Letters

COMMENT & RESPONSE

In Reply I believe RCTs should be routinely used for evaluating drug safety and efficacy during pregnancy, just as they are for nonpregnant individuals. While I agreed in my Viewpoint that observational studies may complement RCTs in detecting rare adverse effects, the broader comments by Drs Locquet and Dogné offer an opportunity to address common concerns about RCTs in pregnant individuals.

Locquet and Dogné argue that RCT statistical power would be insufficient to detect rare or delayed outcomes such as neurodevelopmental disorders. Adequate power is indeed important, but required sample sizes for informative trials may be smaller than suggested. Teratogens typically cause a pattern of correlated birth defects rather than a single rare anomaly.[1] Composite outcomes can therefore provide clinically useful safety signals with sample sizes of approximately 200 first-trimester exposures, as used for US perinatal HIV guidelines.[2,3] While larger RCTs may sometimes be warranted, observational studies generally require samples at least as large to support similarly informative conclusions, with less-definitive findings due to unmeasured confounding. In addition, because observational studies are conducted after market release, most exposures occur outside systematic observation, leaving more patients exposed to poorly characterized risks.

Locquet and Dogné further warn that underpowered RCTs may produce null findings that falsely reassure. Indeed, null results should be appropriately interpreted in terms of adverse effect sizes that can be ruled out with high confidence. However, the argument that imperfect data are reason to avoid RCTs implies a worrying alternative: waiting for tens of thousands of pregnant individuals to take medications without safety data—some to be studied observationally—prior to gaining information on major adverse events. Having rigorous, prerelease information about which risks can and cannot be excluded is better than having no data. Even a modestly powered trial can strengthen interpretation of subsequent observational studies and reduce reliance on exploratory observational analyses of small samples that may flag spurious findings. This combination of RCTs followed by observational studies is how regulators handle rare adverse events in the general population.

The COVID-19 vaccine example that Locquet and Dogné cite in fact illustrates the human toll of excluding pregnant participants from RCTs. The only evidence on pregnancy safety prior to broad rollout was from a small number of individuals (<25 vaccinated) who became pregnant during RCTs (and received no further injections).[4] By the end of February 2021, approximately 200 000 pregnant individuals in the US had been vaccinated amid enormous uncertainty.[5] Had there been an adverse effect on, for example, outcomes detectable at 20-week ultrasound, hundreds of thousands of exposures would have occurred before a signal emerged. Meanwhile, many pregnant individuals avoided vaccination due to uncertainty about safety, resulting in avoidable maternal deaths and stillbirths.[5] Delaying evidence was not without costs.

Many of Locquet and Dogné's concerns about RCTs apply to studies in nonpregnant populations, which do not detect all rare effects. However, the benefits have been observed of a rigorous preauthorization framework for the general population, which ensures that effective medications are broadly trusted and adverse effects detected. Pregnant individuals deserve no less.

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