PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence, risk factors, and perinatal outcomes for placenta accreta in Australia and New Zealand: A case-control study
AUTHORS	Farquhar, Cynthia; Li, Zhuoyang; Lensen, Sarah; McLintock, Claire; Pollock, Wendy; Peek, Michael; Ellwood, David; Knight, Marian; Homer, Caroline; Vaughan, Geraldine; Wang, Alex; Sullivan, Elizabeth

VERSION 1 – REVIEW

REVIEWER	Carolyn Weiniger Hadassah Hebrew University Medical Center, Jerusalem, Israel
REVIEW RETURNED	22-May-2017

GENERAL COMMENTS	General. This huge project and important, performed across 2 nations, that investigated placenta accretas using a robust system to identify the denominator and thus report accurate prevalence. In addition the authors added a case-control methodology that detracts from the overall message of the paper, particularly in light of the huge number of women who did not have accretas identified prior to delivery - of itself an important group to consider in further detail. This manuscript in my opinion would be of great interest and improved authority if the identified versus non-identified accretas were compared in terms of incidence and outcome. In addition it would be important to identify the suspected accretas that were not confirmed at surgery/pathology and desite what is written in the limitations section it is not clear why this was not possible. Please review the terminology – for example you should be consistent using delivery, baby previously, birth; multiparous, many children. Specific comments Abstract: Objective – clearly stated, yet do not incorporate the case-controls Inclusion criteria – clearly stated as either women with antenatal imaging diagnosis or surgical diagnosis. The authors used any 2 births in time-relation to the accreta deliveries, however they are not matched at all. Outcomes clearly stated but not reported in the abstract. What is the control group – abstract doesn't state if its women at risk or any women and what are they matched for? Likelihood of the women before or after being at risk is tiny so the risks are super-exaggerated.

	Introduction P5 L87. You are not discussing management in your paper so why are you raising the issue here? You state that you are looking at complications, so I suggest that you do not digress in your introduction. Although you mention management later on you really only discuss hysterectomy and not the surgical/anesthesia strategies. It is important in the final paragraph of the introduction to clearly state your study aims as you did in the abstract and to explain the context that this is a case-control (if that is how you plan to continue to present your data) with a negative surveillance system to maximize the accuracy of the denominator. Methods P6 L101 – can you give more details about AMOSS, your active negative surveillance system? Were there parallel conditions being identified as in UKOSS? Were staff only looking for accreta cases. How do they note this and report? Do they hunt files, how do they gather the information per month? How did other staff know to alert the contact-staff in their institution? Please give more details about your selection of the control cases – surely comparing a complicated multiparous woman against a nulliparous uneventful delivery gives an erroneously high complication factor? Why did you not match for similar parity? Similar mode of delivery (assuming all suspected accreta cases are having CS you are not looking for mode of delivery as an outcome variable) Results Your primary outcome – incidence of all suspected/true accretas is clearly stated. As you discussed in your limitation section, you may not have removed women with suspected accreta who did not have a confirmatory diagnosis at surgery. Thus you are reporting suspected and true accretas. Was there any way you could search these 295 charts to seek a confirming surgical or pathological diagnosis? Your incidence is clearly raised because of this issue, as you discuss. P8 L153 – these are perinatal neonatal or maternal deaths? Pls clarify. From the context I assume neonatal. L155 – the causes of maternal death? L158. How many of the 143 cases did not have placenta accreta confirmed at surgery/pathology? 132 cases not diagnosed until surgery is a very high incidence. L161 – sonographic, pathological and or surgical diagnosis? Pls confirm? L164 pls confirm you are talking about accreta cases, or all the cases including the controls? Table 3 primiparity is a risk factor for a surprise intraoperative diagnosis. Did all these primiparas have placenta previa? L189 – and how many were primiparous or multiparous without prior CS? L191 hysterectomy was related to prior vs intraoperative diagnosis of accreta L195 can you be specific either here or in the statistical methods regarding the confounders you are adjusting for, particularly how you decided on them? Why did you not control for nulliparity? This is your most striking confounder. I have a concern about the case controls.

	Such a methodology of healthy time-related controls is relevant to compare against accretas that were unknown and turned out to be accretas; many of these women appear to have labored prior to the diagnosis of accreta. But to compare all the accretas cases, including those that are known about does not seem a useful and helpful comparison. P10 L201- is this in any way a function of a decision for early delivery in known accretas? In your comment you discussed the denominator related to potential inclusion of non-true accretas however this will be problematic for those reading the bottom line and not the manuscript. You should discuss why you chose not to identify and remove the non-true accretas. You should discuss the other potential reasons for hysterectomy in multiparous women and need to provide evidence for your statement that there is a higher motivation for uterine preservation in primiparas as you have not presented details regarding blood loss, transfusion requirements and other complications. And if you are correct, what is the morbidity cost of this uterine preservation? P12, L 273. Pls discuss why there are so many cases that are not anticipated accretas? Tables P values should be rounded to 2-decimal places if not significant Table 1. You have a huge % of nulliparous controls relative to the cases. Pls explain and discuss why these have not skewed the data interpretation. You did control for prior cesarean deliveries, but I am concerned that you noticed the parity difference (reflected by your noting the significant difference) yet have neither mentioned it nor controlled for it. This is a major flaw of your study that could perhaps be rectified either by taking cases that control for parity, or by performing the case-control only for women who labored Table 2 – is this a risk factor analysis for the entire cohort of cases and controls? Pls amend the title to reflect this Table 3 – pls select a title that explains what data are presented in the table I note that there are no controls with PA not suspected prior to the labor. This is not obvious as there were 51 women in the cases who labored without a prior accreta diagnosis. Can you discuss why the 7 women with accreta labored prior to delivery, and 1 was induced! Can you discuss the reasons for early delivery of the accreta-suspected cohort, that presumably drive many of the neonatal findings. This table is a very important one, and gives a lot of information that is relevant and necessary. However the cases that are compared do not add any information in this table – you have a huge number of non-identified accretas and this can be your comparison group.

REVIEWER	Offer Erez M.D. Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel
REVIEW RETURNED	06-Jun-2017

GENERAL COMMENTS	The population based case controlled study by Cynthia Farquhar and her team is interesting, yet the major questions that come across is what's new. The parameters presented here is major outcomes as gestational age of delivery, admission to intensive care unit, hysterectomy are all well known and been previous described in the literature. 1) Why did the author choose a design of a case-control rather than a cohort study? 2) In the limitation of the study, the author states that at least part of the cases were diagnosed anti-nataly, but were not subsequently verified during operation or with the results of placental pathology. This casts a big shadow regarding the validity of the results presented in this manuscript. In the discussion the authors state that the study audited the clinical records of the patients therefore the information necessary to classify a patient as having a placenta accreda can not rely solely on prenatal imaging. 3) The author presents in Table 1 and Table 2 that the rate of assisted reproduction is higher in a woman with placenta accreta and it confers an independent risk factor, but they do not discuss this point in the manuscript. I would suggest them to add a paragraph in the discussion assessing the mode of conception, the risk for placenta previa, and placenta accreta. 4) What was the rate of an intrauterine procedures prior to the detection to placenta accreta? this information is important as it has been previously reported as a risk factor for placenta accreta. 5) Were there differences in the morbidity of the patients according to the site of placenta implantation? 6) What was the rate of the DIC in these patients, and what was the proportion/number of blood product transfusion that this patient received and was the number related to antepartum detection of placenta accreta? 7) Do the authors have information regarding the use of advanced technique to reduce intrapartum bleeding, such as intraunterine artery balloons or gelfoam injection? 8) How many of the patients needed a ligation of the anterior illac artery? 9) There are missing references and I encourage the authors to perform a thorough literature review.l

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Carolyn Weiniger
General. This huge project and important, performed across 2 nations, that investigated placenta accretas using a robust system to identify the denominator and thus report accurate prevalence. In addition the authors added a case-control methodology that detracts from the overall message of the paper, particularly in light of the huge number of women who did not have accretas identified prior to delivery - of itself an important group to consider in further detail.

Comment 1:
This manuscript in my opinion would be of great interest and improved authority if the identified versus non-identified accretas were compared in terms of incidence and outcome.

Response:
Thank you for this comment. In answering the suggestion about comparing the identified vs non-identified accretas in terms of

1) Outcome: In this study the case definition was “women giving birth who were diagnosed with placenta accreta by either antenatal imaging, at operation or by pathology specimens. The type of diagnosis was re-coded according to the earliest diagnosis”. 48.5% of PA cases were diagnosed prior to delivery, and 57.3% were suspected prior to delivery. We have compared the suspected vs unsuspected PA in Table 3 and 4 in terms of management (e.g. labour or not) and maternal and perinatal outcomes. We hope this will satisfy the comparison requested in terms of outcome.
2) Incidence: One of the limitations of this study was that the definition of PA may have allowed for inclusion of accretas which were identified prior to delivery, and not confirmed at delivery. Unfortunately, we did not collect this data in such a way as to be able to confirm whether the cases were diagnosed at delivery also, however we believe that the majority cases were confirmed cases of PA (as
described in 2. below). Therefore we are not able to report on the incidence of confirmed PA (at delivery) in women with and without a suspected PA. All included cases had PA (as per our definition of PA), therefore the incidence is 100% in the case group and 0% in the control group.

Comment 2:
2. In addition it would be important to identify the suspected accretas that were not confirmed at surgery/pathology and desite what is written in the limitations section it is not clear why this was not possible.

Response:
To be eligible as a case the women needed to have been diagnosed either by ultrasound, operation, or histology; which allowed the potential for inclusion of cases who were diagnosed only at ultrasound and not confirmed as PA at delivery. Further, the data collections forms used may have inadvertently prompted staff to record the earliest diagnosis of PA, and not to record whether or not PA was confirmed at delivery. This issue was only picked up at the time of data analysis. It would have therefore been difficult to return to the individual sites and request this confirmation.

However, we believe the majority of the cases were cases of true PA. We have added to the discussion a paragraph describing how 85% of the cases recorded as having PA diagnosed by antenatal imaging only, had a hysterectomy as part of their care – thereby indicating clinical/true PA was present. Further, ultrasound imaging has high sensitivity and specificity at diagnosing PA. However, we cannot be sure that all cases had PA diagnosed at delivery/pathology, hence the limitation in the Discussion.

Comment 3:
Please review the terminology – for example you should be consistent using delivery, baby previously, birth; multiparous, many children.

Response:
We have edited the manuscript so mostly the word ‘birth’ is used rather than delivery

Comment 4:
Abstract: Objective – clearly stated, yet do not incorporate the case-controls

Response:
'Case-control' is listed in the 'design' section of the abstract

Comment5:
Abstract: Inclusion criteria – clearly stated as either women with antenatal imaging diagnosis or surgical diagnosis. The authors used any 2 births in time-relation to the accreta deliveries, however they are not matched at all.

Response:
The reviewer is correct. The controls are the two women delivering immediately prior to the case in the same hospital – the controls were selected using a methodology that UKOSS had employed, with controls selected on timing of birth proximal to the case. Planned multivariable analysis was used to adjust for any differences between cases and controls, rather than matching.

Comment 6:
Abstract: Outcomes clearly stated but not reported in the abstract. What is the control group – abstract doesn't state if its women at risk or any women and what are they matched for? Likelihood of the women before or after being at risk is tiny so the risks are super-exaggerated
As above we have clarified no matching was used.

Response:
The outcomes are reported in the results section of the abstract. This study used the two births immediately prior to the case for the control arm, which therefore represents the cohort of women giving birth at each centre. Women with PA were selected as cases and were not eligible for the control arm. As the incidence of PA is very low, the chance of the controls being at risk is very low, and therefore is appropriately representative of the control population. We do not believe this exaggerates the reported risks of PA in this paper.

Comment7:
Introduction: P5 L87. You are not discussing management in your paper so why are you raising the issue here? You state that you are looking at complications, so I suggest that you do not digress in your introduction. Although you mention management later on you really only discuss hysterectomy and not the surgical/anesthesia strategies.

Response:
Thank you, we have removed the term management from the introduction, and refer to the use of hysterectomy etc. as 'clinical practice' instead.

Comment 8:
Introduction: It is important in the final paragraph of the introduction to clearly state your study aims as you did in the abstract and to explain the context that this is a case-control (if that is how you plan to continue to present your data) with a negative surveillance system to maximize the accuracy of the denominator.

ResponsE:
Thank you, we have amended the final paragraph as suggested

Comment 9:

Methods: P6 L101 – can you give more details about AMOSS, your active negative surveillance system? Were there parallel conditions being identified as in UKOSS? Were staff only looking for accreta cases. How do they note this and report? Do they hunt files, how do they gather the information per month? How did other staff know to alert the contact-staff in their institution?

Response:
Thank you, we have added further information on these methods to the Methods section

Comment 10:
Methods: Please give more details about your selection of the control cases – surely comparing a complicated multiparous woman against a nulliparous uneventful delivery gives an erroneously high complication factor? Why did you not match for similar parity? Similar mode of delivery (assuming all suspected accreta cases are having CS you are not looking for mode of delivery as an outcome variable)

Response:
Parity was collected in this study as a potential risk factor for placenta accreta. If we matched on parity we would not be able to test if this was a risk. At the time of data analysis, we found that primiparous and multiparous women had different risk factors of placenta accreta (e.g. number of previous caesarean deliveries is a strong risk factor of placenta accreta for multiparous women but not relevant to primiparous women). Therefore, risk factor analysis was stratified by parity (results presented in Table 2). The methodology section has been revised to clarify this. We did look at mode of delivery as an outcome variable, for example abstract states “Women with placenta accreta were more likely to have a caesarean section (AOR: 4.6, 95% CI: 2.7 – 7.6)”

Comment 11:
Results: Your primary outcome – incidence of all suspected/true accretas is clearly stated. As you discussed in your limitation section, you may not have removed women with suspected accreta who did not have a confirmatory diagnosis at surgery. Thus you are reporting suspected and true accretas. Was there any way you could search these 295 charts to seek a confirming surgical or pathological diagnosis? Your incidence is clearly raised because of this issue, as you discuss.

Response:
Please see our answer to question 2 above.
Results: P8 L153 – these are perinatal neonatal or maternal deaths? Pls clarify. From the context I assume neonatal.
The sentence clarifies they are perinatal deaths in the brackets: “There were 12 perinatal deaths among the cases (perinatal death rate 38.7 per 1,000 births) and 10 among the controls (perinatal death rate 17.2 per 1,000 births). We have added a sentence to the methods to define perinatal, neonatal and fetal deaths for this study.

Commet 13:
Results: L155 – the causes of maternal death?

Response:
The causes of maternal death are listed in the very next sentence, however we have added the word ‘maternal’ here for further clarity.

Comment 14:
Results: L158. How many of the 143 cases did not have placenta accreta confirmed at surgery/pathology?

Response:
Of the 143 cases recorded as first diagnosed by antenatal imaging, 36 were confirmed at surgery/pathology, leaving 107 as being recorded as diagnosed only by antenatal imaging. However, (as mentioned in 2 above) of the 107 women, 85% (91 out of 107) had a hysterectomy. Considering hysterectomy is a devastating outcome for woman and her family and it is the last resort after explored all other options, these women are mostly likely to be confirmed placenta accrete cases but not recorded as diagnosed at operation/pathology specimen. We have added this to the Discussion.

Comment 15:
Results: 132 cases not diagnosed until surgery is a very high incidence.

Response:
In this study, 44.7% of the PA reported were not diagnosed until operation, and 5.4% were not diagnosed until pathology. Similarly, only 53% of cases had PA suspected prior. This incidence correlates well with that of the UKOSS study which reported that PA was suspected prior to delivery in 50% of their cases. Therefore we do not agree that this is a high incidence compared to usual practice.

Comment 16:
Results: L161 – sonographic, pathological and or surgical diagnosis? Pls confirm?

Responsse:
We believe this query relates to the sentence “There were 213 (72.2%) cases with placenta accreta, 37 (12.5%) with placenta increta and 45 (15.3%) with placenta percreta.” This diagnosis was as per any and all of the methods permitted by the case definition (ultrasound, operation, or histology) and we have added a sentence to clarify this.

Comment 17:
Results: L164 pls confirm you are talking about accreta cases, or all the cases including the controls?

Response:
The term ‘cases’ is used throughout the paper to refer to the cases only (those with PA). The controls are referred to only as controls, and not cases (case-control study). We have added the words ‘placenta accreta’ in this sentence for absolute clarity.

Comment 18:
Results: Table 3 primiparity is a risk factor for a surprise intraoperative diagnosis. Did all these primiparas have placenta previa?

Response:
We are unclear what question the reviewer is asking, as Table 3 does not present any data regarding risk factors or parity. However, we expect it relates to that fact we did not report the proportions of multiparous and primiparous cases with placenta praevia, so we have added this to the results.

Comment:
19. Results: L189 – and how many were primiparous or multiparous without prior CS?

Response:
We have added this sentence to further describe women with suspected/unsuspected PA based on CS history: “Women with suspected placenta accreta were also more likely to have had a prior caesarean section (93%), than women with unsuspected placenta accreta (72%)”

Comment 20: Results: L191 hysterectomy was related to prior vs intraoperative diagnosis of accreta
Thank you, we have amended this sentence to compare suspected vs. unsuspected also

Comment 21:
Results: L195 can you be specific either here or in the statistical methods regarding the confounders you are adjusting for, particularly how you decided on them? Why did you not control for nulliparity? This is your most striking confounder.

Response:
The methodology section has been revised to clarify that the risk factor analysis was stratified by parity (results presented in Table 2). As primiparous and multiparous women had different risk factors of placenta accreta (e.g. number of previous caesarean deliveries is a strong risk factor of placenta accreta for multiparous women but not relevant to primiparous women), it would be more appropriate to stratify the risk factor analysis by parity. Parity was adjusted for the comparison of maternal and perinatal outcomes between cases and controls. The methodology section has been revised to clarify this.

Comment 22:
Results: I have a concern about the case controls. Such a methodology of healthy time-related controls is relevant to compare against accretas that were unknown and turned out to be accretas; many of these women appear to have labored prior to the diagnosis of accreta. But to compare all the accretas cases, including those that are known about does not seem a useful and helpful comparison.

Response;
Thank you and we agree there is an important distinction between cases which were suspected prior to delivery and therefore able to be managed as PA cases, compared to those which were only diagnosed at operation or pathology; it is for this reason that we have separated the results in Tables 3 and 4 based on whether the case was suspected or not, prior to delivery.

Comment 23:
Results: P10 L201- is this in any way a function of a decision for early delivery in known accretas?

Response:
We believe this relates to the sentence “Babies born to mothers with placenta accreta were more likely to be preterm (median gestational age at birth 36 vs. 39 weeks)” Any further (statistical) comparisons between cases with suspected and unsuspected accretas will be the topic of a following paper.

Comment 24:
Discussion: In your comment you discussed the denominator related to potential inclusion of non-true accretas however this will be problematic for those reading the bottom line and not the manuscript. You should discuss why you chose not to identify and remove the non-true accretas.

Response:
As discussed in depth in the above questions, we are not able to identify the non-true accretas; however we expect there to be few and we have stated reasons for this in the amended Discussion.

Comment 25:
Discussion: You should discuss the other potential reasons for hysterectomy in multiparous women and need to provide evidence for your statement that there is a higher motivation for uterine

preservation in primiparas as you have not presented details regarding blood loss, transfusion requirements and other complications. And if you are correct, what is the morbidity cost of this uterine preservation?

Response:
Thank you. We agree this is an important implication. We plan to report the management of PA cases (including blood transfusions etc) in detail in a following paper.

Commen 26:
Discussion: P12, L 273. Pls discuss why there are so many cases that are not anticipated accretas?

Response:
Thank you. As per 15 above, the incidence of cases with suspected and unsuspected PA prior to delivery is similar to that reported for the UKOSS study. We will further discuss management in the following paper.

Commne 27:
Tables: P values should be rounded to 2-decimal places if not significant

Response:
Thank you, we have rounded all p-values to 2dp

Comment 28:
Table 1. You have a huge % of nulliparous controls relative to the cases. Pls explain and discuss why these have not skewed the data interpretation. You did control for prior cesarean deliveries, but I am concerned that you noticed the parity difference (reflected by your noting the significant difference) yet have neither mentioned it nor controlled for it. This is a major flaw of your study that could perhaps be rectified either by taking cases that control for parity, or by performing the case-control only for women who labored

Response:
Thank you. As per 21 above, we had stratified based on parity however this was not previously clear in the paper and we have amended the methods to reflect this.

Comment 29:
Table 2 – is this a risk factor analysis for the entire cohort of cases and controls? Pls amend the title to reflect this

Response:
Thank you, yes it is for cases and controls, the title has been amended.

Commen 30:
Table 3 – pls select a title that explains what data are presented in the table
Title changed

Comment 31:
Table 3- I note that there are no controls with PA not suspected prior to the labor. This is not obvious as there were 51 women in the cases who labored without a prior accreta diagnosis.

Response:
Can you discuss why the 7 women with accreta labored prior to delivery, and 1 was induced! Can you discuss the reasons for early delivery of the accreta-suspected cohort, that presumably drive many of the neonatal findings.
The management of these cases and controls will be the topic of a further paper, as described earlier. However, we have added this sentence to the discussion “which may reflect the management of suspected accreta with planned caesarean section” and we have listed in the results the reason the one case was induced.

Comment 32: This table is a very important one, and gives a lot of information that is relevant and necessary. However the cases that are compared do not add any information in this table – you have a huge number of non-identified accretas and this can be your comparison group.
Thank you, and we agree that it would be interesting and important to compare the PA that were suspected compared to those that were unsuspected, and this will be covered in the following paper.

Reviewer 2: Offer Erez

The population based case controlled study by Cynthia Farquhar and her team is interesting, yet the major questions that come across is what's new. The parameters presented here is major outcomes as gestational age of delivery, admission to intensive care unit, hysterectomy are all well known and been previous described in the literature.

Comment 1:
Why did the author choose a design of a case-control rather than a cohort study?

Response:
The advantage of the case-control design in the study of rare diseases is well described in the literature, and it was for these reasons that a case-control study was employed. It would not have been practical to collect information on all women giving birth at all participating sites during the same period as this study collected information.

Comment 2:
In the limitation of the study, the author states that at least part of the cases were diagnosed anti-nataly, but were not subsequently verified during operation or with the results of placental pathology. This casts a big shadow regarding the validity of the results presented in this manuscript. In the discussion the authors state that the study audited the clinical records of the patients therefore the information necessary to classify a patient as having a placenta accreda can not rely solely on prenatal imaging.

Response:
As discussed in depth in the previous reviewers comments, unfortunately we are unable to seek further clarification on the confirmation of diagnosis post-hoc, however we believe there is good reason to assume that the majority of included cases are true PA cases (as most with only antenatal diagnosis had a hysterectomy)

Comment 3:
The author presents in Table 1 and Table 2 that the rate of assisted reproduction is higher in a woman with placenta accreta and it confers an independent risk factor, but they do not discuss this point in the manuscript. I would suggest them to add a paragraph in the discussion assessing the mode of conception, the risk for placenta previa, and placenta accreta.

Response:
Assisted conception was not an independent risk factor in this study, after adjusting for confounding variables; therefore we already have this sentence in the Discussion “Previous studies have also reported risk factors that this study did not find to be independent, specifically: smoking,(1) use of assisted reproductive technologies,(2) and sex of fetus.(3)”

Comment 4:
What was the rate of an intrauterine procedures prior to the detection to placenta accreta? this information is important as it has been previously reported as a risk factor for placenta accreta.

Response:
Unfortunately this risk factor was not available in the dataset. We have added prior intrauterine surgery to the list of risk factor not collected in the Discussion, and we have added this sentence to the Discussion “A further limitation is that information was not collected on all possible risk factors, and therefore we were not able to assess these”

Comment 5:
Were there differences in the morbidity of the patients according to the site of placenta implantation?

Response:
Unfortunately we did not collect the site of placentation.

Comment 6:
What was the rate of the DIC in these patients, and what was the proportion/number of blood product transfusion that this patient received and was the number related to antepartum detection of placenta accreta?

Response:
As mentioned previously, we are planning a second paper which will detail this management.

Comment 7:
Do the authors have information regarding the use of advanced technique to reduce intrapartum bleeding, such as intraunterine artery balloons or gelfoam injection?

Response:
As above in 7

Commnet 8:
How many of the patients needed a ligation of the anterior illac artery?

ResponsE:
As above in 7

Commnet 9:
There are missing references and I encourage the authors to perform a thorough literature review.

Response:
Thank you, we have added additional references. We would be happy to include any further references the reviewer may request.

Thank you for considering this manuscript for publication in BMJ Open. We consider that this paper will be of interest to all health professionals who look after pregnant women. I am happy to provide

further details if required. All named authors have directly contributed to the manuscript and approved the updated version.

VERSION 2 – REVIEW

REVIEWER	Offer Erez Offer Erez M.D. Professor Department Obstetrics and Gynecology Hutzel Women Hospital Wayne State University Service in support of the Perinatology Research Branch NICHD, NIH 3990 John R Detroit 48201 MI Phone 313-577-1913 Cell 248-516-9118 oerez@med.wayne.edu
REVIEW RETURNED	12-Jul-2017

GENERAL COMMENTS	The authors did not address my concerns. I still think that a cohort design versus a case control study is preferable especially when the authors had the ability to collect this data. Case control studies are used when we have a problem to collect the data of a cohort. The author did not look for the needed information, such a previous surgical procedures in the uterus, location of the placenta, this data is of importance in a paper on placenta accreta and need to address that. The fact that the authors did not validate the diagnosis made by ultrasound is a major limitation that needs to be addressed, since all those cases were not validated in actual life and can cause a bias and misrepresentation of the results.

VERSION 2 – AUTHOR RESPONSE

Comment 1:
The authors did not address my concerns. I still think that a cohort design versus a case control study is preferable especially when the authors had the ability to collect this data. Case control studies are used when we have a problem to collect the data of a cohort.

Response:
We thank the reviewer for his comments on our revised manuscript. While we agree that a cohort design has some advantages over case-control, a case-control study is commonly used when the disease is rare, as is the case of placenta accreta. It would have been very difficult to conduct a cohort study of this detail, as we collected much additional information on the included cases/controls than is collected in routine care. Further, the study has been completed already and the design is not amenable to change at this point.

Comment 2:
The author did not look for the needed information, such a previous surgical procedures in the uterus, location of the placenta, this data is of importance in a paper on placenta accreta and need to address that.

Response:
We agree there are a number of additional variables which would have been interesting to investigate as potential risk factors. We have stated in the discussion that “A further limitation is that information was not collected on all possible risk factors, and therefore we were not able to assess these”

Comment 3:
The fact that the authors did not validate the diagnosis made by ultrasound is a major limitation that needs to be addressed, since all those cases were not validated in actual life and can cause a bias and misrepresentation of the results.

Response:We have already extensively discussed the potential for overestimation associated with this issue. It is not possible to return to the clinical records for the individual cases included to validate the data at this point, hence this remains a limitation of the study.

Thank you for considering this manuscript for publication in BMJ Open. We consider that this paper will be of interest to all health professionals who look after pregnant women. All named authors have directly contributed to the manuscript and approved the updated version.