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Study details paired risk factors in preeclampsia

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Although preeclampsia occurs in about 3 percent of pregnancies, it's still unforeseen in many cases. A report of new research, now in press at the *Journal of Reproductive Immunology*, documents how two distinct risk factors combine to affect the odds that a first-time mother could develop the sometimes life-threatening pregnancy complication. The findings suggest there could be new ways to plan pregnancy with improved awareness and management of the risk.

For years evidence has mounted that preeclampsia may have its origin in the mother's immune response to pregnancy. For that reason, researchers have been studying the potential role of two risk factors: the level of similarity between the mother and father or mother and fetus in a set of five human leukocyte antigen (HLA) genes related to immune system compatibility; and the degree of vaginal exposure the mother has had to the father's semen before becoming pregnant.

The new study, first published online in August, measured both of those risk factors in detail and in combination in 118 women who developed preeclampsia and in 106 similar women who did not. The data set came from SOPHIA, the Study of Pregnancy Hypertension in Iowa maintained by the University of Iowa.

The study's main finding is that women who have had relatively little prior vaginal exposure to the father's semen and who had a high-level of matching of the class I group of three HLA genes had 4.5 times greater odds of developing preeclampsia than women with greater exposure and

less gene matching. The analysis accounted for other risk factors, such as Body Mass Index.

"When you have both low seminal fluid exposure and high sharing [of Class I HLA genes], you are at highest risk," said study lead and corresponding author Elizabeth Triche, assistant professor of epidemiology in Brown University's School of Public Health.

The increased odds appear to confirm prior studies that have suggested a higher risk of preeclampsia from a high degree of similarity among HLA genes in the mother and father, and, independently, higher levels of pre-pregnancy semen exposure.

But this study, Triche and co-authors at the University of Iowa wrote, "provides to our knowledge the first examination of the effects of maternal-fetal HLA sharing in the context of history of exposure to seminal fluid."

(Co-author Audrey Saftlas led another study, online Aug. 22 in the journal, showing that increasing degrees of vaginal, but not oral, semen exposure significantly reduced preeclampsia risk among women in the SOPHIA population.)

Different means compatible?

The underlying biology, Triche said, appears to relate to how the mother's immune system comes to view these foreign genes, first as introduced by the father's sperm and then in the fetus.

"At the maternal-fetal interface it appears that for a successful pregnancy to occur it's likely the mother has to recognize it as foreign and develop a tolerance," Triche said.

In other words, unlike a transplanted organ that is most readily accepted if HLA genes are very similar, a fetus will be welcome if it appears genetically distinct. Greater exposure to the father's semen perhaps better primes the mother's immune system to recognize and tolerate that difference.

That said, the study yielded a nuanced secondary finding, which is that similarity between mother and fetus for the Class II gene HLA-DQB1 was associated with a smaller but still significant increase in preeclampsia odds among women who had higher degrees of exposure to semen.

"That is something that has to be looked at in further studies," Triche said. It could be, she said, that those results simply confirm a unique role in preeclampsia for sharing of that particular gene.

Potential for planning

If the higher odds from these particular combinations of maternal-fetal HLA gene similarities and levels of semen exposure are confirmed in further studies, Triche said, that could yield future pregnancy planning strategies.

Couples who want to conceive a baby could, for example, first seek genetic testing to determine the likelihood that a future fetus could have Class I or Class II HLA similarities with the mother. Many couples already elect for genetic testing before pregnancy to determine the risk of potential genetic disease for their future baby.

With the genetic results, a couple that has committed to having a baby could then consider the level of vaginal exposure to paternal semen. For example, pregnancy-committed couples with a high likelihood of Class I HLA similarity between mother and fetus could use a means of birth

control, such as the pill, that allows for vaginal exposure to seminal fluid before they are ready to conceive.

Couples not attempting to produce a pregnancy and couples at risk for sexually transmitted infection, however, should always continue to consider "barrier" contraception such as condoms that are designed to fully prevent vaginal exposure to semen, Triche said.

Provided by Brown University