Author's response to reviews

Title: The Prenatal Ultrasonographic Detection of Myelomeningocele in Patients Referring to Children's Hospital Medical Center

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Author's response to reviews: see over
Dear Editor

In response to your letter dated 2006-06-01, I would like to submit the revised version of our manuscript: **The Prenatal Ultrasonographic Detection of Myelomeningocele in Patients Referred to Children's Hospital Medical Center.**

The manuscript has been prepared according to the journal's guidelines (including reference list, references in the text and the list of the abbreviations). I also revised it by considering the English language and style.

All comments of the reviewers have been answered point to point and I marked them as bold and underlined in the revised manuscript.

**Reviewer: Mario Merialdi**

**Major compulsory revisions:**

1) Through the text “referring” should be replaced with “referred”:

**Answer:** I did this. The change is as bold words in: page 1 line 2, page 2 line 3, 5, page 3, the last line 2 , page 4 line 2, page 8 line 19.

2) The authors should give, …a more detailed description of the population studied:

a. Where the all cases coming from the same population?

**Answer:** As mentioned in the text our hospital is a tertiary care center and the patients are coming from the local population most from Tehran (Capital of Iran) and the nearby cities.

b. Where there differences in the populations the cases were coming from that could be related to differences in the detection rates? E.g. were the ultrasonographic examinations done in the same settings? Could the sonographic standards have changed in the interval between the first and last reported cases were detected? Were the patients referred to ultrasonography for some specific reasons as the authors suggest could be the case on page 6?

**Answer:** As mentioned in page 6, there is no national policy in Iran for prenatal detection of anomalies “it is a usually performed modality for assessing fetal biometric parameters in most pregnancies”. Most were done for pregnancy related matters not for anomaly
detection, but the family was happy that there is no news from anomalies in repeated sonography. We could not find a higher prevalence in a specific race; it was not very important for us at that moment and was therefore not much considered. The ultrasound was done by different operators in different centers of Tehran as well as nearby cities and was not all done in the same settings for all the patients. The ultrasound was done on the request of the patient, the choice of the health care provider or center and therefore no specific standards existed. It depends on the skill and the experience of the operator that how best he or she can do to get the best results. So a question of change in the standards does not exist at all.

c. The 140 cases included all the cases referred in the year examined?

**Answer:** Yes. They are all MMC cases in the age of less than five years that referred to neurosurgery service for MMC or the related complications (page 4, paragraph one).

d. Patients who had multiple sonographic examinations had better chances of being detected? It seems most patients were diagnosed in the third trimester, could this be due to the fact that previous sonograms showed suspicious images?

**Answer:** Comparing cases of multiple sonographic examinations with one sonography with exact test, $p$ was 0.389. So multiple sonographic examinations in this study is not important tool to detect the anomaly, as the quality and experience were not in high rank.

e. Are there reports that could suggest potential risk factors in the Iranian population that may explain the high rate?

**Answer:** I add the reference 4 address in page 5, last paragraph, line 1. As mentioned in the text the incidence has been reported 1.6 that is relatively high. More work should be done for the potential risk factors.

3) The conclusions of the authors are reasonable but might not be totally justified by the sample examined if they do not provide more evidence to support the generalizability of their findings to the whole Iranian population.

**Answer:** We only suggested the steps for earlier detection of the anomaly and more suggestions to decrease the birth of a pregnancy product with a crippling anomaly.

4) The conclusions should focus more on the results of the study that showed an alarmingly low prenatal detection rate. This observation may warrant advocating for
better and broader screening programs, as well as efforts to assure quality of the ultrasonographic examination.

**Answer:** We advised these in the discussion and so in the conclusion.

5) Recommendations on changing the abortion laws … more ethically acceptable and cost effective to improve the screening quality.

**Answer:** We emphasized on the screening at the discussion and so in conclusion at page 9, paragraph one. But in places with higher screening modalities and equipment, the detection of MMC is not possible before 18-2- weeks of gestation by skilled ultrasound operators. So the issue of early pregnancy termination has been discussed.

6) Those recommendations could be better presented as suggestions and should include also suggestions for primary prevention (folic acid supplementation) if nutritional deficiency are among the identified risk factors for the Iranian population.

**Answer:** We mentioned folic acid supplementation as primary prevention in page 5 in several lines.

**Minor essential revisions**

Abstract. Indicate location of the Children Hospital

**Answer:** I described the location in the abstract, page 2 paragraph 1, line 3 and so in method: page 4 paragraph 1, line 3.

The sentence: the data was collected reading the prenatal ultrasound reports…. Is not clear and could be changed as: ultrasound reports were examined.

**Answer:** This change has been done in the abstract, method paragraph.

The words: “results were interpreted accordingly” could be deleted

**Answer:** It was deleted as above.

Introduction. MMC should be spelled out at first use

**Answer:** It was done at the first word of the introduction.

Provide more information on the potential causes of the high incidence reported in Iran.

**Answer:** We do not have any documents working on risk factors. The most probable are low socioeconomic state of the families and bad nutritional state of the mothers, but I do not have a document. We are conducting a study on the probable risk factors and the result will come later.
Methods. Provide, if possible, more information on the characteristics of the hospital and of the attended population and how they compare to the general population.

**Answer:** I add a sentence related to this in page 4 paragraph 1 line 1,2.

Provide, if possible, more details on the ultrasonographic scans (who performed, why they were performed, type of machinery used, range and type of services)

**Answer:** I do not have any data for this The ultrasound was done by different operators in different centers of Tehran as well as nearby cities and was not at all done in the same settings for all the patients. As mentioned in the article that there is no national policy for prenatal screening in Iran and the ultrasound is done on the request of the patient, the choice of the health care provider or center and therefore no specific standards exist. It depends on the skill and the experience of the operator that how best he or she can do to get the best results..

Discussion. The authors could eliminate part of the technical details o…more information from other studies investigating potential causal factors in the population.

**Answer:** We would not like to discuss about risk factors as they are unrelated to the issue of early detection and abortion that are the center of this study.

**Reviewer:** Awi Wiesel

**Major Compulsory Revisions**

1. If prenatal detection rate and a possible termination are the points of interest the location of the defect is of minor importance, but the time of diagnosis is in the centre of interest. Therefore, table one is merely nice in terms of description but of no interest to the study question. Site of the lesion, if mentioned, is important to assure comparability to other data sources (international) and a table would be appropriate. A p-value in this issue does not lead us to any conclusion, especially if we do not know which numbers are compared to each other (just a description would be sufficient).

**Answer:** I deleted the table one as the respected reviewer has mentioned. So we have only one table.

2. On the time scale (week of diagnosis) a p-value may be more useful.
**Answer:** The data has been collected according to trimester so I do not have all of the time of sonography according to week. So this can not be taken.

3. It would be helpful to know if these are isolated MMC’s or if they are in association with syndromes or other multiple congenital anomalies (these are included in most other studies and mainly easier diagnosed prenatally and thus a selection could take place concerning the study question).

**Answer:** In collecting the data only CNS anomalies were interested, so other anomalies were not collected. We do not have the ultrasound reports in hand and therefore can not precisely mention the associated anomalies. However I do not remember a serious anomaly extra CNS in these 140 cases.

4. If the prevalence of MMC is really so high in Iran (the Ketabchi publication is out of reach for us) there should be at least a hypothesis why (MTHFR-mutation?). Otherwise a folic acid supplementation would be even more worthwhile.

**Answer:** Folic acid supplementation is a key preventive matter in this anomaly. Our goal of study here was to emphasize on the detection, especially early detection of anomaly and if possible pregnancy termination. This study was conducted in a tertiary care center having a pediatric neurosurgery department and the number of cases referring are therefore more, there is no such study that could explain the MTHFR mutation and supplementing folic acid would be a better option in our setting. Folic acid supplementation has briefly been described in the discussion.

5. To quote Boyd et al (2000) Introduction:…. In my opinion this is the way the issue of terminations should be addressed. Using modern techniques to improve human health implies adopting human ethical rules as well.

**Answer:** Ethical values have an important place in every society and are always considered in valued research projects and so have been considered in our work. As a developing country and the high burden of this disease on the family and society, most families can not answer their handicapped children needs. Most families in my country, as mentioned in the text, like to terminate the pregnancy in the legal and religious permitted period. According to this matter, the issue of termination has been discussed. In our part of the world where such children have no support either from the government or NGO’s, early abortion of such fetuses is in no ways a non-human act.
Minor Essential Revisions

1- With a n=140 all percentages must be given as whole numbers only.

Answer: we did this.

For your convenience to find the changes in the revised manuscript I have listed all changes as below:

* Table one has been deleted from the manuscript.

* Page 2 paragraph 1, line 2-3: in Tehran, Iran from July 2004 to July 2005 in stead of in Tehran from July 2004 to July 2005

* Page 2 Paragraph 2 line 3: ultrasound reports were examined….in stead of … the data was collected reading the prenatal ultrasound reports…

* Page 2 Paragraph 3 line 2 where… in stead of … in whom..

* Page 2 Paragraph 3 line 7: The detection rate of thoracic /thoracolumbar lesions was significantly more (p=0.05)….in stead of … thoracic /thoracolumbar lesions were significantly more detected (p=0.05).

* Page 4 Paragraph 1 line1 to describe more the center and population: …Iran from July 2004 to July 2005 (A tertiary care center with coverage of most myelomeningocele cases born in Tehran and nearby cities). In stead of … from July 2004 to July 2005.

* Page 4 Paragraph 2 line 3. Due to deletion of table 1 this sentence has been added : The most common level of MMC was in thoracolumbar area and distal to it(91.4%).

* Page 5 Paragraph 1 line 3: …folic acid supplementation, along with prenatal detection… in stead of .. folic acid supplementation, prenatal detection

* Page 5 Paragraph 1 line 4: …it… in stead of …MMC…

* Page 5 the last Paragraph line 6 : …second month of gestation when …in stead of …second month when….
In a large study across Europe, the range varied from 33% to 100% in different countries, instead of in a large study across Europe in different countries,

an overall instead of overall

…large difference… instead of …large gap….

…request. On the other… in stead of …request, on the other…

…referred… in stead of …referring…

I appreciate your comments and favours. I am looking forward to receive your answer.

Sincerely yours
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