

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Birth characteristics in a clinical sample of women seeking infertility treatment: A case control study
AUTHORS	Vikström, Josefin; Hammar, Mats; Josefsson, Dr Ann; Bladh, Marie; Sydsjö, Gunilla

VERSION 1 - REVIEW

REVIEWER	Dr. Ruby Nguyen University of Minnesota U.S.A.
REVIEW RETURNED	18-Nov-2013

GENERAL COMMENTS	<p>The authors list the limitations of the control group. However, further discussion is warranted -- and perhaps even sensitivity analyses (in which different classifications of controls is used to determine if the results differ in any substantial manner).</p> <p>With regards to the English, there are parts of the manuscript that could use editing, particularly when referring to the exposure as the mother's/women's birth characteristics. In some places, it is unclear from the English whether the authors refer to the mother's/women's characteristics or that of the offspring.</p> <p>I think this is a very interesting, but limited investigation. The authors define the problem with the small-ish sample size but it is representative for this geographic area. Further discussion on limitations (as discussed above) would be beneficial.</p>
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REVIEWER	William A. Freije, M.D., Ph.D. University of California, Los Angeles
REVIEW RETURNED	04-Dec-2013

GENERAL COMMENTS	<p>This manuscript associates the cause of the couple's infertility (either male factor, female factor, or unexplained) to the infertile woman's birth characteristics (such as low birth weight, small for gestational age, large for gestational age, and preterm delivery). The authors conclude that female infertility is associated with a 2.5 fold increased risk of being born LBW than if associated with unexplained or male factor infertility. In addition, women with female infertility were 2.7 times more likely to be born SGA than women with unexplained infertility. This data importantly addresses the association of birth characteristics to the development of infertility later in life.</p> <p>Unknown is not a category of infertility. What I believe the authors</p>
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	<p>are referring to is the unexplained category, those couples who have a workup which fails to identify either a female or male cause despite carrying the diagnosis of infertility.</p> <p>What exactly is the unit of analysis- the couple or the female partner? In the methods section please explicitly define. On page 8, line 21 please indicate that LGA, SGA, preterm, and LBW refer to maternal birth weight and not paternal birth weight.</p> <p>On page 6, lines 16-27 and 43-54 there are many variables that are not reported in the manuscript and which would greatly aid in describing the three groups. These variables include age, marital status, work, smoking, snuff use, chronic illness, number of prior pregnancies, children, abortions, miscarriages, IVF, ICSI, AID, FET, AIH, results of pregnancy tests, and stimulation. Highest education received would also be important. A table showing the comparability of the 3 groups for these factors would be nice.</p> <p>Were the birth characteristics of the father's examined?</p> <p>The methods section does not elaborate on how the bivariate regression analysis was performed.</p> <p>With multinomial regression the odds ratio is usually presented first, followed by the confidence interval and p-value.</p> <p>A figure displaying the overall experimental approach with the numbers of couples in each group and other descriptors would be very helpful in understanding the approach.</p> <p>Data on the outcome/treatments of the three groups would be interesting (ie IVF, Icsi...and successful pregnancy, miscarriage...).</p>
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VERSION 1 – AUTHOR RESPONSE

Dr Nguyen:

- The authors list the limitations of the control group. However, further discussion is warranted and perhaps even sensitivity analyses (in which different classifications of controls is used to determine if the results differ in any substantial manner).
 - o Response: Please see page 12, line 3-9 where we have expanded the subsection on limitations in the discussion section. We understand the rationale of why a sensitivity analysis could be performed, however, we have compared the female/combined group to the male and unexplained groups together and separately in the multi- and bivariate analyses. We could of course do another regression analysis comparing all four groups. However, since the unit of analysis is the woman, the female and combined groups together make up all women with a female cause of infertility which is why we believe that a regression analysis of all four groups would be misleading.

- With regards to the English, there are parts of the manuscript that could use editing, particularly when referring to the exposure as the mother's/women's birth characteristics. In some places, it is unclear from the English whether the authors refer to the mother's/women's characteristics or that of the offspring.
 - o Response: We have attempted to clarify that it is, in all cases, the women who we refer too. Please see page 5, line 23-24 as well as minor changes throughout the manuscript.

- I think this is a very interesting, but limited investigation. The authors define the problem with the

small-ish sample size but it is representative for this geographic area. Further discussion on limitations (as discussed above) would be beneficial.

o Response: We have added to the subsection on limitations in the discussion section. Please see page 12, line 3-9.

Dr Freije:

• Unknown is not a category of infertility. What I believe the authors are referring to is the unexplained category, those couples who have a workup which fails to identify either a female or male cause despite carrying the diagnosis of infertility.

o Response: It is indeed the unexplained category that we wanted to refer to and have thus replaced “unknown” by the term “unexplained” throughout the manuscript.

• What exactly is the unit of analysis- the couple or the female partner? In the methods section please explicitly define.

o Response: We have attempted to clarify this in the methods section. Please see page 5, line 22-23.

• On page 8, line 21 please indicate that LGA, SGA, preterm, and LBW refer to maternal birth weight and not paternal birth weight.

o Response: We have attempted to clarify this statement. Please see page 8, line 12-16.

• On page 6, lines 16-27 and 43-54 there are many variables that are not reported in the manuscript and which would greatly aid in describing the three groups. These variables include age, marital status, work, smoking, snuff use, chronic illness, number of prior pregnancies, children, abortions, miscarriages, IVF, ICSI, AID, FET, AIH, results of pregnancy tests, and stimulation. Highest education received would also be important. A table showing the comparability of the 3 groups for these factors would be nice.

o Response: We have added information on this in the results section and two tables (Table 1 and 2) displaying age, smoking, snuff use, self-reported chronic illnesses, prior pregnancies, parity, abortions and miscarriages. All women accepted for infertility treatment in Sweden are cohabiting/married which we have clarified on page 6, line 7-8. In regard to type and result of treatment this will be the subject of future studies and is thus not included in the present study. We wanted to include all the information collected from the medical charts in the methods section but have now realized that this might be confusing for the reader which is why we have removed this information on page 6 line, 21-24. Unfortunately there was an error in printing regarding work which was not included in the introductory questionnaire.

• Were the birth characteristics of the father's examined?

o Response: We thank you for this excellent suggestion and agree that this would be an interesting topic to examine and will examine the birth characteristics of the fathers in future studies.

• The methods section does not elaborate on how the bivariate regression analysis was performed.

o Response: We have attempted to clarify the statistics section in regard to the bivariate regression analyses. Please see page 8, line 12-17.

• With multinomial regression the odds ratio is usually presented first, followed by the confidence interval and p-value.

o Response: We have revised this so that OR is presented first. Please see the changes made throughout the manuscript

• A figure displaying the overall experimental approach with the numbers of couples in each group and other descriptors would be very helpful in understanding the approach.

o Response: While a figure is always helpful in explaining the experimental approach there are now several tables and an extensive methods section which we feel is sufficient at present.

- Data on the outcome/treatments of the three groups would be interesting (ie IVF, lcsi...and successful pregnancy, miscarriage...).

o Response: We agree that these data would be interesting to present and aim to include this in a future study.