Reply

We thank Drs Li and Li for their comments. The true procedure-related risk of fetal loss following chorionic villus sampling (CVS) in twin pregnancy can be derived only by randomized trials, but no such trials have been carried out, nor are they likely to be performed in the future. The strategy of deriving pooled estimates from meta-analyses of heterogeneous non-randomized studies is of questionable value in defining the procedure-related risks of invasive procedures[1].

We have used two approaches to estimate risk. First, we have performed multivariable logistic regression analysis to examine whether CVS provides a significant independent contribution in the prediction of risk of fetal loss after adjusting for maternal and pregnancy characteristics[2]. We found that, in twin pregnancies undergoing CVS, compared with those that did not have CVS, there was a 2-fold increased risk of fetal loss; there was a trend towards an increased risk of fetal loss following CVS after adjustment for maternal and pregnancy characteristics, but this did not reach statistical significance. Second, we used propensity score analysis, whereby an attempt was made to emulate a randomized controlled trial by matching every CVS case to a similar non-CVS control, adjusting for maternal and pregnancy characteristics that are known to be risk factors for subsequent fetal loss[3]. This type of analysis creates homogeneous groups suitable for comparison and has emerged as a robust methodology, well suited to estimating causal effects from observational data, while accounting for a greater number of confounder effects than could classical multivariable analysis.

We found that, in women at high prior risk of fetal loss, the risk of fetal loss following CVS could, paradoxically, be lower than if they did not have the invasive test, for the simple reason that prenatal diagnosis often converts the spontaneous loss of a chromosomally abnormal fetus into a pregnancy termination; obviously, we did not prove this, because we could not perform karyotyping in most of the miscarriages or stillbirths in the non-CVS group. We also found that, in women at low background risk of fetal loss, there may be a 3.5% increase in risk following CVS and suggested that this may be a true reflection of the procedure-related risk[3].

In response to the other questions raised by Drs Li and Li, first, the indications for CVS in our study were heterogeneous (some carried a high risk for trisomy, such as having increased nuchal translucency thickness, and others were low risk, undergoing CVS due to, for example, parental carriership of β-thalassemia, maternal request or increased maternal age)[2]; second, women fulfilling certain criteria are offered the option of CVS but some accept and others decline; third, we chose to report on total pregnancy loss, rather than early loss alone, because, ultimately, this is what matters to the parents and fetal medicine specialists; and fourth, in dichorionic twins, the choice of sampling one or both fetuses was based on ultrasound findings, genetic results and the decision of the parents and obstetrician after appropriate counseling.

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