Type 2 diabetes drug trials unnecessarily exclude women

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While women who are pregnant, or breastfeeding or who may become pregnant are often excluded from clinical trials for type 2 diabetes drugs, the exclusion is frequently not based on the risk of fetal harm, according to Penn State College of Medicine researchers and may be contributing to the underrepresentation of women in clinical trials and an incomplete understanding of the effects of drugs on women who become pregnant unexpectedly.

Previous studies show that women are underrepresented in clinical trials. Restrictions limiting the enrollment of pregnant women and women of childbearing potential are at least partly responsible for this disparity, despite a 1993 National Institute of Health mandate stating that women of childbearing potential should not be routinely excluded from participation in NIH-funded clinical research. Although several studies

have looked at clinical trial enrollment restrictions based on existing pregnancies, few have looked at barriers placed on women who might become pregnant.

To investigate limitations to enrollment, the researchers looked at type 2 diabetes, a condition that is highly prevalent among women of childbearing age.

Alannah L. Phelan, a third-year medical student at Penn State College of Medicine, worked with Richard S. Legro, professor of obstetrics and gynecology and public health sciences, to analyze data from almost 700 type 2 diabetes drug trials registered at ClinicalTrials.gov. The studies dated as far back as 1995 and included at least some female participants between 18 and 40 years of age. Phelan and Legro found that 59 percent of studies included at least one fertility-related exclusion criterion for women.

"We found that there are widespread limitations on the participation of women of childbearing age in clinical trials," Phelan said.

The criteria most often excluded women who were currently pregnant or breastfeeding.

However, more than 50 studies excluded all women of childbearing potential.

Particularly restrictive criteria, such as excluding women planning to donate eggs, requiring two contraceptives and requiring contraceptives after the end of the trial, were not uncommon, the researchers reported, while 29 trials required multiple pregnancy tests to continue participation in the trial.

The researchers then sought to understand if the criteria for excluding

women of childbearing potential were commensurate with drug risk.

Until 2015, the Food and Drug Administration used an "A, B, C, D, X" category system to rank a medication's risk of causing birth defects, ranging from the lowest risk, category A, to the highest, category X.

Trials including category X drugs, which are contraindicated in pregnancy, were most restrictive in the current study. However, the exclusion criteria didn't increase in a stepwise fashion as drug risk increased, Legro said. Trials of category B drugs were more likely to exclude women who were currently pregnant or to require contraceptive use than trials of category C drugs, potentially drugs with greater fetal risks, the researchers found.

"There really wasn't a strong association in any direction with drug risk and trial limitations," Phelan said.

Trials initiated by investigators—usually at academic health centers—tended to be more restrictive, to require more contraceptive use and to exclude more women than studies by drug companies.

The researchers speculated that concerns about liability resuly in restrictions that are disproportionate with actual risk. Although liability is a legitimate concern, it does not supersede principles of equity and access in clinical research, the researchers wrote in their paper, which was published in the journal *Diabetes Care*.

Previous studies show that if given the opportunity and provided with appropriate information, many pregnant women will opt to participate in clinical trials for both personal and altruistic reasons.

"There are still widespread restrictions placed on participation of women in clinical drug trials, often without justification," Legro said. "Results

from these trials may not be generalizable to the larger population. Up to half of pregnancies are unplanned, and we don't know what the effects of these drugs will be on women if they take them and conceive while on them or if they are pregnant."

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