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Using meta-analyses to improve risk estimates of specific birth defects

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MINI-COMMENTARY

Meta-analysis is a powerful framework for combining information across several studies and it is a particularly appealing option in birth defect research. Given that individual birth defects are rare, studies of specific birth defects are often hampered by small numbers. To deal with issues stemming from the small number of infants with a given birth defect, it is common to group birth defects, resulting in analyses of outcomes like “all birth defects” or all birth defects in a given body system. Yet this practice may mask associations between exposures and specific birth defects. Meta-analyses that can combine data across several studies to explore teratogenic exposures while maintaining the specificity of individual birth defect outcomes are particularly appealing.

In the current issue of *BJOG*, Zhang et al. have employed meta-analytic techniques to evaluate the association between early pregnancy fluconazole use and several pregnancy outcomes, including birth defects (Zhang et al. *BJOG,* 2019, https://doi.org/10.1111/1471-0528.15913). The authors report a marginal association between early fluconazole use and any birth defect (odds ratio=1.09, 95% confidence interval=0.99-1.21) and any cardiac birth defect (1.31, 1.09-1.57). These associations do not tell us anything about the risk of specific birth defects. Additionally, the underlying epidemiologic studies include different birth defects, and thus have different definitions of “any birth defect” or “any cardiac birth defect”.

The authors also presented pooled estimates for two individual birth defects: tetralogy of Fallot (3.39, 1.71-6.74) and atrial septal defect (1.29, 0.91-1.82). It is also important to be cautious when interpreting the pooled estimates for these specific birth defects. Following the PRISMA checklist, the authors list the number of studies included in the pooled estimate of tetralogy of Fallot (for example), but they do not report the number of exposed cases that informed the estimate. The tetralogy of Fallot pooled estimate comes from two studies with a combined total of 10 exposed cases: 7 cases from a Danish cohort which reported an adjusted estimate of 3.16 (1.49, 6.71) and 3 cases from a US case-control study which reported an unadjusted estimate of 4.81 (0.78, 22.5). Transparency regarding the number of

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exposed cases that go into pooled estimates, particularly when the exposure and outcome are rare events, would serve to better contextualize the findings.

Of course, a limiting factor in conducting a meta-analysis of fluconazole (or any rare exposure) and individual birth defects is the number of existing studies that explore these relationships. Zhang et al. were limited to two existing studies. To improve the estimates derived from future meta-analyses, individual studies that are unable to reliably calculate risks for specific defects, but report grouped estimates, should include the number of exposed cases with each birth defect in a supplementary table. This way, future meta-analyses could include all available birth defect-specific data to calculate the most accurate effect estimate.