PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Is teenage pregnancy an obstetric risk in a welfare society? A population-based study in Finland, from 2006 to 2011.
AUTHORS	Heikinheimo, Oskari; Leppälahti, Suvi; Gissler, M; Mentula, Maarit

VERSION 1 - REVIEW

REVIEWER	Mr Kiron Bhal Consultant Obstetrician & Gynaecologist Cardiff and Vale University Health Board Llandough Hospital, Penlan Road Cardiff CF64 2XX UK No competing interests
REVIEW RETURNED	31-May-2013

GENERAL COMMENTS	Overall an excellent paper with clinically relevant findings that would be useful for planning the care of teenage pregnancies in most societies with a welfare system.

REVIEWER	Terence Lao Department of Obstetrics & Gynaecology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong. Statement of competing interests - None.
REVIEW RETURNED	06-Jun-2013

THE STUDY	The major issues are with the methodology. On the one hand, the welfare system provides antenatal care free of charge, but there were still subjects with <50% attendance. The reasons were not given. It was unclear whether those defaulting from follow-up were traced or recalled. There were 210 subjects with inadequate care and 155 with <50% of expected visits. Why was there such a discrepancy? How was proteinuria, UTI, pyelonephritis screened for or diagnosed? Was there overlap or repetitive but different entries for the same subject on different occasions, e.g. someone with proteinuria ealier was later foudn to have a positive culture and so diagnosed as UTI, but was admitted for preterm labour a few more weeks later when a diagnosis of pyelonephritis was made. If prenatal care was inadeqaute in more teenagers and yet so much more diagnoses on PU/UTI/PN were made, was this group particularly screened for such problems while the controls were not? Also why select 25-29 years old as controls and not 20-29 years

	old? As well, if the SD for the GA at first visit for the teenagers were so wide, how many of the teenagers actually had fetal morphology scan or ultrasound dating before 20 weeks, and how many had received any form of antenatal counseling or supplementation?
RESULTS & CONCLUSIONS	The results seemed to be contradicting. The teenagers had much higher rates of smoking, which should have reduced the incidence of pre-eclampsia, but this was not the case. If the antenatal care was so good and anaemia was diagnosed early, iron suuplementation should have corrected it and the association with preterm birth would have been mitigated. Chorioamnionitis is the commonest factor associated with preterm birth, especially extreme preterm birth, yet there was no difference in the incidence of chorioamnionitis even when the authors proposed increased sexual activity was the explanation for the increased UTI. How was chorioamnionitis diagnosed? Was there histological or bacteriological confirmation? All in all, the results seemed at odds with each other and I feel that something was overlooked or dismissed or omitted. I just do not feel reassured with the results as presented.

REVIEWER	Anwar Nassar, MD Professor of Obstetrics and Gynecology Interim Chairperson American University of Beirut Medical Center Beirut - Lebanon
REVIEW RETURNED	10-Jun-2013

THE STUDY	The authors omitted some important studies that compared teenage pregnancy obstetrical outcome compared with adult pregnancy. They should review the literature and add those studies.
REPORTING & ETHICS	Being a retrospective population-based registry study, the authors conisdered that there is no need to mention anything about ethical approval. It would be advisable to mention something in that regards in the manuscript study design.
GENERAL COMMENTS	This is a very interesting article about teenage pregnancy that might be less common in developing countries but has lots of clinical implications. The data can be used to counsel pregnant teenagers about the potential obstetrical complications and to manage their pregnancies accordingly. I have the following comments that need to be addressed: - The authors defined iadequate prenatal care as attendance of half the recommended number of visits but failed to specify what is recommended in Finland. The high mean prenatal visits ~15 visits is by far higher than the WHO recommended number of visits (at least four visits). It would be interesting if the authors use this definition to see if this will affect their results. - Major congenital anomaly should be defined in the Materials and Methods section. - The more commonly used term for hypertension during pregnancy is hypertensive disorders of pregnancy rather than PIH. It would be probably better to have all those terms lumped together under hypertensive disorders of pregnancy which would include: preeclampsia, eclampsia, gestational hypertension and chronic hypertension. - At what gestational age was the proteinuria detected? This is relevant since a first trimester proteinuria might be of a different clinical implication compared to a third trimester proteinuria, which could be suggestive of risk of preeclampsia, as the authors propose. - A major limitation is the lack of data on socioeconomic and

	educational status which could have affected the results of this study. Unfortunately, the study design didn't allow to have this data readily available. - Can the authors propose an explanation for the noted association between anemia and shoulder dystocia? - The paper would benefit from some English editing.

REVIEWER	Shrim, Alon
REVIEW RETURNED	18-Jun-2013

THE STUDY	Weaknesses of the manuscript are numerous and include the following: 1. English grammar is not sufficient. I suggest that language would be polished. a. The term "as regards…" is very frequent in the text. It appears too frequently and the correct statement is "Regards to…" b. Some concepts are not acceptable terms, such as "premature mortality" (introduction). 2. The main outcome is not clear. It seems that the authors practically looked for many parameters and the busy tables are reporting findings in each of them. Primary outcome should be decided and assessed accordingly. In addition, secondary outcomes should be defined and searched and assessed. a. In this context some parameters that were assessed should be looked at, such as "preterm contractions" (Study variables…and appears again in "pregnancy complications" in results). I think that Preterm delivery is a much stronger parameter. b. Among parameters that were reported, some need to be defined, such as Small for Gestational Age (SGA). Is the definition <10th percentile? By what scale?..Should be defined. 3. Table 1: do the p values refer to differences between "all teenagers" to the rest?.. 4. Material and methods section is almost 6 pages long. Indeed it should be thorough but at the same time not so long and unclear. 5. Pregnancy complications (line 19-31 in page 14.results). The authors report that anemia was a risk factor for several outcomes. How was the calculation done? Which parameters were assessed as confounders and how were they taken into account in the author's model. Needs to clarify…as it doesn't make sense that maternal anemia was a risk factor for shoulder dystocia. 6. Dicussion: How was IUGR defined? In summary The topic is very interesting and the potential is there with a very impressive database. However the manuscript is too long. It deals with too many parameters. Some of the calculations are not clear. English level is not sufficient. The manuscript should be shortened, Primary outcome should be defined and focused on with only relevant findings reported.

VERSION 1 – AUTHOR RESPONSE

Reviewer 2: Terence Lao
Department of Obstetrics & Gynaecology,
The Chinese University of Hong Kong,
Prince of Wales Hospital,
Hong Kong.

Q: On the one hand, the welfare system provides antenatal care free of charge, but there were still subjects with <50% attendance. The reasons were not given. It was unclear whether those defaulting from follow-up were traced or recalled.
R: The register-based data unfortunately does not answer this question, thus only hypothesis can be made. Our belief is that problems in part associated with poor socio-economic status and marginalisation may be reasons for low attendance. This assumption is presented in Discussion (page 23, lines 368-370).

Q: There were 210 subjects with inadequate care and 155 with <50% of expected visits. Why was there such a discrepancy?
R: We thank the referee for noting this mistake. The numbers have now been corrected in the Abstract (page 2, lines 30-31) and in Table 2 (changes highlighted in red).

Q: How was proteinuria, UTI, pyelonephritis screened for or diagnosed? Was there overlap or repetitive but different entries for the same subject on different occasions, e.g. someone with proteinuria earlier was later found to have a positive culture and so diagnosed as UTI, but was admitted for preterm labour a few more weeks later when a diagnosis of pyelonephritis was made.
R: Unfortunately we were not able to see the exact dates of diagnoses in our database. This has been added as a weakness in Discussion (page 22, line 351-352).
However, in our data there were no cases with concomitant diagnoses of proteinuria and UTI, and proteinuria and pyelonephritis. Thus the diagnosis of proteinuria was not used if there was concomitant UTI or pyelonephritis.
As expected, cases with both UTI and pyelonephritis were found (n=6, 7.5% of all pyelonephritis diagnoses) and also UTI and pyelonephritis preceeded preterm labour in 1-7% of all preterm deliveries.

Q: If prenatal care was inadequate in more teenagers and yet so much more diagnoses on PU/UTI/PN were made, was this group particularly screened for such problems while the controls were not?
R: As part of the practice in Finland, the urine dipstick test is carried out on every prenatal visit and urine culture three times during pregnancy for all pregnant women and also in case of symptoms suggestive of UTI.

Q: Also why select 25-29 years old as controls and not 20-29 years old?
R: This is explained in Discussion and we added an explanatory comment to highlight our reasons for this decision (page 22, lines 346-349).

Q: As well, if the SD for the GA at first visit for the teenagers were so wide, how many of the teenagers actually had fetal morphology scan or ultrasound dating before 20 weeks, and how many had received any form of antenatal counseling or supplementation?
R: Antenatal counselling is given to all women on their first antenatal visit. To answer the essential questions concerning ultrasonography and visits prior to 20 weeks, we have now added information in Table 2 (changes highlighted in red).

Q: The teenagers had much higher rates of smoking, which should have reduced the incidence of pre-eclampsia, but this was not the case.
R: In our multivariate model for the risk of pre-eclampsia (Table 3), smoking was included, and it was associated with a reduced risk of pre-eclampsia (adj. OR 0.7, 0.6 to 0.8). This in part explains the higher ORs after adjustment for confounders in Table 3. Also, teenagers who smoked had a lower frequency of pre-eclampsia compared to non-smoking teenagers or those who quit during 1st trimester (2.0% vs. 3.5%). Due to limited space, these figures and figures of other confounding factors

concerning pre-eclampsia, (such as inadequate attendance [1.8, 1.2 to 2.5] and obesity [1.4, 1.2-1.6]) are not presented in the manuscript.

Q: If the antenatal care was so good and anaemia was diagnosed early, iron supplementation should have corrected it and the association with preterm birth would have been mitigated.
R: Anaemia should indeed be diagnosed quite early as it is screened for as part of the antenatal care. However, even after adjustment for variables in our multivariate model (Table 4) anaemia remained associated with very preterm delivery (adjusted OR 2.1 [1.1 to 4.2]). We presume that iron supplementation has failed in these cases as has been reported to happen quite commonly (e.g. Ref: Galloway and McGuire. Determinants of compliance with iron supplementation: Supplies, side effects or psychology. Soc. Sci. Med. 1994;39: 381-390) or there may be other factors underlying.

Q: Chorioamnionitis is the commonest factor associated with preterm birth, especially extreme preterm birth, yet there was no difference in the incidence of chorioamnionitis even when the authors proposed increased sexual activity was the explanation for the increased UTI. How was chorioamnionitis diagnosed? Was there histological or bacteriological confirmation?
R: In our study, only the youngest teenagers (13-15 years of age) had a higher risk of preterm birth (Table 4) compared to reference women. In this group, no cases of chorionamnionitis were diagnosed clinically, presumably due to a small size of the study group.
We did find chorionamnionitis to be a risk factor for preterm birth in the whole study sample (<37 gestational weeks unadj. OR 2.9 [2.2 to 3.9], <28 gestational weeks 17.2 [10.6 to 28.1]) and among all teenagers (<37 gestational weeks 7.1 [3.6 to 14.0], <28 gestational weeks 21.1 [6.1 to 72.5]). However, since no difference in the risk of chorionamnionitis between teenagers and adults were found, this is not presented in the text due to limited space.

Reviewer 3: Anwar Nassar, MD
Professor of Obstetrics and Gynecology
Interim Chairperson
American University of Beirut Medical Center
Beirut – Lebanon

Q: The authors omitted some important studies that compared teenage pregnancy obstetrical outcome compared with adult pregnancy. They should review the literature and add those studies.
R: There are numerous studies on the subject and therefore not all of them could be included. Thus, we focused mainly on larger studies. After re-evaluating recent literature on the subject, we have, however, added 2 studies to our references (References 15 and 19).

Q: Being a retrospective population-based registry study, the authors considered that there is no need to mention anything about ethical approval. It would be advisable to mention something in that regards in the manuscript study design.
R: We have now added a comment in "Ethical approval" (page 28, line 484-486).

Q: The authors defined inadequate prenatal care as attendance of half the recommended number of visits but failed to specify what is recommended in Finland. The high mean prenatal visits ~15 visits is by far higher than the WHO recommened number of visits (at least four visits). It would be interesting if the authors use this definition to see if this will affect their results.
R: We have now added information concerning recommended antenatal visits in Finland in Material and Methods (page 10, line 168). Social support is embedded into the Finnish antenatal care system, increasing the number of visits. In many countries social support may be provided through other channels or not at all. We feel that the recommendation of 4 visits is thus not relevant in our circumstances.

Q: Major congenital anomaly should be defined in the Materials and Methods section.
R: The definition has been added on page 6, lines 110-111.

Q: The more commonly used term for hypertension during pregnancy is hypertensive disorders of pregnancy rather than PIH. It would be probably better to have all those terms lumped together under hypertensive disorders of pregnancy which would include: preeclampsia, eclampsia, gestational hypertension and chronic hypertension.
R: Given the wide range of clinical presentations of hypertensive disorders of pregnancy, we prefer to keep them separate as our data allows this. Hopefully this is acceptable.

Q: At what gestational age was the proteinuria detected? This is relevant since a first trimester proteinuria might be of a different clinical implication compared to a third trimester proteinuria, which could be suggestive of risk of preeclampsia, as the authors propose.
R: We agree this to be a relevant issue. Unfortunately this information is not available in the data. We have added the following sentence "the database did not allow for identification of precise timing of the different events during pregnancy" to the paragraph addressing weaknesses of the study (page 22, line 351-352).

Q: Can the authors propose an explanation for the noted association between anemia and shoulder dystocia?
R: Please see our reply no 5 to Reviewer no 4.
Q: The paper would benefit from some English editing.
R: The English language of the manuscript has been reviewed and corrected by a professional language reviewer. In addition, we have now edited some sentences and terms to improve the readability. All these changes are marked in the manuscript using the track changes mode. We would be delighted if the editorial office would be willing to further improve the English language.

Reviewer 4: Alon Shrim
Hillel Yaffe Medical Center, Ob Gyn

Q: English grammar is not sufficient. I suggest that language would be polished.
a. The term "as regards…" is very frequent in the text. It appears too frequently and the correct statement is "Regards to…"
b. Some concepts are not acceptable terms, such as "premature mortality" (introduction).
R: Please see our last reply above for Reviewer 3.
b. The term "premature mortality" is used in various publications (Reference number 4 in our manuscript: Otterblad Olausson P, Haglund B, Ringback Weitoft G, Cnattingius S. Premature death among teenage mothers. BJOG. 2004;111:793-9. and e.g. Thomas B, Dorling D, Smith G. Inequalities in premature mortality in Britain: observational study from 1921 to 2007. BMJ 2010;341:c3639.) and therefore we hope it can be accepted.

Q: The main outcome is not clear. It seems that the authors practically looked for many parameters and the busy tables are reporting findings in each of them. Primary outcome should be decided and assessed accordingly. In addition, secondary outcomes should be defined and searched and assessed.
a. In this context some parameters that were assessed should be looked at, such as "preterm contractions" (Study variables…and appears again in "pregnancy complications" in results). I think that Preterm delivery is a much stronger parameter.
b. Among parameters that were reported, some need to be defined, such as Small for Gestational Age (SGA). Is the definition <10th percentile? By what scale?..Should be defined.

R: Our aim was to perform a comprehensive study on obstetric outcomes among teenage mothers. Our special interest was on maternal pregnancy complications, as has been stated in Introduction (pages 5 and 6, lines 100-104). We have now added a comment to further clarify this in the Abstract (page 2, line 26). However, all our outcomes are primary.

We decided to report all the results in one manuscript, but we realize this may somewhat decrease the readability of the text.

a. To shorten the manuscript, we have now removed some of the clinically less relevant outcomes, such as premature contractions, phototherapy of the newborn and also IUGR as SGA is a stronger parameter.

b. We have now added the definitions for SGA and LGA in Material and Methods (page 8, lines146-148), as well as for major congenital anomaly (page 6, lines 110-111)

Q: Table 1: do the p values refer to differences between "all teenagers" to the rest?
R: We have now added a footnote in Tables 1 (page 9, line 158) and 2 (page 12, line 204) to clarify this question.

Q: Material and methods section is almost 6 pages long. Indeed it should be thorough but at the same time not so long and unclear.
R: We have now edited and shortened the Material and methods section. Changes can be seen using the track changes mode.

Q: Pregnancy complications (line 19-31 in page 14.results). The authors report that anemia was a risk factor for several outcomes. How was the calculation done? Which parameters were assessed as confounders and how were they taken into account in the author's model. Needs to clarify…as it doesn't make sense that maternal anemia was a risk factor for shoulder dystocia.
R: In the original manuscript the risks were reported as unadjusted OR. However, we realize that this was not the most accurate way of reporting these risks. After adjustment for demographic and clinically relevant factors, the risk remained statistically significant for very preterm delivery. The risk for shoulder dystocia in anemic patients disappeared after adding instrumental vaginal delivery to the model. We have now rewritten the text in this part and we decided to omit the data concerning the unadjusted ORs from the manuscript (Results, page 15, lines 233-236, Discussion, page 23, line 381).

6. Discussion: How was IUGR defined?
R: Diagnosis of IUGR was based on the follow-up data at the maternal-fetal units during pregnancy. However, given the much stronger nature of SGA as an outcome, we decided to remove IUGR from the manuscript.

VERSION 2 - REVIEW

REVIEWER	Anwar Nassar, MD Professor of Obstetrics and Gynecology American University of Beirut Medical Center Beirut - Lebanon
REVIEW RETURNED	22-Jul-2013

GENERAL COMMENTS	The authors have replied to almost all queries raised by the reveiwer with the exception for some data that their database doesn's allow them to answer.