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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Version: 1 Date: 02 Jul 2017

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Cover letter with a point-by-point response to the comments and requested revisions:

Peer review: 1. The author implies in the cover letter that the reviewers only wanted wording changed and that there were no problems with the methods or results. That is not the case.

Comment: I apologize for implying that the problems were minor. I agree major revision was necessary and carried out. In this cover letter, I present clear responses, point by point. In addition, I have improved the grammar and writing style as requested.

2. Peer review: The purpose of the study "was to identify the prevalence of first trimester miscarriage per woman in parous women." This is stated clearly in lines 103-104, but there should also be a clear-cut statement at the end of the Background section of the Abstract. In addition, it should be clarified that this is a study on "spontaneous" miscarriages.

COMMENT: Agreed. Changed the Background Section in the abstract:

“The purpose of this study was to quantify spontaneous first trimester miscarriages per woman among parous women. A vast amount of data has accumulated regarding miscarriage rates per recognized pregnancy as well as about recurrent miscarriage. This is the first study of spontaneous miscarriage rates per woman in a parous population with a fertility rate of 3 and an induced abortion rate of 10%.”

3. Peer review: Lines 56-104 - Much of this long Introduction is a critique of other studies and would be better placed in the Discussion section.

Comment: Agreed. Those lines were moved to the DISCUSSION section.
Peer review: There is still unusual wording (lines 62-63)

Comment: Previously lines 62-63: “to how and when the pregnancy is identified. (1,2) Eclipsed behind this mound of (63:) knowledge is the hole in our knowledge as to what are the recurrent and nonrecurrent

Change made: Lines were removed completely.

Peer review: and some unreferenced opinions (lines 72-74, 92-93). The statement that D&C may increase subsequent miscarriage rates is unproven and needs a reference (line 93).

Lines 72-74: = Previously (line 72): “study concerned only primiparous women.(4) Aside from the studies being confounded (line 73) by small sized, non-randomized study groups, both are confounded by Sweden’s 20% (line 74) rates of first trimester induced abortion.

Comment: Agreed: Corrected version: “Only 2 previous studies explore the rate at which women experienced one or more non recurrent miscarriages. (7,8) Both are from Sweden. One is a prospective study intending to study 474 non-randomly recruited ‘volunteers’ to age 29, of unknown generalizability, and 320 non-randomly recruited volunteers up to age 39, for whom 48% of the 794 women were lost to follow up during the study. (7) The second study is a large study group of only primiparous women. (8) The miscarriage rates in both studies might be artificially lowered by Sweden’s induced abortion rate of 20%, since in the absence of induced abortion, spontaneous miscarriage rates are somewhat higher.”

Peer review: Previous Lines 92-93: “where miscarriage is routinely treated by dilation and curettage, which may increase (line: 93) subsequent miscarriage rates.

COMMENT: Agreed. Previously, the reference for the statement on lines 92-3 did not appear until lines 221-223. The error has been corrected by moving the reference from lines 221-223 to follow the statement that appeared on lines 92-93:

“Even if these rates were adjusted to accurately reflect the correct numbers as well as ages of the women, they only provide recurrent miscarriage rates, and only in the Danish population where miscarriage is routinely treated with dilation and curettage. Dilation and curettage could theoretically increase subsequent recurrent miscarriage due to the 25% rate of adhesions left after a single dilation and curettage (11), the same as after a single cesarean (12). To date, the influence of the routine use of dilation and suction vacuum aspiration on subsequent spontaneous miscarriage is unknown. (13,14)”

4. Peer review: Methods: Line 113 - "whenever possible" - How often was it not possible?
Comment: AGREED. Changed to: “Double questioning of the client by both the midwife and the admitting doctor is routine, and takes place almost without exception, as a method of ensuring the reliability of the data.”

Peer review: Line 116 & 136 - What is the definition of "practitioners"? Do you mean midwives, physicians or both?

Comment: AGREED, changed from

Previous line 116: reopened and the patient history is updated by practitioners

Previous line 136: At Hadassah, the data is entered by motivated practitioners

Changed to:

line 116 to “updated by the midwives and doctors who fill in the patient record”

Changed practitioners on line 136: to midwives and doctors.

Peer review: Line 142 - What is the "standard equation"?

Comment: AGREED. Added the equation:

5. Results: The study relies on patient recall rather than documentation of spontaneous miscarriages.

Comment: Agreed patient recall is less than ideal, but I am unaware of a way to efficiently study rates of first trimester spontaneous miscarriage among 60,000 women without it being based on patient recall. One thing is certain, no one has published a study using this way or any other way. This is the first study to look at miscarriage rates in a parous study group larger than 320 women and the second study on the topic to date.

Peer review: Results: Since 18% of patients were excluded because of a blank field, there is still a question about whether that group is the same as those included and whether that would affect the results.

Agreed. But a large database in a busy ward of thousands of records would be equally suspect if every field to be filled out for over 60,000 patient records. So it remains a question what percent would the peer reviewer suggest is ideal? While it is true that “18% of the 65,536 patient files had a blank field for ‘spontaneous miscarriage’ and were excluded from the study.” The following studies concur that while not ideal, an 18% blank field does not disqualify the database as unreliable:


Peer review: “Moreover, these are all inpatients admitted for delivery. Isn't it possible that there are a significant number of patients who had miscarriages and who have not had a successful pregnancy and would not be included because they would not be admitted for delivery?”

Answer appears in the Discussion: “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. In addition, in a system where 3 IVF cycles per woman are included in the health basket, the number of women who are interested in having a child, yet never achieve a 24 weeks pregnancy, is small. The study also does not differentiate between recurrent and nonrecurrent miscarriages, as that was also not the aim of this study. The study also did not determine the effect of paternal age on miscarriage rates.”

6. Peer review: Discussion: Rather than attempting to embellish the results by stating "almost half" (line 177), it is better to stick to the facts(43%) about the number of women with one or more miscarriage.

Comment: AGREE: I have removed the phrase “almost half” when referring to the 43% of women who experienced miscarriage, from the paper

Peer review:Line 193 - The statement that recurrent miscarriage is associated with high rates of infertility is questionable and needs a reference.

Agreed. Removed from the paper.

Peer review: Statements about future studies (lines 221) add little to the paper.

Agreed. Removed from the paper.
Peer review: There are a significant number of limitations listed that limit the accuracy and validity of the results. The statement that "all large databases suffer from data entries and missing data" is an opinion and is incorrect.

Agreed: I have removed the incorrect statement.

7. Peer review: Conclusions: For the reader, what do you consider "young"? How would your counselling differ with a 24 year old woman vs a 39 year old?

Comment: Agree: I have removed the word Young, which appear in three places. I have changed ‘Young’ to ‘ up to their late 30s”

1. Abstract: Parous women up to their late 30s are likely to carry a future pregnancy to term if they so desire.

2. Conclusions: Parous women up to their late 30s who have experienced multiple miscarriages, can be counseled that if they keep trying, they will likely carry a pregnancy to term.

3. Short English Summary: Parous women up to their late 30s who have experienced multiple miscarriages, can be counseled that if they keep trying, they will likely carry a pregnancy to term.

In answer to the question how I would counsel a parous 39 year old who has just had multiple spontaneous miscarriages: I would say that depending on her health, nutrition and lifestyle choices, there is still a good chance of her carrying a future pregnancy to term but she should act expeditiously.

Peer review: Definition of first trimester spontaneous miscarriage is missing. Is a pregnancy based on HCG or ultrasound?

Comment: Corrected. The data reported is based on pregnancies recognized by either ultrasound or urine pregnancy test.

Peer review: The miscarriage rates will be very different when reported by HCG compared to gestational sac or fetal heart.

Correct: The miscarriage rates are rates of pregnancies recognized by HCG in urine pregnancy tests and/or ultrasound recognition of pregnancy. The miscarriage rate of pregnancies recognized after a missed period by ultrasound or pregnancy tests is 15%. This study concurs with this research finding, confirming that the miscarriage rate is the 15% rate found when pregnancy is identified by ultrasound or urine pregnancy test. The introduction states, "establishes that 15% of recognized pregnancies spontaneously miscarry in the first trimester"
with the rate varying between from 10% to 20% according to how and when the pregnancy is identified. (1,2)" These references found that there are different miscarriage rates depending on when pregnancy is recognized. It found that when one does routine ultrasounds on all sexually active women four weeks after the last menstrual period, the miscarriage rates are 20%. But this was not done on this large study group. The women missed a period and then used either ultrasound or urine blood test to recognize the pregnancy.

Peer review: Line 96, you stated 'Accurately completed computerized patient records have been in use at Hadassah Hospital Delivery Rooms since 2004'. Do you have reference for this statement, regarding the accuracy of the data?

The accuracy of the data was established previously, during reliability testing during the following research projects:


My expertise includes 9 years of working for E&C Medical Intelligence, Inc. in Jerusalem, designing and testing computerized patient records for the delivery room. I am a midwife with 35 years of practice, and I have 4 nuclear family members who are currently doctors working at Hadassah Hospital.

Peer review: Line 152, "Women had an average of 3.6 pregnancies". Do these pregnancies include miscarriages? Where is the data?

ANSWER:

Data: Correct again. This peer reviewer is very sharp. I rounded 3.645 to 3.6, but in fact the average number of pregnancies was 3.645 pregnancies per woman. There were a total of 237,755 documented pregnancies among 65,227 admissions, documenting an average of 3.645 or 3.65 pregnancies per woman admitted, including 35,862 miscarriages.

Peer review: Line 162: " Demographics: There were 4.5% smokers, 0.17% drug abusers, 0.2% alcohol abusers, 0.9% of women with a history of 1 or more ectopic pregnancies, 7% of women underwent some fertility treatment, documented as either Clomid, Pergonal, IVF, egg donation, sperm donation, or other." How were these percentages calculated?
Answer: Extracted using Excel. Total # of smokers divided by total number of women. Same for drug abusers, alcohol abusers, ectopic pregnancies, and fertility treatments.

Peer review: There multiple appearances of same woman in your dataset. Do you have a demographics table?

Answer: I added a demographics section in the results. There are no multiple appearances of the same women in the calculation of miscarriages. Doubles were carefully eliminated. Yes, there was a small amount of women who were both smokers and drug users, but this was irrelevant to the findings in this paper.

Peer review: Line 195: You stated: In this study, three or more miscarriages were not associated with infertility. Where is the data to support this statement?

Comment: Changed to

Parous women up to their late 30s who have experienced multiple miscarriages, can be counseled that if they keep trying, they will likely carry a pregnancy to term.

Peer review: How is the infertility defined?

Agree. I was incorrect. The word infertility was removed from conclusions.

Peer review: If a woman has infertility, how can she have three or more miscarriages? Is this related to fertility treatment?

Agree. I was incorrect. The word infertility was removed from conclusions.

Peer review: In Table 2, please footnote what is AB=0, P=0.

Changed. AB --> changed to Misc for Miscarriage

P=0 → changed to Primiparous