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Metformin treatment for Type 2 diabetes in pregnancy?

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Metformin lowers blood glucose by reducing hepatic glucose output, increasing insulin sensitivity and enhancing peripheral glucose uptake. Metformin is widely used in women with Type 2 diabetes of child-bearing age, many of whom become pregnant. Studies to date in Type 2 diabetes in pregnancy, gestational diabetes and polycystic ovarian syndrome are reassuring. Metformin is not considered teratogenic. There is sufficient evidence that metformin is safe used throughout pregnancy, with no worsening of obstetric or perinatal outcomes. Women may benefit from the lesser weight gain. The long-term risks to the offspring remain inadequately researched, with no evidence of harm up to 2 years, and no suggestions of later complications in countries using metformin for many years. Metformin is recommended for use in pregnancies complicated by Type 2 diabetes, but women should be informed of the evidence regarding its associated risks and benefits to enable an informed choice over its use.

The latter part of the 20th century saw the start of an epidemic of obesity and Type 2 diabetes.[1] This has manifested as not only growing numbers of people with Type 2 diabetes overall, but an increasingly younger age at onset, such that more children, adolescents, and women of child-bearing age are developing Type 2 diabetes. Not surprisingly, the numbers of women with Type 2 diabetes in pregnancy are therefore increasing rapidly. Even the time between developing gestational diabetes (GDM) and Type 2 diabetes is shortening [2] and many women have their Type 2 diabetes diagnosed during pregnancy.[3] This is a significant concern as Type 2 diabetes in pregnancy is known to be

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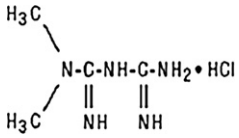
Practice points

- *The numbers of women with Type 2 diabetes in pregnancy are increasing.*
- *Metformin is usually a drug of choice in Type 2 diabetes and many women are becoming pregnant while on metformin.*
- *Metformin is not considered teratogenic and can be used in the peri-conceptual period.*
- *Metformin should not be stopped until after the first 8–12 weeks of pregnancy (if at all) to avoid exposing the fetus to worsening hyerpglycamia during embryogenesis.*
- *Metformin can be useful during pregnancy for improved glucose control in insulin resistant states and where women refuse insulin therapy*
- *Metformin is now considered safe for use during pregnancy in terms of obstetric and perinatal outcomes.*
- *Metformin does cross the placenta and the long-term safety of transplacental metformin on the offspring has not been demonstrated beyond two years.*
- *Use of metformin requires women to be able to make an informed choice over the balance between its known benefits and any unknown future harm.*

associated with pregnancy outcomes which are at least as bad as in Type 1 diabetes in pregnancy.[4] Furthermore, there is growing evidence that exposure to hyperglycaemia *in utero* is not only responsible for fetal malformations, but for an increased risk of diabetes, the metabolic syndrome and obesity in the offspring later in their lives.[5] What is clear is that pre-conceptual and antenatal hyperglycaemia requires anti-hyperglycaemic therapy and a growing debate has arisen over the optimal approach to glycaemic control during this time.

Metformin has now become an anti-hyperglycaemic drug of choice for many non-pregnant adults on diagnosis of their Type 2 diabetes.[6] As a result, a growing number of women are becoming pregnant while taking metformin therapy. Experience with metformin during pregnancy is growing. Early data came from South Africa, where there has been a history of metformin use during pregnancy.[7,8] Women with some other clinical conditions are also taking metformin to either prevent diabetes developing (some of those with impaired glucose tolerance (IGT),[9] even though this therapy is not within guidelines to date) or to promote fertility (those with the polycystic ovarian syndrome (PCOS), even though clomiphene has now been shown to be superior[10]).

Metformin or metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is the surviving biguanide (the others being phenformin and buformin, which were withdrawn after deaths from lactic acidosis and other problems). Lactic acidosis is rarely reported with metformin (0.03 cases/1000 patients) and even then only in those with significant renal, hepatic or cardiac dysfunction. Although introduced to the United Kingdom in 1958 and Canada in 1972, it was not used in the United States until 1995. It is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. The structural formula is:



Metformin reduces hyperglycaemia by suppressing hepatic glucose output (hepatic gluconeogenesis), increasing insulin sensitivity and enhancing peripheral glucose uptake.[11] These effects are potentially particularly useful during pregnancy where glucose control deteriorates with changes to pre-prandial and postprandial glucose metabolism and insulin resistance.