Author’s response to reviews

Title: Spontaneous First Trimester Miscarriage Rates Per Woman Among Parous Women with 1 or more pregnancies of 24 weeks or more

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Answers to Editor's Comments

#1. The question was posed to me: what are the chances of another full term pregnancy in a multiparous woman after 3 spontaneous first trimester miscarriages? I searched the search terms on Pubmed: ‘First Trimester Miscarriage Rate’ ‘Miscarriage Rate’ ‘Recurrent Miscarriage’ and ‘Nonrecurrent Miscarriage’ yet only found the 2 Swedish studies which failed to answer the research question since one of them concerned ONLY primiparous women and the other had a relatively small N of about 400. I read all the articles cited by the 2 Swedish studies and all of Regan’s work on recurrent miscarriage. After exhaustive search for previous research on the topic, I established that it had never been researched beyond the one Swedish study of about 400 women, and set out to do it myself.

I changed the sentence in the abstract to: This is the first large study of recurrent and non recurrent, spontaneous first trimester miscarriage rates per woman in a parous population.

I added the sentence to the Methods: “Pubmed was searched for the search words: Miscarriage, Recurrent Miscarriage, Non-recurrent miscarriage, and First Trimester Miscarriage.”

Question # 2. Line 162 - In your description on verification of the accuracy/reliability of the data, please clarify how and why you decided on 114 charts (files) to check and who checked them?

Answer: The computer expert who maintains the Hadassah Medical Center’s server and archives and Judy Slome Cohain compared the charts of the women with the highest rates of miscarriage starting from those who had experienced 17 (n=1) 16 (n=4) 15 (n=8) 14 (n=15), 13 (n=56) and 12 (n=87) miscarriages. We stopped after comparing the data in 114 patient records to that in the Excell spreadsheets due to time limitations. In every case Excell extraction reflected the data in the actual charts, so we concluded that we could rely on the extracted data.
Question # 3. Lines 179-180 - Please double check the numbers of reported patients included in the study. If I understand this right, the first manuscript lists 65,536 different women and the revised manuscript lists 65,227 before excluding those with a blank field. Please explain this discrepancy.

Answer- Cool that you noticed that. In the revision, I noticed that I had put 65,536 instead of the correct number = 65,541 files. 65,541 is the correct number.

Question 4. Line 226 - Please rephrase - the prevalence of chromosome abnormalities in products of conception in spontaneous abortions is not a "belief." as it has been proven by published studies.

Changed to -->.This concurs with current research showing about 50% (2) to 60% (4) of miscarriage are the result of random fetal chromosomal abnormalities incompatible with life.

# 5. Line 309 - It is stated that the rates of miscarriage among women having fertility treatments were similar to rates for women not having any fertility studies, but no data are given. Please provide the data.

Table 3 shows 6-16 miscarriages / woman vs. Living children and Fertility Treatments
The data for 0-5 miscarriages /woman and Fertility Treatments can be unearthed but I find it difficult to fulfill this request after so much time has passed since I submitted. If this is necessary to publish, I will unearth it. What about this is interesting? You dont believe this one point?

REVISED: The rates of miscarriage among women having fertility treatment were similar to the rates for women not having any fertility treatments. 4466 (7%) underwent fertility treatment of Ikaclomid, Pergonal, IVF, egg or sperm donation and/or Other but their miscarriage rates were nearly identical to the general population. Perhaps fertility treatment was not associated with higher rates of miscarriage because fertility treatment often followed a relatively short history of not conceiving rather than a history of miscarriage.

Question # 6. The original review asked for more details about what type of evaluation these women had for potential causes of their miscarriages. This was not addressed in the cover letter or the revised manuscript but could have an important effect on the results.

This is a first study looking at a large sample of nonrecurrent miscarriages in a parous population using data extracted from patient records from the labor and delivery ward. The labor and delivery chart did not have a field to document cause of her spontaneous first trimester miscarriage. Nor would one expect a labor and delivery chart to do so. We know what causes most first trimester miscarriage. 50% to 60% of first trimester miscarriages are proven to be random genetic errors and that may be an underestimate. Most first trimester miscarriage do not have a linked 'cause' but rather are random events. There are genetic defects in blood clotting
genes, such as Factor V, etc, that are linked to miscarriage, observed to have increased miscarriage rates, but a causal relationship is not certain for any particular miscarriage. Would the peer reviewer please articulate the type of evaluations and the unnamed causes that he or she feels were not evaluated. The obvious risk factors such as smoking, drug abuse, etc for miscarriage were evaluated.

7. Question Lines 326-331- I am unclear about these points. Some readers will not be familiar with the "health basket."

Health basket changed to--->Women who never reached 24 weeks of pregnancy were not included in this study. These women have been studied extensively elsewhere and were not relevant to the aim of this study, which was to get a first look at miscarriage rates per woman in a parous population. In most settings, one could expect a significant population of women who experience many miscarriages but no pregnancy of 24 weeks or more. However in Israel, the socialized medical program provides up to 3 IVF cycles per woman. In fact 4% of births in Israel are conceived using IVF. Therefore, the number of women who are interested in having a child, yet never achieve a 24 weeks pregnancy, is estimated to be minimal.