL, Amaral AR, Oliveira DS, Martins L, Silva MR, Silva JC. Neonatal outcomes according to different therapies for gestational diabetes mellitus. J Pediatr (Rio J). 2017 Jan-Feb;93(1):87–93. https://doi.org/10.1016/j.jped.2016.04.004
25. Balani J, Hyer SL, Rodin DA, Shehata H. Pregnancy outcomes in women with gestational diabetes treated with metformin or insulin: a case-control study. Diabet Med. 2009 Aug;26(8):798–802. https://doi.org/10.1111/j.1464-5491.2009.02780.x
26. Balani J, Hyer S, Johnson A, Shehata H. Pregnancy outcomes after metformin treatment for gestational diabetes: a case-control study. Obstet Med. 2012 Jun;5(2):78–82. https://doi.org/10.1258/om.2012.110092
27. Moore LE, Briery CM, Clokey D, Martin RW, Williford NJ, Bofill JA, Morrison JC. Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison. J Reprod Med. 2007 Nov;52(11):1011–5. PubMed PMID: 18161398.
28. Silva JC, Pacheo C, Bizato J, deSouza BV, Ribeiro TE, Bertini AM. Metformin compared with glyburide for the management of gestational diabetes. Int J Gynaecol Obstet. 2010 Oct;111(1):37–40. https://doi.org/10.1016/j.ijgo.2010.04.028
29. Moore LE, Clokey D, Rappaport VJ, Curet LB. Metformin compared with glyburide in gestational diabetes: a randomized controlled trial. Obstet Gynecol. 2010 Jan;115(1):55–9. https://doi.org/10.1097/AOG.0b013e3181c52132
30. Ijäs H, Vääräsmäki M, Morin-Papunen L, Keravuo R, Ebeling T, Saarela T, Raudaskoski T. Metformin should be considered in the treatment of gestational diabetes: a prospective randomised study. BJOG. 2011 Jun;118(7):880–5. https://doi.org/10.1111/j.1471-0528.2010.02763.x
31. 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 Dec;98(3):422–9. https://doi.org/10.1016/j.diabres.2012.09.031
32. Silva JC, Fachin DR, Coral ML, Bertini AM. Perinatal impact of the use of metformin and glyburide for the treatment of gestational diabetes mellitus. J Perinat Med. 2012 Jan 10;40(3):225–8. https://doi.org/10.1515/jpm-2011-0175
33. 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 Mar;4(3):327–33. PubMed Central PMCID: PMC3634172.
34. Spaulonci CP, Bernardes LS, Trindade TC, Zugain M, Francisco RP. Randomized trial of metformin vs insulin in the management of gestational diabetes. Am J Obstet Gynecol. 2013 Jul;209(1)34.e1–7. https://doi.org/10.1016/j.ajog.2013.03.022
35. Tertti K, Ekblad U, Koshinen P, Vahlberg T, Ronnemaa T. Metformin vs. insulin in gestational diabetes. A randomized study characterizing metformin patients needing additional insulin. Diabetes Obes Metab. 2013 Mar;15(3):246–51. https://doi.org/10.1111/dom.12017
36. Ruholamin S, Eshaghian S, Allame Z. Neonatal outcomes in women with gestational diabetes mellitus treated with metformin in compare with insulin: a randomized clinical trial. J Res Med Sci. 2014 Oct;19(10):970–5. PubMed Central PMCID: PMC4274575.
37. George A, Mathews JE, Sam D, Beck M, Benjamin SJ, Abraham A, Antonisamy B, Jana AK, Thomas N. Comparison of neonatal outcomes in women with gestational diabetes with moderate hyperglycaemia on metformin or glibenclamide – a randomised controlled trial. Aust N Z J Obstet Gynaecol. 2015 Feb;55(1):47–52. https://doi.org/10.1111/ajo.12276
38. 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 Feb:107(2):290–9. https://doi.org/10.1016/j.diabres.2014.10.001
39. Ashoush S, El-Said M, Fathi H, Abdelnaby M. Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus. J Obstet Gynaecol Res. 2016 Jun;42(6):640–7. https://doi.org/10.1111/jog.12950
40. Nachum Z, Zafran N, Salim R, Hissin N, Hasanein J, Gam Ze Letova Y, Suleiman A, Yefet E. Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: a randomized controlled study. Diabetes Care. 2017 Mar;40(3):332–7. https://doi.org/10.2337/dc16-2307

41. Arshad R, Khanam S, Shaikh F, Karim N. Feto-maternal outcomes and Glycemic control in Metformin versus insulin treated Gestational Diabetics. Pak J Med Sci. 2017 Sep-Oct;33(5):1182–7. https://doi.org/10.12669/pjms.335.13286
42. Gui J, Liu Q, Feng L. Metformin vs insulin in the management of gestational diabetes: a meta-analysis. PLoS. 2013 May 27;8(5):e64585. https://doi.org/10.1371/journal.pone.0064585
43. Poolsup N, Suksomboon N, Amin M. Efficacy and safety of oral antidiabetic drugs in comparison to insulin in treating gestational diabetes mellitus: a meta-analysis. PLoS One. 2014 Oct 10;9(10):e109985. https://doi.org/10.1371/journal.pone.0109985
44. Su DF, Wang XY. Metformin vs insulin in the management of gestational diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2014 Jun;104(3):353–7. https://doi.org/10.1016/j.diabres.2013.12.056
45. Jiang YF, Chen XY, Ding T, Wang XF, Zhu ZN, Su SW. Comparative efficacy and safety of OADs in management of GDM: network meta-analysis of randomized controlled trials. J Clin Endocrinol Metab. 2015 May;100(5):2071–80. https://doi.org/10.1210/jc.2014-4403
46. Kitwitee P, Limwattananon S, Limwattananon C, Waleekachonlert O, Ratanachotpanich T, Phimphilai M, Nguyen TV, Pongchaiyakul C. Metformin for the treatment of gestational diabetes: an updated meta-analysis. Diabetes Res Clin Pract. 2015 Sept; 109(3):521–32. https://doi.org/10.1016/j.diabres.2015.05.017
47. Li G, Zhao S, Cui S, Li L, Xu Y, Li Y. Effect comparison of metformin with insulin treatment for gestational diabetes: a meta-analysis based on RCTs. Arch Gynecol Obstet. 2015 Jul;292(1):111–20. https://doi.org/10.1007/s00404-014-3566-0
48. Amin M, Suksomboon N, Poolsup N, Malik O. Comparison of glyburide with metformin in treating gestational diabetes mellitus: a systematic review and meta-analysis. Clin Drug Investig. 2015 Jun;35(6):343–51. https://doi.org/10.1007/s40261-015-0289-3
49. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ. 2015 Jan 21;350:h102. https://doi.org/10.1136/bmj.h102
50. Singh KP, Rahimpanah F, Barclay M. Metformin for the management of gestational diabetes mellitus. Aust N Z J Obstet Gynaecol. 2015 Aug;55(4):303–8. https://doi.org/10.1111/ajo.12311
51. Zhu B, Zhang L, Fan YY, Wang Li, Li XG, Liu T, Cao YS, Zhao ZG. Metformin versus insulin in gestational diabetes mellitus: a meta-analysis of randomized clinical trials. Ir J Med Sci. 2016 May;185(2):371–81. https://doi.org/10.1007/s11845-016-1414-x
52. Liang HL, Ma SJ, Xiao YN, Tan HZ. Comparative efficacy and safety of oral antidiabetic drugs and insulin in treating gestational diabetes mellitus: an updated PRISM-compliant network meta-analysis. Medicine (Baltimore). 2017 Sep;96(38):e7939. https://doi.org/10.1097/MD.0000000000007939
53. Brown J, Martis R, Hughes B, Rowan J, Crowther CA. Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes. Cochrane Database Syst Rev. 2017 Jan 25;1:CD011967. https://doi.org/10.1002/14651858.CD011967.pub2
54. Brown J, Grzeskowiak L, Williamson K, Downie MR, Crowther CA. Insulin for the treatment of women with gestational diabetes. Cochrane Database Syst Rev. 2017 Nov 5;11:CD012037. https://doi.org/10.1002/14651858.CD012037.pub2
55. Feng Y, Yang H. Metformin – a potentially effective drug for gestational diabetes mellitus: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2017 Aug;30(15):1874–81. https://doi.org/10.1080/14767058.2016.1228061
56. Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S, Lawlor DA. Treatments for gestational diabetes: a systematic review and meta-analysis. BMJ Open. 2017;7:e015557. https://doi.org/10.1136/bmjopen-2016-015557
57. Butalia S, Gutierrez L, Lodha A, Aitken E, Zakariasen A, Donovan L. Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: a systematic review and meta-analysis. Diabet Med. 2017 Jan;34(1):27–36. https://doi.org/10.1111/dme.13150
58. Gante I, Melo D, Dores J, Ruas L, Almeida MDC. Metformin in gestational diabetes mellitus: predictors of poor response. Eur J Endocrinol. 2017 Oct 25. pii: EJE-17-0486. https://doi.org/10.1530/EJE-17-0486
59. Corbould A, Swinton F, Radford A, Campbell J, McBeath S, Dennis A. Fasting blood glucose predicts response to extended-release metformin in gestational diabetes mellitus. Aust N Z J Obstet Gynaecol. 2013 Apr;53(2):125–9. https://doi.org/10.1111/ajo.12018
60. Wong VW, Jalaludin B. Gestational diabetes mellitus: who requires insulin therapy? Aust N Z J Obstet Gynaecol. 2011 Oct;51(5):432–6. https://doi.org/10.1111/j.1479-828X.2011.01329.x
61. McGrath RT, Glastras SJ, Hocking S, Fulcher GR. Use of metformin earlier in pregnancy predicts supplemental insulin therapy in women with gestational diabetes. Diabetes Res Clin Pract. 2016 Jun;116:96–9. https://doi.org/10.1016/j.diabres.2016.04.051
62. Feng L, Lin X-F, Hu D, Du Y-K. Efficacy of metformin on pregnancy complications in women with polycystic ovary syndrome: a meta-analysis. Gynecol Endocrinol. 2015;31(11):833–9. https://doi.org/10.3109/09513590.2015.1041906
63. Tan X, Li S, Chang Y, Fang C, Liu H, Zhang X, Wang Y. Effect of metformin treatment during pregnancy on women with PCOS: a systematic review and meta-analysis. Clin Invest Med. 2016;38(4):E120-E131.
64. Hellmuth E, Damm P, Molsted-Pedersen L. Oral hypoglycaemic agents in 118 diabetic pregnancies. Diabet Med. 2000 Jul;17(7):507–11.
65. Hughes RC, Rowan JA. Pregnancy in women with type 2 diabetes: who takes metformin and what is the outcome? Diabet Med. 2006;23:318–22. https://doi.org/10.1111/j.1464-5491.2006.01750.x

66. Ekpebegh CO, Coetzee EJ, van derMerwe L, Levitt NS. A 10-year retrospective analysis of pregnancy outcome in pregestational type 2 diabetes: comparison of insulin and oral glucose-lowering agents. Diabet Med. 2007;24:253–58. https://doi.org/10.1111/j.1464-5491.2007.02053.x
67. Hughes RC, Rowan JA. Pregnancy in women with type 2 diabetes: who takes metformin and what is the outcome? Diabet Med. 2006 Mar;23(3):318–22. https://doi.org/10.1111/j.1464-5491.2006.01750.x
68. Refuerzo JS, Gowen R, Pedroza C, Hutchinson M, Blackwell SC, Ramin S. A pilot randomized, controlled trial of metformin versus insulin in women with type 2 diabetes mellitus during pregnancy. Am J Perinatol. 2015 Feb;30(2):163–70. https://doi.org/10.1055/s-0034-1378144
69. Rai L, Meenakshi D, Kamath A. Metformin – a convenient alternative to insulin for Indian women with diabetes in pregnancy. Indian J Med Sci. 2009 Nov;63(11):491–7. https://doi.org/10.4103/0019-5359.58878
70. Hickman MA, McBride R, Boggess KA, Strauss R. Metformin compared with insulin in the treatment of pregnant women with overt diabetes: a randomized controlled trial. Am J Perinatol. 2013 Jun;30(6):483–90. https://doi.org/10.1055/s-0032-1326994
71. Ibrahim MI, Hamdy A, Shafik A, Taha S, Anwar M, Faris M. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. Arch Gynecol Obstet. 2014 May;289(5):959–65. https://doi.org/10.1007/s00404-013-3090-7
72. Ainuddin JA, Karim N, Zaheer S, Ali SS, Hasan AA. Metformin treatment in type 2 diabetes in pregnancy: an active controlled, parallel-group, randomized, open label study in patients with type 2 diabetes in pregnancy. J Diabetes Res. 2015;2015:325851. https://doi.org/10.1155/2015/325851
73. Tieu J, Coat S, Hague W, Middleton P, Shepherd E. Oral anti-diabetic agents for women with established diabetes/impaired glucose tolerance or previous gestational diabetes planning pregnancy, or pregnant women with pre-existing diabetes. Cochrane Database Syst Rev. 2017 Oct 18;10:CD007724. https://doi.org/10.1002/14651858.CD007724.pub3
74. Feig DS, Murphy K, Asztalos E, Tomlinson G, Sanchez J, Zinman B, Ohlsson A, Ryan EA, Fantus IG, Armson AB, Lipscombe LL, Barrett JFR on behalf of fthe MiTy Collabortive Group. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multi-center randomized controlled trial. BMC Pregnancy Childbirth. 2016 Jul;16(1):173. https://doi.org/10.1186/s12884-016-0954-4
75. Kalra B, Gupta Y, Singla R, Kalra S. Use of oral anti-diabetic agents in pregnancy: a pragmatic approach. N Am J Med Sci. 2015 Jan;7(1):6–12. https://doi.org/10.4103/1947-2714.150081
76. Glueck CJ, Salehi M, Sieve L, Wang P. Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. J Pediatr. 2006 May;148(5):628–32. https://doi.org/10.1016/j.jpeds.2006.01.011
77. Rowan JA, Rush EC, Obolonkin V, Battin M, Wouldes T, Hague WM. Metformin in gestation diabetes: the offspring follow-up (MiG TOFU): body composition at 2 years of age. Diabetes Care. 2011 Oct;34(10):2279–84. https://doi.org/10.2337/dc11-0660
78. Carlsen SM, Martinussen MP, Vanky E. Metformin's effect on first-year weight gain: a follow-up study. Pediatrics. 2012 Nov;130(5):e1222–6. https://doi.org/10.1542/peds.2012-0346
79. Rø TB, Ludvigsen HV, Carlsen SM, Vanky E. Growth, body composition and metabolic profile of 8-year old children exposed to metformin *in utero*. Scand J Clin Lab Invest. 2012 Nov;72(7):570–5. https://doi.org/10.3109/00365513.2012.712319
80. Ijäs H, Vääräsmäki 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 Jun;122(7):994–1000. https://doi.org/10.1111/1471-0528.12964
81. 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 and continued metformin through pregnancy. Hum Reprod. 2004 Jun;19(6):1323–30.
82. Wouldes TA, Battin M, Coat S, Rush EC, Hague WM, Rowan JA. Neurodevelopmental outcome at 2 years in offspring of women randomised to metformin or insulin treatment for gestational diabetes. Arch Dis Child Fetal Neonatal Ed. 2016 Feb 24. pii: fetalneonatal-2015-309602. https://doi.org/10.1136/archdischild-2015-309602
83. Luciano-Mateo F, Hernandez-Aguilera A, Cabre N, Camps J, Fernandez-Arroyo S, Lopez-Miranda J, Menendez JA, Joven J. Nutrients in energy and one-carbon metabolism: learning from metformin users. Nutrients. 2017 Feb 10;9(2). pii: E121. https://doi.org/10.3390/nu9020121
84. Lee HY, Wei D, Loeken MR. Lack of metformin effect on mouse embryo AMPK activity: implications for metformin treatment during pregnancy. Diabetes Metab Res Rev. 2014 Jan;30(1):23–30. https://doi.org/10.1002/dmrr.2451
85. Rojas J, Chávez-Castillo M, Bermúdez V. The role of metformin in metabolic disturbances during pregnancy: polycystic ovary syndrome and gestational diabetes mellitus. Internet J Reprod Med. 2014;2014:797681. http://dx.doi.org/10.1155/2014/797681
86. Amador RR, Longo JP, Lacava ZG, Dorea JG, Almeida Santos Mde F. Metformin (dimethyl-biguanide) induced DNA damage in mammalian cells. Genet Mol Biol. 2012 Jan;35(1):153–8. PubMed PMID: 22481889. PubMed Central PMCID: PMC3313505.
87. Cassina M, Dona 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 Sep-Oct;20(5):656–69. https://doi.org/10.1093/humupd/dmu022

88. Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. Fertil Steril. 2006 Sep;86(3):658–63. Epub 2006 Jul 31. PubMed PMID: 16879826.
89. Finer S, Saravanan P, Hitman G, Yajnik C. The role of the one-carbon cycle in the developmental origins of Type 2 diabetes and obesity. Diabet Med. 2014 Mar;31(3):263–72. https://doi.org/10.1111/dme.12390
90. Yanqing Wu, Fang Wang, Mao Fu, Cheng Wang, Michael J. Quon, Peixin Yang. Cellular stress, excessive apoptosis, and the effect of metformin in a mouse model of type 2 diabetic embryopathy. Diabetes. 2015 Jul;64(7):2526–36. https://doi.org/10.2337/db14-1683
91. Salomäki H, Vähätalo LH, Laurila K, Jäppinen NT, Penttinen AM, Ailanen L, Ilyasizadeh J, Pesonen U, Koulu M. Prenatal metformin exposure in mice programs the metabolic phenotype of the offspring during a high fat diet at adulthood. PLoS One. 2013;8(2):e56594. https://doi.org/10.1371/journal.pone.0056594
92. Salomäki H, Heinäniemi M, Vähätalo LH, Ailanen L, Eerola K, Ruohonen ST, Pesonen U, Koulu M. Prenatal metformin exposure in a maternal high fat diet mouse model alters the transcriptome and modifies the metabolic responses of the offspring. PLoS One. 2014 Dec 26;9(12):e115778. https://doi.org/10.1371/journal.pone.0115778
93. Gregg B, Elghazi L, Alejandro EU, Smith MR, Blandino-Rosano M, El-Gabri D, Cras-Meneur C, Bernal-Mizrachi E. Exposure of mouse embryonic pancreas to metformin enhances the number of pancreatic progenitors. Diabetologia. 2014 Dec;57(12):2566–75. https://doi.org/10.1007/s00125-014-3379-5
94. Gatford KL, Houda CM, Lu ZX, Coat S, Baghurst PA, Owens JA, Sikaris K, Rowan JA, Hague WM. Vitamin B12 and homocysteine status during pregnancy in the metformin in gestational diabetes trial: responses to maternal metformin compared with insulin treatment. Diabetes Obes Metab. 2013 Jul:15(7):660–7. https://doi.org/10.1111/dom.12080
95. Yajnik CS, Deshpande SS, Jackson AA, Refsum H, Rao S, Fisher DJ, Bhat DS, Naik SS, Covaji KJ, Joglekar CV, Joshi N, Lubree HG, Deshpande VU, Rege SS, Fall CH. Vitamin B12 and folate concentrations during pregnancy and insulin resistance in the offspring: the Pune Maternal Nutrition Study. Diabetologia. 2008 Jan;51(1):29–38. https://doi.org/10.1007/s00125-007-0793-y
96. Tartarin P, Moison D, Guibert E, Dupont J, Habert R, Rouiller-Fabre V, Frydman N, Pozzi S, Frydman R, Lecureuil C, Froment P. Metformin exposure affects human and mouse fetal testicular cells. Hum Reprod. 2012 Nov;27(11):3304–14. https://doi.org/10.1093/humrep/des264
97. Carlsen SM. Vanky E. Metformin influence on hormone levels at birth, in PCOS mothers and their newborns. Hum Reprod. 2010 Mar;25(3):786–90. https://doi.org/10.1093/humrep/dep444
98. Tertti K, Toppari J, Virtanen HE, Sadov S, Ronnemaa T. Metformin treatment does not affect testicular size in offspring born to mothers with gestational diabetes. Rev Diabet Stud. 2016 Spring;13(1):59–65. https://doi.org/10.1900/RDS.2016.13.e2015013
99. Practice Bulletin No. 180: Gestational Diabetes Mellitus. Committee on Practice Bulletins – Obstetrics. Obstet Gynecol. 2017 Jul;130(1):e17-e37. https://doi.org/10.1097/AOG.0000000000002159. PubMed PMID: 28644336.
100. American Diabetes Association, Standards of Care. Management of diabetes in pregnancy. Diabetes Care. 2017 Jan;40(Supplement 1):S114-S119. https://doi.org/10.2337/dc17-S016
101. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, Roura LC, McIntyre HD, Morris JL, Divakar H. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. Int J Gynecol Obstet. 2015;131:S173–S211. https://doi.org/10.1016/S0020-7292(15)30033-3
102. Diabetes in pregnancy: management from preconception to the postnatal period. NICE guideline. Published 25th Feb 2015. Available at: https://www.nice.org.uk/guidance/ng3
103. Blumer I, Hadar E, Hadden DR, Jovanovič L, Mestman JH, Murad MH, Yogev Y. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013 Nov;98(11):4227–49. https://doi.org/10.1210/jc.2013-2465
104. IDF GDM Model of Care: Implementation Protocol: Guidelines for Healthcare Professionals. Available at: https://www.idf.org/e-library/guidelines/77-idf-gdm-model-of-care-implementation-protocol-guidelines-for-healthcare-professionals.html
105. IDF Clinical Guidelines Task Force. Global Guideline on pregnancy and diabetes. Brussels: International Diabetes Federation, 2009. Available at: https://www.idf.org/e-library/guidelines/84-pregnancy-and-diabetes.html
106. Seshiah V, Banerjee S, Balaji V, Muruganathan A, Das AK. Consensus evidence-based guidelines for management of gestational diabetes mellitus in India. J Assoc Physicians India. 2014 Jul;62(7 Suppl):55–62. PubMed PMID: 25668938.
107. Kalra B, Gupta Y. Pragmatic use of metformin in pregnancy based on biopsychosocial model of health. Indian J Endocrinol Metab. 2013 Nov-Dec;17(6):1133–35. https://doi.org/10.4103/2230-8210.122654
108. Lindsay RS, Loeken MR. Metformin in pregnancy: promises and uncertainties. Diabetologia. 2017;60:1612–19. https://doi.org/10.1007/s00125-017-4351-y