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Letter to the Editor

Maternal lead exposure, secondary sex ratio and dose-exposure fallacy

Sir,

Jarrell *et al.* (2006) conclude that they did not find evidence for an association between maternal and fetal lead exposure and lower secondary sex ratio among newborns in a large sample in Mexico City. The odds ratio for a male child initially increased by quintile of maternal blood lead concentration and then decreased, despite more exposure. To them, this result appears to be in contrast with reduced proportions of male births in several examples of maternal exposures to other environmental chemicals. The authors refer to changes in the sex ratio postulated by us to represent pathology involving the conceptus, and more specifically the variable rate of occult loss of male embryos (Jongbloet *et al.*, 2001, 2002). Although they assert that lead exposure has been associated with overt spontaneous abortion, they feel that their findings do not suggest an association between relatively high levels of environmental lead exposure and a reduction in the proportion of male births.

The increase in the odds ratio of male births up to the third quintile of maternal blood lead concentration, apparent in the Fig. 1 of their article and to a lesser extent in the three figures that follow (Figs 2–4), related to other biomarkers (cord lead concentration, maternal patella and tibia bone lead) seems to us but illustrations of what the over-ripeness ovopathy concept predicts (Jongbloet, 2004): the increase is due to preferential fertilization of non-optimally matured oocytes by Y-bearing sperm in a dose–response fashion, but after having reached a certain plateau, inversion occurs to male-biased loss of fetuses before birth, either occult or overt, as a result of non-optimal embryo development, inherent ill-implantation and fetal arrest. A decrease in the secondary sex ratio does not necessarily imply sex reversal, but still represents a dose–response fallacy, as evident in the decline in the sex ratio over the past half century and among decreasing socio-economic income categories. This interpretation could be substantiated by comparison of the rate of male preponderance among the overt abortuses in the increasing quintiles of lead exposure.

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Reply: Maternal lead exposure, secondary sex ratio and dose-exposure fallacy

Sir,

We appreciate the comments and suggestions of Dr Jongbloet who points out that the increase in the sex ratio among children of those mothers in the third quintile of blood lead measurements in our data (Jarrell *et al.*, 2006) may represent changes predicted by the overripeness ovopathy concept (Jongbloet, 2004). We had noted this increased sex ratio, but had concluded, in light of the data with respect to our other biomarkers of lead, that overall there did not appear to be any consistent association between any of the lead biomarkers and the sex ratio.

We have undertaken a secondary analysis to determine if there is evidence of an increase in the sex ratio over the first three quintiles ($n = 507$) when using the blood lead measurements as a continuous variable. In this re-analysis, we found a significant increase in the adjusted odds ratio (OR) for male birth per unit (μg/dl) increase in blood lead [OR: 1.14; 95% confidence interval (CI): 1.02–1.28; $P = 0.03$]. There was not a significant change in the sex ratio from the third to fifth quintiles ($n = 476$). For each unit increase in maternal blood lead over the last three quintiles the OR for a male was 0.98 (95% CI: 0.93–1.03, $P = 0.43$).

The fact that the other biomarkers of lead did not show similar patterns, however, should be considered. With respect to other birth outcomes—such as birth weight, infant weight gain, head circumference, birth length and scores on the Bayley scales of mental development at age 2 years—maternal bone lead biomarkers have proven to be better predictors of

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adverse outcomes than blood lead (Gonzalez-Cossio *et al.*, 1997; Gomaa *et al.*, 2002; Hernandez-Avila *et al.*, 2002).

The mechanism of the overripeness ovopathy concept that might account for the predicted initial increase in sex ratio as a result of lead exposure would imply that circulating lead levels at the time of conception would be most relevant for any effect. The maternal blood lead in our study was taken at the time of delivery and the bone lead measurements at one month post-partum. The half-life of lead in blood is $\sim$30 days, while that of patella lead is several years. The question is which is a better indicator of circulating lead at conception? In our cohort, we have very little data on this. However, in the few mothers for whom we do have this data, we find a higher correlation of pre-pregnancy blood lead with maternal blood lead at delivery (0.67; $P = 0.0002$; $n = 26$) than with cord blood at delivery (0.53; $P = 0.08$; $n = 12$), patella bone (0.33; $P = 0.10$; $n = 26$) or tibia bone (0.21; $P = 0.33$; $n = 24$) at one month post-partum (all correlations are Spearman). We do not have the relevant data for the assessment of spontaneous abortion that Dr Jongbloet recommends to do.

These results do appear to at least be in part consistent with Dr Jongbloet's overripeness ovopathy concept. It should be noted, however, that we have been unable to identify reports that indicate lead might act as a reproductive endocrine disruptor or that lead is associated with either altered cervical mucous production or altered ovulation patterns—factors usually invoked to explain the overripeness ovopathy concept.

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Establishing the safety profile of sperm washing followed by ART for the treatment of HIV discordant couples wishing to conceive

Sir,

We read with interest the ample clinical series of HIV discordant couples undergoing sperm washing and ART, reported by Savasi *et al.* (2007) in your March issue. The title and abstract of the article indicate it focuses on the safety of the sperm washing procedure which, according to the authors was investigated by serological follow-up of treated women at three and six months after each cycle. Yet, the results section only contains a general reference to the three months follow-up, and consisting in the general statement, that all tests performed were negative.

It is regretable that the authors have chosen not to support the ambitious safety statement reported in the article abstract, of complete serological follow-up, with actual serological follow-up results. Similarly, no mention is made to the rate of the loss to follow-up or, if really none of the three and six months serologies were missing, to the system employed by the authors to ensure such complete post-treatment follow-up. It would be so remarkable that we would be delighted to know how PCR testing were made available to 100% of HIV negative women after the end of the treatment period and how obtaining perfect compliance with post-treatment follow-up was achieved.

Since its development in 1989 in Italy (Semprini *et al.*, 1992), sperm washing and IUI have been employed as a risk reduction method in HIV discordant couples wishing to conceive. *In vitro* testing following sperm washing showed that the method reduced the HIV titre in washed semen by $>$1000 fold (Anderson *et al.*, 1992). However, HIV heterosexual transmission is a relatively rare event, in the order of 1 to 500–1000 acts of unprotected intercourse (Gray *et al.*, 2001) and probably much lower for patients with undetectable viral load. Hence, such determination of safety requires not only a careful description of the follow-up methods and the eventual numbers lost to follow-up but needs a sufficiently large sample that has been evaluated between 3000 and 30 000 cycles (Englert *et al.*, 2004). The results section of this article should in our eyes be cautious before claiming to have reached this ambitious goal. Moreover, the authors declare that sperm washing was provided only to couples where the man was aviraemic. The risk of HIV transmission has been shown to correlate with blood viraemia levels. Gray *et al.* (2001) showed lack of HIV transmission through unprotected intercourse in couples in which the man's viral load was $<$1500 copies/ml. It is unclear how a patient population in which the risk of the event of transmission is minimal can be used to indicate the safety of the intervention. In addition, the authors supply no indication or explanation of how and whether the difference in risk was foreseen and dealt with in their population and sum their results to those of other groups who reported the outcome of sperm washing in populations at different degree of transmission risk.

The evidence of low risk of HIV transmission from aviraemic men, gave way to the debate on whether these couples could be offered timed unprotected intercourse (Vernazza

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