



The Medical **Bulletin**

In Diabetology

Preconception Paternal Metformin and Birth Defects

Ann Intern Med 2022 Mar 29 Preconception use of metformin by fathers was associated with excess risk for major birth defects in progeny. In a study from Denmark, researchers sought to determine whether paternal use of metformin during sperm development, prior to conception, might cause birth defects. Their interest in this question derived — at least in part — from observations that metformin can lower testosterone levels, which could affect sperm quality.

Using nationwide databases covering a 20-year period, they examined the incidence of birth defects in children whose fathers (but not mothers) were taking diabetes medications during the 3 months before conception, when sperm would be developing. Major birth defects occurred in 3.3% of 1.1 million children whose fathers took no diabetes drugs and in 3.3% of children whose fathers used insulin. In contrast, these incidences were 5.2% among children whose fathers used metformin and 5.1% among children whose fathers used sulfonylurea. With adjustment for several confounders, metformin was associated with significant excess risk for major birth defects (adjusted odds ratio, 1.40), but insulin and sulfonylureas were not. The findings for metformin held up in several other comparative analyses.

Genital birth defects in boys were the most strongly metformin-associated defects. COMMENT This observational study suggests a relation between paternal pre-pregnancy metformin use and birth defects. Without confirmation in another patient population, it would be premature to prohibit metformin use by men of reproductive age who have overt type 2 diabetes. However, clinicians are increasingly giving metformin to men with prediabetes; in my view, these results provide one reason to avoid metformin in such patients when they are in the reproductive age group.

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