Metformin Exposure in the First Trimester of Pregnancy and Risk of All or Specific Congenital Anomalies

Given, Joanne E.; Loane, Maria; Garne, Ester; Addor, Marie Claude; Bakker, Marian; Bertaut-Nativel, Bénédicte; Gatt, Miriam; Klungsoyr, Kari; Lelong, Nathalie; Morgan, Margery

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preeclampsia, but it appears that the easier-to-modify risk factors like vitamin levels may not be the quick fixes that we hoped for. Meanwhile, we can keep using aspirin, and probably should move to the higher dose (2 low-dose aspirin pills), to be given before 16 weeks' gestation.—ABC)

Metformin Exposure in the First Trimester of Pregnancy and Risk of All or Specific Congenital Anomalies: Exploratory Case-Control Study

Joanne E. Given, Maria Loane, Ester Garne, Marie-Claude Addor, Marian Bakker, Bénédicte Bertaut-Nativel, Miriam Gatt, Kari Klungsoyr, Nathalie Lelong, Margery Morgan, Amanda J. Neville, Anna Pierini, Anke Rissmann, and Helen Dolk

Administrative Data Research Centre Northern Ireland (J.E.G.) and Institute of Nursing and Health Research (M.L.), Ulster University, Belfast, United Kingdom; Paediatric Department, Hospital Lillebaelt, Kolding, Denmark (E.G.); Medical Genetics, CHUV, Lausanne, Switzerland (M.-C.A.); University of Groningen, University Medical Center Groningen, Department of Genetics, Eurocat Northern Netherlands, the Netherlands (M.B.); Registre des Malformations Congenitales de la Reunion, Saint-Pierre, Ile de la Reunion (B.B.-N.); Directorate for Health Information and Research, Guardamangia, Malta (M.G.); Division of Mental and Physical Health, Norwegian Institute of Public Health (K.K.); Department of Global Public Health and Primary Care, University of Bergen (K.K.), Bergen, Norway; Inserm UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (Epopé), Center for Epidemiology and Statistics Sorbonne Paris Cité and DHU Risks in Pregnancy, Paris Descartes University, Paris, France (N.L.); Congenital Anomaly Register and Information Service for Wales, Public Health Wales, Swansea, United Kingdom (M.M.); IMER Registry (Emilia Romagna Registry of Birth Defects), University of Ferrara and Azienda Ospedaliero Universitaria di Ferrara, Ferrara (A.J.N.); Tuscany Registry of Congenital Defects, Institute of Clinical Physiology, National Research Council/Fondazione Toscana Gabriele Monasterio, Pisa (A.P.), Italy; Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty Otto-von-Guericke University Magdeburg, Magdeburg, Germany (A.R.); and Institute of Nursing and Health Research, Ulster University, Belfast, United Kingdom (H.D.)

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ABSTRACT

Metformin affects stem cell function and has been shown to cross the human placenta at term, exposing the fetus to concentrations approaching those in the maternal circulation. Limited evidence from 3 meta-analyses and a cohort study suggests that the rate of all major congenital anomalies combined is not significantly increased after exposure to metformin. As teratogens tend to increase the risk of specific, rather than all, congenital anomalies, an increased risk of specific congenital anomalies after first trimester metformin exposure cannot be ruled out.

The researchers designed a population-based exploratory case-control study using malformed controls. Cases of 29 specific subgroups of nongenetic anomalies, and all nongenetic anomalies combined, were compared with controls (all other nongenetic anomalies or genetic syndromes). Eleven EUROmediCAT European congenital anomaly registries surveying 1,892,482 births in Europe between 2006 and 2013 were used. There were 50,167 babies affected by congenital anomaly (41,242 nongenetic and 8925 genetic) including live births, fetal deaths from 20 weeks' gestation, and terminations of pregnancy for fetal anomaly.

EUROCAT population-based registries record all major congenital anomalies among live births, fetal deaths at 20 weeks' gestation or later, and terminations of pregnancy for fetal anomaly, using *ICD-10* (*International Classification of Diseases, 10th Revision*) codes. Detailed descriptions of registries and the methods used have been published previously. The EUROmediCAT database includes data, since 1995, from those EUROCAT registries that record first trimester drug exposure either directly or through linkage with healthcare databases with information on prescribing and dispensing of drugs. Exposure to metformin in the first trimester was rare before 2006, so this study was based on data from 2006 onwards. Registries with less than 3 exposures were excluded.

The researchers recorded 53,689 babies affected by congenital anomaly in the EUROmediCAT database (2006–2013), of 1,892,482 births surveyed, across the 11 registries that were eligible to take part in this study. After exclusions, 50,167 babies with congenital anomaly were left for analysis, consisting of 41,242 with a nongenetic anomaly and 8925 with a genetic

syndrome. In all, 168 babies affected by congenital anomaly (141 nongenetic and 27 genetic) were exposed to metformin (3.3 per 1000 babies affected by congenital anomaly), of which 2 had a combined preparation (A10BD02 metformin and sulfonylureas). Overall, metformin exposure among fetuses with all nongenetic anomalies combined compared with controls was not statistically significantly different (adjusted odds ratio, 0.84; 95% confidence interval, 0.55–1.30). The only significant result was for pulmonary valve atresia (adjusted odds ratio, 3.54; 1.05–12.00, compared with nongenetic controls; 2.86, 0.79–10.30, compared with genetic controls). This one significant association was no more than would be expected by chance given the number of comparisons that were made. Further surveillance is needed to increase the sample size and follow up the signal related to the cardiac anomaly seen, but these findings are reassuring given the increasing use of metformin in pregnancy.

EDITORIAL COMMENT

(It seems likely, barring some unforeseen findings, that the use of metformin in pregnancy will increase. As organizations such as ACOG and the American Diabetes Association recommend against the routine use of glyburide in pregnancy, for clinicians and patients who wish for an oral hypoglycemic agent, metformin is the common go to medication. In fact, in a recent statement, the Society for Maternal-Fetal Medicine supported the use of metformin in conflict with the recent ACOG Practice Bulletin regarding the care of women with GDM (*Am J Obstet Gynecol*. 2018;218:B2–B4). Their justification was that the efficacy with the use of metformin as compared with insulin appears to be just as good.

The evidence for efficacy is pretty good, although certainly based on only a few studies. The best and largest of these studies was a 2008, adequately powered randomized trial in which there were no differences in outcomes between pregnancies treated with metformin versus insulin (*N Engl J Med* 2008;358:2003–2015). In a recent meta-analysis, there were no differences in the primary outcomes between metformin and insulin and there were trends toward improvement in glycemic control with metformin over insulin (*BMJ*. 2015;350:h102).

Unfortunately, efficacy is not the only concern about metformin in pregnancy. Metformin crosses the placenta and it is unclear what its effect will be on the developing fetus and eventually baby and child. In the largest randomized study of metformin versus insulin, although many of the parameters were not different, there was an increased risk of preterm birth in the primary analysis. This finding was also confirmed on systematic review (*BMJ* 2015;350:h102). In a recent study that examined the children born to women randomized to insulin or metformin. In this study, although their metabolic profiles were not different, the children whose mothers had been randomized to metformin were heavier with larger skin-fold thicknesses (*BMJ Open Diab Res Care.* 2018;6:e000456).

Thus, there are potential effects on the developing embryo and fetus and the need for larger, well-designed studies to examine this question is critical. The study abstracted previously attempts to do this very thing. It is a large, population based, case-control study that examines the association between metformin and congenital anomalies. In a large, European, congenital anomaly registry of nearly 2 million women, the association between anomalies and the use of metformin were examined. Overall, there was no association identified, and when individual anomalies were examined, the only one that was statistically significant was pulmonary valve atresia. The authors pointed out that because of the number of comparisons that they made that having a single positive finding was not specifically surprising.

So, can we be entirely reassured about the impact of metformin on fetal development? Perhaps not. Although this study is reassuring, there is still the issue of preterm birth. If metformin does lead to a higher rate of preterm births in a significant sector of the population, it should not be used. In addition, the long-term outcomes are only just being studied and one recent study demonstrated some differences in weight and skin-fold thicknesses. I think this current study helps us, but I would still carefully counsel all patients that I offered metformin about the preterm birth findings and about the potential long-term impact of a medication that impacts metabolism and crosses the placenta.—ABC)