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Paternal metformin use and congenital malformations in offspring

Latest big study is reassuring for potential fathers and their partners

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The antidiabetic drug metformin reduces hyperglycaemia by inhibiting hepatic glucose production and increasing insulin sensitivity.[1] It is used as initial treatment for type 2 diabetes and off-label to manage a range of other conditions associated with metabolic dysregulation, including obesity and polycystic ovary syndrome.[2] More than 24 million prescriptions for metformin were issued in the UK during 2022-23.[3]

With widespread use comes additional concern for characterising safety at the population level. During pregnancy, metformin crosses the placenta.[4] A growing body of literature has consequently focused on characterising any potential effects of maternal metformin use on offspring.[5-8] Reassuringly, such use has not been convincingly linked with an increased risk of congenital abnormalities.[5,6]

By comparison, the potential effect of paternal metformin use on risk of congenital abnormalities among offspring has been understudied. The first major study to examine this association was published in 2022: using population based data from Denmark (n=1 116 779), the authors found that prescription of metformin to fathers during the preconception period (for any indication) was associated with an increased risk of major congenital malformations among offspring, compared with insulin.[9] Specifically, this study reported a 3.3-fold increase in the likelihood of genital birth defects in male offspring (adjusted odds ratio 3.39 (95% confidence interval (CI) 1.82 to 6.30)). Offspring of mothers with pre-existing and gestational diabetes were excluded from the analysis given the well described association between maternal diabetes and congenital malformations.[10] However, a subsequent study using the same dataset found that the association between paternal metformin use and increased risk of major congenital malformations persisted when including the offspring of mothers with diabetes.[11]

These findings understandably caused concern. The UK Teratology Information Service's best use of medicine in pregnancy (BUMP) database was updated to include a caution for fathers using metformin during the preconception period, acknowledging possible risks and the need for further research.

The linked paper by Meng and colleagues (doi:10.1136/bmj-2024-080127) provides a welcome re-evaluation of paternal metformin use and risk of congenital abnormalities among offspring.[12] Using population based data from Taiwan (n=2 563 812) and Norway (n=619 389), the authors found an increased risk of major congenital anomalies after paternal metformin use (prescribed for any indication) during the period of sperm development in unadjusted analyses in Norway (relative risk 1.29 (95% CI 1.07 to 1.55)) but not in Taiwan (1.08 (0.99 to 1.17)). Critically, however, after adjusting for relevant covariates and restricting analyses to fathers with type 2 diabetes, no association was found between paternal metformin use and major congenital anomalies in offspring for either cohort alone (propensity score weighted relative risk in Norway 0.98 (95% CI 0.72 to 1.33) and in Taiwan 0.87 (0.74 to 1.02)) or combined in a meta-analysis (0.89 (0.77 to 1.03)).

This lack of association persisted across several prespecified sensitivity analyses. Data on organ specific malformations were limited in the Norwegian cohort. While these data were available in the Taiwanese cohort, evidence of an association between metformin use and risk of genital malformations in male offspring was lacking—unadjusted results actually suggested a reduced risk (0.57, 95% CI 0.33 to 0.95), but additional large studies accounting for relevant confounders are needed before further conclusions can be drawn.

In light of Meng and colleagues' publication, two large population based studies with inconsistent findings now exist. How can this inconsistency be explained? As with all retrospective cohort studies, findings depend on the quality of the data available and on the analyses conducted. The earlier Danish studies were possibly limited by the lack of descriptive data on participants' comorbidities, including diabetes. Although insulin (the comparator used in the Danish studies) is uniquely prescribed for diabetes, metformin is prescribed for other conditions, raising the possibility that the group using metformin might include a different population from the group using insulin.

Indeed, the cohort that used metformin were more commonly prescribed antihypertensives, cholesterol lowering drugs, and diuretics than the insulin control cohort, hinting at the presence of comorbidities associated with the metabolic syndrome.[9] This is highly relevant: a US study found that metabolic syndrome in fathers was associated with a 26% increased risk of hypospadias in their offspring.[13] Unobserved confounders and underlying paternal disease could therefore help to explain the association observed between metformin use and major congenital malformations in the Danish cohort.

In contrast, the Taiwanese and Norwegian datasets analysed by Meng and colleagues contained detailed paternal data on comorbidities, including severity of diabetes, which were included in the adjusted model. This study also spanned two countries and included more than double the number of participants compared with the Danish cohort. Finally, lack of a known biological mechanism also adds to the case

against a link between paternal metformin use and fetal malformations. Human and animal studies generally indicate a neutral or beneficial effect of metformin on steroidogenesis and spermatogenesis.[14]

For some, Meng and colleagues' findings may not completely lay to rest concerns raised by the Danish analyses, and further confirmatory studies are worthwhile. At the very least, however, these findings provide some reassurance for clinicians, and for fathers-to-be prescribed metformin preconception.

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