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To the Editor:

We would like to comment on the paper titled "Malformations reported in chorionic villus sampling exposed children: a review and analytic synthesis of the literature," by Stoler et al.,[1] whose data differ from those of other authors.

Considering that the statistical approach is excellent, we think that differences may be attributed to the following reasons:

1. Stoler et al.[1] do not take "gestational age" at sampling into consideration, as the span between weeks is very wide in the analytical synthesis, with cases included from week 8. This is relevant because in one of the most complete series that has been published in the synthesis, Mastroiacovo et al.,[2] refer to increased malformations only in CVS carried out before week 11, which accounts for more than 10% of total cases considered in the series of Stoler et al.[1]
2. Stoler et al. do not take the operator's experience into account, which is also of great importance (Brambati et al.[3]; Nicolaides, K., personal communication). As the work of Stoler et al.[1] comprises information from several centers and some of these centers group data from other smaller institutions in the same region, each operator's experience is likely to be more reduced than that of operators in centers where all samples are always taken by one or two people who, as a result, have greater expertise. Our group have performed more than 16,000 TACVs.
3. As regards sampling methods—transcervical or transabdominal—centers using one, or the other, or both, are grouped together. What is more, the method is sometimes not specified. Since some years ago, almost all centers—with a few exceptions—use transabdominal sampling as the transcervical method must be used at an earlier stage and entails more complications. Heterogeneity in the sampling method in the series included in Stoler and colleagues' work[1] could also be responsible in part for the greater incidence of malformations (it is more correct to speak about "disruptions" rather than malformations) referred to in their work.

This is why we think that, in order to evaluate CVS as a cause of fetal disruptions, it would be more useful to homogenize some variables regarding gestational age, sampling method, and operator's expertise since CVS, as a method, demands more experience and therefore should be restricted to fewer operators.

CVS has many advantages; among them, it allows an earlier diagnosis, thus reducing parental anxiety; increases the knowledge of many factors, such as the incidence of placental mosaicism and its consequences on pregnancy; and allows early detection of pregnancies with risk of fetal uniparental disomy.

Finally, Stoler et al.[1] strangely report an increased incidence of some vascular disruptions and a reduced incidence of other disruptions if compared with the general population. The hypothesis that the latter is due to under registration is not wholly convincing as we find no reason for clubfoot cases to be more frequently reported and cleft lip less often, the latter being as or even more noticeable, even for the commonest observer.

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References

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2. Mastroiacovo P, Tozzi AE, Agosti S, Bocchino G, Bovicelli L, Dalpra L, Carbone LD, Lituania M, Luttichau A, Mantegazza F, Nocera G, Pachi A, Passamonti U, Piombo G, Vasta AF. Transverse limb reduction defects after chorion villus sampling: a retrospective cohort study. GIDEF—Grupo Italiano Diagnosi Embriosi-Fetali. *Prenat Diagn* 1993;13:1051–1056.
3. Brambati B, Tului L, Cislaghi C, Alberti E. First 10,000 chorionic villus samplings performed on singleton pregnancies by a single operator. *Prenat Diagn* 1998;18:255–266.

In Response:

We agree completely with Dr. Sanchez that timing of the procedure in terms of gestational age, operator experience, and sampling method could all influence the outcome of a CVS procedure. However, taking account of these factors requires the availability of a data set that provides outcome data stratified according to several levels of these variables. Our analysis is based on a synthesis of published literature, which normally does not provide the kinds of detailed breakdowns needed to perform these more detailed analyses. Ideally, one would need to obtain subject-specific data containing information on outcome as well as on all these factors in order to properly assess their effects. Such an effort is currently under way by Dr. Ryan and her colleagues in Biostatistics. That being said, some of the published papers do provide some information about gestational age at the time of the procedure. However, the level of detail on gestational age varies considerably from study to study. Some studies report detailed age breakdowns for all subjects, while others provide it only for the subjects who had an adverse event. Even when gestational age breakdowns are provided, they are often grouped into broad intervals, for example 8–12 weeks or 10–15 weeks. Thus it is quite difficult to tease apart this information to gain a quantitative assessment of the role of gestational age on the risk of an adverse effect. Dr. Ryan, the statistician on our project, has been working on methodologies to achieve this, however, and has recently published the methodology in the statistical literature.[1] This paper focuses primarily on statistical methodology but does provide an example related to the effect of gestational age on the risk of a terminal transverse limb defect. The results suggest that the risk does indeed decline linearly with gestational age, with the result that the risk of a terminal transverse limb defect is minimal for procedures performed at 12 weeks or later.

In terms of the sampling methods, our data do not support the suggestion that there is a higher rate of abnormalities after