Status report

Prospective study of reproductive health outcomes in the mid-Ohio valley

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Background: PFOA reduces birth weight in mice and causes neonatal death in rats. There are few studies of adverse reproductive outcomes in humans to date, with the exception of a number of cross-sectional studies of birthweight and blood PFOA levels in populations exposed to low levels of PFOA, and the previous reports from the C8 Science Panel. The previous reports of the C8 Science Panel were retrospective analyses (prior to 2005-2006) of birth outcomes in the same highly exposed population in the mid-Ohio valley which is studied here.

Methods: The C8 Science Panel has conducted a prospective study, in which we interviewed approximately 15,000 women from the mid-Ohio valley in 2009-2010 about their reproductive outcomes since 2005. All women had participated in the C8 Health Project in 2005-2006, at which time their serum PFOA levels were measured. C8 Health Project participants were exposed to relatively high levels of PFOA coming from a DuPont chemical plant in the area.

The C8 Science Panel studied miscarriages that occurred after enrollment the C8 Health Project, based on interviews. Exposure was defined as measured blood levels of PFOA in 2005-2006, which were adjusted downward for pregnancies occurring in 2008-2010 given that drinking water in all study areas was filtered by the end of 2007.

In addition, self-reported births from 2005 onward among these women were matched to birth records for 2005-2010 from Ohio and West Virginia. We studied preterm births (<37 weeks), pregnancy-induced hypertension, and low-birth weight based on data from state birth records, in relation to PFOA blood levels.

Analyses were restricted to white women since there were few births among non-white women (less than 5%). Pregnancies were restricted to women ages 14-45, and twin births were excluded. Results were adjusted for mother's age, education, smoking, number of prior births, self-reported diabetes, and body-mass index.

PFOA exposure was considered as a continuous variable, either as serum concentration or log of serum concentration, in order to perform statistical tests of trend in risk with increasing concentration. It was also considered by exposure categories, with exposure groups formed by quintiles. The lowest quintile was <6.9 ng/ml in the blood, and the next four quintiles were 6.9-11.0, 11.1-18.8, 18.9-37.1, and greater than or equal to 37.2 ng/ml.

Results: There were 1808 reported pregnancies in our analysis of miscarriage, of which 321 (18%) ended in miscarriage (after excluding induced abortion, stillbirths, ectopic and tubal pregnancies, and missing data). We were able to match 83% of self-reported births from 2005-2010 with state birth records in Ohio and West Virginia (some births occurred in other states). In analyses restricted to births with state birth records, pregnancy-induced hypertension was indicated on birth records for 7% of births (2% was chronic hypertension which was excluded as the hypertension preceded the pregnancy), while preterm birth (<37 weeks) was indicated for 10% of births, low birth weight (<2500 grams, or <5.5 pounds) was indicated for 5% of births, and low birth weight for full term babies (37+ weeks) was indicated for 2% of births.

There was little evidence supporting an association between blood PFOA levels at time of birth and self-reported **miscarriage,** with no statistically significant positive relationship between miscarriage and blood PFOA considered as a continuous or categorical variable. For the latter analysis, the risk of miscarriage comparing those in the highest PFOA group (80%-100% highest levels) vs. those in the lowest levels (0%-20%) was 1.21, with a 95% confidence interval of 0.78-1.88, indicating the 21% excess risk in this group may well have occurred by chance.

There was little evidence supporting an association between blood PFOA levels at time of birth and **preterm birth (<37 weeks)**, for PFOA considered as a continuous or categorical variable. Considering PFOA as a continuous variable, increased PFOA appeared associated with a lower risk of a preterm birth, although this result was likely due to chance. For the latter analysis, the risk of preterm birth for the highest 20% of exposure vs. the lowest 40% was 0.78, with a 95% confidence interval of 0.47-1.29, indicating the decreased risk associated with highest exposure may well have occurred by chance.

There was some evidence supporting an association between blood PFOA levels at time of birth and **pregnancy-induced hypertension (PIH),** for PFOA considered as a continuous or

categorical variable. Considering PFOA as a continuous variable, increased PFOA appeared to be associated with an increased risk of PIH. However, trends fell somewhat short of statistical significance, indicating that the association may have been due to chance (we did find a significant positive trend with the log of PFOA serum level, after excluding diabetics from the analysis). The relative risk of PIH by increasing quintiles of PFOA exposure were 2.25 (95% CI 0.99-5.11), 2.89 (95% CI 1.30-6.44), 2.61 (95% 1.16-5.87), and 2.82 (95% CI 1.25-6.37), all compared to the lowest exposure quintile. Thus, all four exposure groups above the lowest one had a 2-3 fold increased risk of PIH, but there was little trend among these four groups.

There was little evidence supporting an association between blood PFOA levels at time of birth and **low birthweight** (<2500 grams, or <5.5 lbs). Considering PFOA as a continuous variable, increased PFOA showed no relation to increased risk of preterm birth. The highest quintile of exposure had a risk of 1.12 vs. the lowest quintile, with a 95% CI of 0.53-2.36, indicating no significant difference in risk between the two groups.

There was a small decrease in birthweight with increasing PFOA as a continuous variable. For each 100 ng/ml increase in the serum there was a decrease of 33 grams in birthweight. Change in birthweight for each increasing quintile of PFOA blood level, compared to the first quintile, were 23, -14, -9, and -9, well within the range of random error. None of the observed associations for birthweight were statistically significant.

Conclusions: There was suggestive evidence that pregnancy-induced hypertension among mothers giving birth in 2005-2010 in Ohio and W. Virginia was associated with increasing levels of PFOA in the blood measured in 2005-2006. However, positive trends fell just short of statistical significance and categorical analyses did not indicate a continually increasing trend in risk as exposure increased. There was little evidence of an association of PFOA blood levels for other adverse reproductive outcomes, including preterm birth and low birthweight.

Pregnancy-induced hypertension is defined as an elevation in blood pressure into the range considered hypertensive (systolic over 140 or diastolic over 90) that begins after the 20^{th} week of pregnancy. Preeclampsia refers to the same elevation in blood pressure when it is accompanied by leakage of protein into the urine. Both types of pregnancy induced hypertension, preeclampsia and hypertension without protein in the urine, are common complications of

pregnancy, and preeclampsia in particular can cause serious problems for the mother and for the fetus. Preeclampsia can cause severe maternal health problems that can only be ended by delivering the fetus. Blood pressure and protein in the urine are routinely monitored during pregnancy in order to detect and manage these conditions.