Author's response to reviews

Title: Intra- versus retroplacental hematomas: A retrospective case-control study on pregnancy outcomes

Authors:

Johannes Ott (johannes.ott@meduniwien.ac.at)
Philipp Pecnik (pecnikphilipp@gmail.com)
Regina Promberger (regina.promberger@chello.at)
Sophie Pils (sophie.pils@meduniwien.ac.at)
Julia Wild (julia.wild@meduniwien.ac.at)
Kinga Chalubinski (kinga.chalubinski@meduniwien.ac.at)

Version: 1 Date: 05 May 2017

Author’s response to reviews:

Dear Editors,

Dear Reviewers,

We thank you for your valuable comments that helped us improve our manuscript. We took care in revising our manuscript accordingly. We provide a point-by-point answer letter for all recommendations.

We hope that the revisions made to the manuscript will make it acceptable for publication in “BMC Pregnancy Childbirth”.

Respectfully yours,

Regina Promberger-Ott

- in the name of all authors –

Reviewer #1: The manuscript is well written and very original because it assessed the clinical implications of IUH according with its location (intra/retroplacental). However I have some queries that need to be clarified before drawing the Authors' conclusions.
Major revision

Parameters analyzed- statistical analyses


Reply: In the revised manuscript, we provide an explanation for excluding these women: “The latter patients were excluded from the subsequent analyses on pregnancy outcomes (Tables 2 and 3), since data on the evaluated outcome parameters were available only from week 24+0 onwards.”

2. The clinical outcomes are well defined, however it is unclear to me whether you considered previous IUGR and abruptio placentae in the multivariate logistic regression model?

Reply: We thank the reviewer for this comment. We included these parameters in the revised manuscript as follows:

- We included an according statement in the Methods Section that placental abruption was also analyzed as an outcome parameter.
- We added the information about placental abruption to Table 2.
- We added the information about previous IUGR to Table 1.
- We added previous IUGR as a predictive factor to the multivariate models presented in Table 3.
- We also added a sentence about these new results to the main text (Results Section): “The presence of a retroplacental hematoma outweighed all other tested parameters apart from previous IUGR as a predictor of its recurrence.”

3. Why did not you assess the multivariate logistic regression model to predict the risk of preterm delivery? Please specify if IUH increased the risk of PTD independently of its location.

Reply:

- The analysis was added. See the new Table 4 and the according paragraph in the Results Section: “When performing a similar analysis for early preterm delivery <34+0 weeks (Table 4), both intra- and retroplacental hematomas, lower parity and presence of IUGR increased the risk significantly (women with IUFD excluded).”
We also added the additional univariate analysis of any kind of hematoma and its associated risk for ePTD: “When taking intra- and retroplacental locations together, the presence of hematoma was also associated with a significantly increased risk for early preterm delivery ($\beta= 2.00 \pm 0.63$, $p= 0.001$).”

Discussion: These new results are also discussed:

- “both intra- and retroplacental hematomas were associated with increased incidences of pregnancy-related complications, including placental insufficiency, intrauterine growth retardation, and preterm labor and (early) preterm delivery”

- “women with an intraplacental hematoma were at an even higher risk for these complications than those with a retroplacental hematoma.”

- “Notably, in multivariate analyses, intraplacental hematomas were an important risk factors for the development of placental insufficiency and growth retardation (Table 3) as well as for early preterm delivery (Table 4).”

Results

1. Did you consider the gestational age at diagnosis in the predictive model of adverse outcome? This key point is very important because prognosis may differ according to first or second trimester diagnosis (i.e. Xiang L et al. Symptoms of an intrauterine hematoma associated with pregnancy complications: a systematic review. PLoS One. 2014 Nov 4;9(11):e111676 / Maso e al. First trimester intrauterine hematoma and outcome of pregnancy. Obstet Gynecol 2005; 105: 339-344)

Reply: Gestational age at diagnosis could not be included into the multivariate models directly, since this parameter was available only for the case groups, not for the control group. However, we provide the following additional analyses:

- Results: “Then, the impact of gestational age at hematoma diagnosis on pregnancy outcome was assessed. Women with placental insufficiency revealed a higher median gestational age at diagnosis (23 completed weeks, IQR 15-27) than those without (15 weeks, IQR 12-24; $p= 0.034$), whereas there was no difference between women with and without IUGR (median 21 weeks, IQR 12-24, versus median 15, IQR 12-25, respectively; $p= 0.851$). Median gestational age at diagnosis was higher in women with early preterm delivery (23 weeks, IQR 14-27) than in patients who delivered after 34+0 weeks (14, IQR 12-24; $p= 0.038$). When dividing women into those with a first-trimester diagnosis of hematoma (n= 70) versus those with a second-trimester diagnosis (n= 73), placental insufficiency was more frequent after a second- (15/73, 20.5%) than after a first-trimester diagnosis (5/70, 7.1%; $p= 0.029$). The same was found for early preterm delivery (patients with IUFD excluded: 18/71, 25.4% versus 5/66, 7.6%, respectively; $p= 0.006$) but not for IUGR (14/73, 19.2% versus 8/70, 11.4%, respectively; $p= 0.249$).”
We thank the reviewer for the interesting references. We included them in the revised Discussion Section: “Moreover, it has been mentioned that gestational age at diagnosis might predict pregnancy risks.[20,21] However, we consider hematoma type of higher predictive value for pregnancy complications than age at diagnosis; women with a second-trimester diagnosis which is associated with the finding of an intraplacental hematoma in the majority of cases carried the highest risks.”

Discussion

Please provide any other different conclusion according to the replies to reviewer's queries

Reply: All new or changed results are discussed in the revised manuscript as described above.

Minor revision

Table 1. Please provide the list of abbreviations used (i.e SIH?)

Reply: Done. Sorry for “SIH”, this should have been “PIH”.

Please replace Intrauterine Growth Retardation with Fetal or Intrauterine Growth Restriction in the manuscript

Reply: Done.

Reviewer reports:

Haixiang Sun (Reviewer 2): Intrauterine hematoma is a common pregnancy complication. As the authors mentioned that the previous literature focused on intrauterine hematoma is general in nature, and no studies have evaluated the outcomes of intraplacental hematomas separately. While this study compared pregnancies complicated between intraplacental hematoma and retroplacental hematoma. They found intraplacental and retroplacental hematomas have different risk profiles for the affected pregnancy and act as independent risk factors. With this merit, the report may be of interesting to many readers; however, many concerns need to be addressed.

1. In the BACKGROUND section, the ultrasound diagnosis criteria both for intraplacental hematoma and retroplacental hematoma should be stated. It is better if the authors provide the ultrasound figures both for intraplacental hematoma and retroplacental hematoma, so the authors can easily figure out the differences between them.

Reply:
We provide the following definition in the revised Background Section: “Sonographically, intraplacental hematomas are located in the intervillous cavity of the placenta, whereas retroplacental hematomas are located between the basal plate and myometrium, lifting the placental parenchyma toward the amniotic cavity.”

Ultrasound figures have been added as Figure 1A-D. The Figure is cited in the Methods Section.

2. The data for birth weight, gestational weeks of delivery, cesarean section rate should also be showed in the results section. What is the difference between placental abruption and intraplacental hematoma or retroplacental hematoma? Did some patients in your study also diagnosis as placental abruption?

Reply:

Data on birth weight, Cesarean section rates and gestational age at delivery are now provided in Table 2.

The new findings are mentioned shortly in the main text of the Results Section: “In short, the intraplacental hematoma group (p< 0.05) revealed significantly higher rates of placental insufficiency, intrauterine growth retardation, premature preterm rupture of membranes, preterm labor, preterm delivery <37 weeks, and early preterm delivery <34 weeks (Table 2). These findings were associated with differences in gestational age at delivery, birth weight, and rates of Cesarean section between the groups (p< 0.001).”

We discuss these new results briefly: “These findings are underlined by the differences in birth weight and gestational age at delivery between the groups;”

We added the information about placental abruption to Table 2.

We agree that one might get confused with the definitions of retroplacental hematoma and complete and acute placental abruption. In the revised Methods Section, we provide a definition that derives from a clinical (and retrospective) point of view: “[...] complete placental abruption which was defined as a complete separation of the placental lining from the uterus (in contrast to a retroplacental hematoma)”

3. Some patients were diagnosed intraplacental hematoma or retroplacental hematoma in the earlier gestation, did the intraplacental hematoma or retroplacental hematoma was absorbed during the following-up? If not, the author should provide the placenta pathological results to conform the ultrasound diagnosis.

Reply: We thank the reviewer for this comment. Unfortunately, we cannot provide exact data on these issues and discuss this as a new study limitation: “We cannot provide exact data on changes in sonographic presentation of the hematomas which has to be considered a study
limitation. From our clinical experience, hematomas did not get absorbed during follow-up, but their sonographic appearance changed to a more inhomogeneous structure with varying degrees of echogenicity. Neither we are able to provide data about histo-/pathological examinations of the affected placentae. Only a minority of the placentae have been sent for pathological examination, a limitation that is associated with the retrospective study design. Moreover, in case of retroplacental hematomas such an examination seems of only minor impact, since these hematomas are stripped off easily.”

4. In the methods section, how were the controls chosen?

Reply: We provide the following information in the revised manuscript: “As a control group, 113 age-matched women with no signs of placental abnormalities who had also delivered at our department within the same time period were also included. For selection of controls, a large database including all deliveries at the department was used and the procedure was performed by “case-control-matching” in SPSS 17.0 software (SPSS Inc., 1989-2009).”

5. The authors showed that cases of IUFD occurred only in the retroplacental hematoma group, more details about the IUFD should be showed, such as gestation weeks when found, whether has birth defect, etc.

Reply: We provide the following information on these cases: “IUFD occurred only in women with retroplacental hematoma (Table 2). None of the affected fetuses revealed any birth defects. Median gestational age at diagnosis of IUFD was 24 completed weeks (IQR 23-25).”

6. As the retroplacental hematoma occurred at 12-21 weeks, while intraplacental hematoma occurred at 22-29 weeks, whether can we get the conclusion that if it happens at 12-21 weeks it is retroplacental hematoma, if it happens at 22-29 weeks it should be intraplacental hematoma? And the different mechanisms for these two diseases should be discussed in the discussion section, as Fitzgerald B et al mentioned that rounded intraplacental haematomas form as a result of disruption of vasculopathic decidual arterioles in a setting of maternal vascular underperfusion and are thus aetio logically distinct from classically described intervillous thrombi (J Clin Pathol. 2011 Aug;64(8):729-32).

Reply:

- We discuss this issue as follows: “Thus, if a hematoma is found early in pregnancy, i.e. within the first 21 weeks of gestation, its location will likely be retroplacental, whereas intrauterine hematomas found at a higher gestational age will be intraplacental in the majority of cases. However, gestational age at diagnosis will not predict hematoma location with apodictic certainty, since the presented median gestational ages at diagnosis were associated with quite a big interquartile range.”
We thank the reviewer for making us aware of this interesting statement. We take the liberty to use the reviewer’s wording in the Discussion Section: “Moreover, it has already been mentioned that rounded intraplacental haematomas form as a result of disruption of vasculopathic decidual arterioles in a setting of maternal vascular underperfusion and are thus etiologically distinct from retroplacental hematomas.[6]”