BJOG-21-0722 Statistical associations versus causal inference.

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Many clinicians are of the opinion that observational studies may provide only "statistical associations", but not "causal inference". And further, that only randomized designs ensure causal interpretation. For the same reason, many medical journals have made rules for all observational studies finding significant statistical associations to be presented as just "associations" often emphasizing that a causal inference is not possible.

I hereby sign up to the growing group of epidemiologists, who are of the opinion that just well confounder controlled observational studies are the very design most often providing convincing evidence of a causal interference. Prospective cohort studies better than retrospective case-control studies, but even the latter design has given us important knowledge of risk factors of rare clinical outcomes such as thrombotic diseases, a long list of cancers, obstetrical complications, including latest stillbirths.

In a new original Swedish study, Heiddis Valgeirsdottir et al. demonstrate in a nationwide historical follow-up study, that women with polycystic ovary syndrome (PCOS) once pregnant have a 50% increased risk of experiencing stillbirth, as compared to women without PCOS (1). Further, that the rate ratio of stillbirth between women with and without PCOS increased by increasing gestational age, peaking at 42 weeks with 4.3 deaths per 1000 ongoing pregnancies in women with PCOS versus 1.0 deaths per 1000 ongoing pregnancies in women without PCOS.

Any such association should certainly be controlled for a long list of potential confounders, the most important being maternal age, calendar year, parity, hypertensive disorders, diabetes, and educational length. Adiposity (BMI) was undertaken in an additional adjustment, because this covariate correctly could be considered as both a confounder (adiposity being a risk factor for stillbirth, and PCOS women more often being adipose), but also as a mediator; women with PCOS are more likely to develop adiposity due to their PCOS. The authors chose carefully to present the BMI adjusted results as the main results, thereby if anything underestimating the risk of stillbirths in women with PCOS.

This is far from the first contribution from Scandinavian National Health Registers, identifying and quantifying risk factors for different diseases. We should always be aware that some unknown or unmeasured potential confounders not being controlled for, could reduce (or enhance) the results, and that other research groups should confirm the Swedish findings. A causal inference was made more likely with a suggested biomedical mechanism by which PCOS could confer such a risk. But already with this new carefully provided observational evidence, we should reasonably consider pregnant women with PCOS not to go too far beyond term, to prevent stillbirths in this group, which according to the study results accounts about 5% of all stillbirths. A pragmatic first recommendation could be induction of women with PCOS at 41 gestational weeks.

Valgeirsdottir H et al. BJOG 2021; 128: xxx-xxx.