Author's response to reviews

Title: False positive morphologic diagnoses at the anomaly scan; marginal or real problem? A population-based cohort study.

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Author's response to reviews: see over
To: The Editor in Chief of BMC Pregnancy and Childbirth

Clermont-Ferrand, December 18, 2013

Dear Sir,

We thank the reviewers for their thorough comments, which were globally favorable to our study, "False positive morphologic diagnoses at the anomaly scan; marginal or real problem? A population-based cohort study." [Ref.: 1212872309107808].

Modifications to the article are in red in the text.

Reviewer #1: Gabriele Tonni
- Comment 1: Are the methods appropriate and well described?
  Reviewer: The methods are appropriate and well described. However, authors need to define abnormal amniotic fluid and IUGR in this section (it is only defined later as <3rd centile in Table 3).

  Answer to reviewer: Both definitions were added in the methods (methods: p 6) “An abnormal quantity of amniotic liquid was defined as either oligoamnios [AF index < 5th percentile] or polyhydramnios [AF index > 95th percentile] (Magann et al. 2000). Intrauterine growth restriction (IUGR) was defined as a birth weight <3th percentile for gestational age (international consensus), defined according to the Audipog (Association des Utilisateurs de Dossiers Informatisés en Pédiatrie, Obstétrique et Gynécologie biometric curves [http://www.audipog.net/].

- Are the data sound?
  Reviewer: Yes the data are correctly analyzed and reported. However, I do suggest to restructured the style of the Tables as values regarding SD are reported in squared brackets only in Table headings generating difficult interpretation for Readers.

  Answer to reviewer: We have corrected the tables as requested. We have made them easier to read by reformatting them and inserting new notes below the table. Consequently, however, some tables no longer fit on a single page.

- Are the discussion and conclusions well balanced and adequately supported by the data?
  Yes, discussion and conclusions are well balanced and supported by the data. However, I suggest authors to describe and analyze the reasons why “no false positive diagnoses led to termination of pregnancy”.

  Answer to reviewer:
We have added the following sentence (to the discussion, on p10):
No termination of pregnancy was performed for any of these false-positive malformation, most of them isolated. None of the malformations observed in that group suggested that "there was a strong probability that the child to be born would have a severe condition recognized as incurable at diagnosis," the criterion for termination under French law.

I disagree with authors statement of reduced accuracy of the prenatal ultrasonography in case of multiple congenital anomalies. I suggest authors to expanded this paragraph and to report robust publications to support their statement.

**Answer to reviewer**: These references were given in the text (10,22,23,33). We note this finding every year in the analysis of our regional malformation registry, and it is also observed in other registries. The question that we cannot answer is: why? It is possible that once they have discovered one or two severe malformations that justify a voluntary termination of the pregnancy, ultrasonographers – perhaps due to empathy – do not prolong the ultrasound examination by looking for other minimal malformations. This would require a qualitative study among ultrasonographers. …

I totally disagree with authors statement that NMR (nuclear magnetic resonance) could better detect callosal anomalies at an early stage of pregnancy compared with prenatal ultrasound. Fetal neuroscan currently rely upon multiplanar ultrasound, using either transabdominal or transvaginal approach. However, as the use of real-time 2D/3D ultrasound equipment and technology is increasing and diagnostic clusters of brain anomalies clarified, accurate reconstruction of the midline echo can be obtained (I suggest to report published works by Rizzo G et al. and the recent work by Tonni G. et al. regarding the role of 3D reslicing technique in the study of brain anomalies and cerebral midline echo). Therefore, it is my opinion that NMR should always be performed as a complementary, ultrasound-targeted second step examination. Moreover, using 3D ultrasound, volume data sets can be send to remote site for expert consultation using DICOM technology. Accurate prenatal ultrasound diagnosis of brain and callosal anomalies can be thus achieved at lower cost comparing with that of antenatal NMR requiring dedicated radiologist/s. I suggest this paragraph be expanded accordingly to Reviewer's suggestions and rewritten.

**Answer to reviewer**:

We agree with the reviewer and have modified the manuscript as follows (discussion, p11): “Three-dimensional sonography makes it possible to acquire the fetal head volume from the axial view and then, by reconstructing the image with the multiplanar technique, to obtain a suitable view of the corpus callosum without the technical difficulties of 2D-sonography. Second-step complementary NMR remains, however, a clinically valuable adjunct to ultrasound and provides additional information when the ultrasound diagnosis is uncertain (Rizzo G et al.) (Tonni G. et al.).”

**Reviewer #2**: Juliana S Gebb

**Major Essential Revisions:**
The introduction, particularly the first and second paragraphs needs to be edited so that it flows better...ie I believe that the authors are trying to say that there are more ultrasounds being performed despite constant, relatively small percent of anomalous pregnancies and therefore it becomes important to look at
the false positive rate, but this needs to be more clearly stated.

**Answer to reviewer:**

The reviewer is right about what we meant to say, and we have therefore modified the introduction to make this point more clearly (see line 8, page 3).

**Minor Essential Revision 1:**
The authors state that none of the false positive patients had a termination of pregnancy...does this mean that this group was mainly composed of suspected minor anomalies that can often resolve postnatally (ex pyelectasis or VSD)? in my opinion, this is the biggest flaw with this study (see comment 1 of discretionary revisions). Although it is not imperative for publication, I think the paper would be much stronger if the false positive rate for only major anomalies (ie those that threaten life, lead to significant disability or require major surgery) were included or at least if they were separated out.

**Answer to reviewer:** From a strictly medical point of view, we agree with the reviewer, but from the woman’s point of view, the announcement of any malformation – major or minor – is a source of major anxiety (and stress) and leads to more examinations (imaging) or even invasive examinations. All of these have a cost for society.

**Minor Essential Revision 2:**
And to add to this, the authors mention that ventriculomegaly can resolve spontaneously, but it is also important to mention that VSDs resolve spontaneously and that it is common for a renal sono on day of life 1 to show no pyelectasis even when there is renal pathology since newborns are relatively dehydrated and it sometimes takes several days or weeks to again see the pyelectasis that was present in utero

**Answer to reviewer:** We agree with the reviewer that pyelectasis should be checked at an examination late after birth. In our series, malformations are identified up to the age of 1 year (see page 4, bottom of the page). In our database, pyelectasis is therefore observed if it exists up to the age of 1 year; and if it disappeared, the information is also recorded. In the article, the final malformation is recorded at the child's first birthday. An important part of this article’s value lies in its reliance on a registry of malformations. We have also modified (p11, top) in response to this comment : However, pyelectasies can disappear because of newborn dehydration at birth and be detected at a later check-up. Infants in our study were followed up to one year of age and thus received the maximum duration of postnatal renal monitoring.

**Minor Essential Revision 3:**
Did any of the patients in the misclassification group terminate for what they thought was a major anomaly when in fact the fetus was found on pathology to only have a minor anomaly?

**Answer to reviewer:** No patients in the misclassification group terminated for what they thought was a major anomaly when in fact the fetus was found on the pathology examination to have only a minor anomaly. All the cases with malformations in the misclassification group had a malformation sufficiently severe to justify a termination of the pregnancy.
For example, as we have mentioned in the manuscript (end of table 5 and discussion), false positive diagnoses in cases of misclassification in the heart were mostly VSDs that were in fact valve anomalies (that is, what appeared to be a minor anomaly turned out to be major). In cases of cerebral malformations, even if corpus callosum was present, severe ventriculomegaly was enough to justify termination of pregnancy.

Discretionary Revisions:
1. It may be more clinically interesting to look at only major anomalies. The stress involved with telling the patient that the fetus has a major cardiac malformation is obviously much higher than that of telling the patient the fetus has mild pyelectasis or unilateral ventriculomegaly. In my opinion, the importance lies more with getting things right with the big diagnoses...if a kid has an extra renal ultrasound which is fine before leaving the hospital, it is of little importance compared to if the mother thought the fetus would have a major problem and it had radiation exposure for evaluation postnatally and nothing was found or even worse if the mother had a termination of pregnancy for a fetus that turned out to be pathologically normal. This being said, I do recognize that the renal ultrasound mentioned above does add financial burden and time to the medical system.

Answer to reviewer: We agree with the reviewer that diagnosis of major malformation have great impact on parents’ anxiety and medical management. However, it has been demonstrated that even false positive findings of soft markers during pregnancy are a source of stress for parents and can also disrupt the mother-newborn relationship. We have referred to this study in the introduction section (reference n°25 Viaux-Savelon S et al.). Also see the previous response on this topic.

2. I am not sure I really understand the importance of detailing every misdiagnosis in fetuses with multiple malformations. If we know that the fetus has multiple anomalies and therefore a worse prognosis overall, is it imperative that all of the diagnoses be exactly right? I agree for example if a fetus was noted to have clubbed feet and then was misdiagnosed as also having a VSD or other cardiac malformation, this would be a problem because we would suspect that this fetus could have some sort of a syndrome. But if in fact, the fetus had a crooked spine and a limb reduction and a GU anomaly, I think it is less important that a suspected VSD be diagnosed perfectly. The authors rightly mention that the misdiagnoses in cases with multiple malformations would not have influenced medical management, so I guess I wonder what the point of classifying them as misdiagnoses is.

Answer to reviewer: The reviewers appear to have somewhat contradictory opinions on this question. As already mentioned, the objective of this paper was to give a global rate of false positive, which includes all wrong diagnoses of malformation. It is important to note that false positive diagnoses involve in the misclassification group may be clinically relevant of suspected syndromes. Thus false-positives may not influence medical issue of the pregnancy but can nonetheless wrongly induce specific unnecessary complementary examinations, be the source of stress and have a cost for society.

3. The tables should have a decreased number of variables. For example, Table two does not need to include number of ectopics and hypertension in my opinion.
Answer to reviewer:

To shorten the tables, we have deleted the "ectopic pregnancies". On the other hand, pregnancy-related diseases such as hypertension are important precisely because they may be associated with a better ultrasound analysis, as the physician knows that maternal diseases can cause abnormalities in children (FGR for hypertension, ...), as some aspects of maternal history can lead to more meticulous ultrasound examinations (e.g., obstetrical history, maternal BMI, chronic maternal disease, etc.).