

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)	Development of the OPAL prediction model for prediction of live birth in couples with recurrent pregnancy loss: protocol for a prospective and retrospective cohort study in the Netherlands
AUTHORS	Youssef, Angelos; van der Hoorn, Marie-Louise; van Eekelen, Rik; van Geloven, Nan; van Wely, Madelon; Smits, Myrthe A.J.; Mulders, Annemarie; van Lith, Jan; Goddijn, Mariëtte; Lashley, Eileen

VERSION 1 – REVIEW

REVIEWER	Carlo Ticconi University of Rome Tor Vergata
REVIEW RETURNED	31-May-2022

GENERAL COMMENTS	<p>This study protocol is aimed to predict pregnancy success in couples with Recurrent Pregnancy Loss (RPL). The issue is clinically relevant and debated in the field of RPL and is worth to be investigated.</p> <p>The proposing group is engaged in the research on RPL with success and already published relevant articles on this matter.</p> <p>Overall, the protocol is very well structured in all its parts. There are several points that should be addressed/considered by the authors in order to further improve the protocol as well as the final outcomes of this relevant and challenging study.</p> <p>Introduction There are recently published studies showing that the successive pregnancy after intake visit for RPL can have significant rates of obstetrical complications (Ticconi C., Pietropolli A., Specchia M., Nicastrì E., Chiramonte C., Piccione E., Scambia G., Di Simone N. Pregnancy-Related Complications in Women with Recurrent Pregnancy Loss: A Prospective Cohort Study. J. Clin. Med. 2020;9:2833. doi: 10.3390/jcm9092833.)(Roepke E.R., Christiansen O.B., Källén K., Hansson S.R. Women with a History of Recurrent Pregnancy Loss are a High-Risk Population for Adverse Obstetrical Outcome: A Retrospective Cohort Study. J. Clin. Med. 2021;10:179). This could be taken into account in the introduction section.</p> <p>Study outcomes The pregnancy complications since intake should be reported in detail</p> <p>Tab. 1, RPL examination: did the authors consider to include TSH assay, that is strongly recommended by ESHRE 2019 Guidelines?</p> <p>The study population to be included in the research protocol will be</p>
-------------------------	---

	<p>composed by women with known causes of RPL (“explained RPL”) and by women with unexplained RPL. Did the authors plan to stratify the outcomes according these two major diagnostic categories?</p> <p>Some of the study women underwent or will undergo treatments, whose impact should be taken into account in a predictive model.</p>
--	---

REVIEWER	Frederic Blavier UZ Brussel
REVIEW RETURNED	04-Jul-2022

GENERAL COMMENTS	<p>The article is well written. The objective, the method and the discussion are clear and relevant. But some important predicting or prognostic factors are forgotten. After minor revisions, this manuscript could be accepted.</p> <p>Some previously published predicting/prognostic factors are missing. They should be studied or at least discussed. Serum progesteron levels, serum uric acid levels, corpus luteum aspect or corpus luteum score (Doppler) and eventually endometrial microbiotome should be considered.</p>
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Carlo Ticconi, University of Rome Tor Vergata

Comments to the Author:

This study protocol is aimed to predict pregnancy success in couples with Recurrent Pregnancy Loss (RPL). The issue is clinically relevant and debated in the field of RPL and is worth to be investigated.

The proposing group is engaged in the research on RPL with success and already published relevant articles on this matter.

Overall, the protocol is very well structured in all its parts. There are several points that should be addressed/considered by the authors in order to further improve the protocol as well as the final outcomes of this relevant and challenging study.

- We thank the reviewer for the compliments and comments which will be answered on a point-to-point basis.

Introduction

There are recently published studies showing that the successive pregnancy after intake visit for RPL can have significant rates of obstetrical complications (Ticconi C., Pietropolli A., Specchia M., Nicastrì E., Chiramonte C., Piccione E., Scambia G., Di Simone N. Pregnancy-Related Complications in Women with Recurrent Pregnancy Loss: A Prospective Cohort Study. J. Clin. Med. 2020;9:2833. doi: 10.3390/jcm9092833.)(Roepke E.R., Christiansen O.B., Källén K., Hansson S.R. Women with a History of Recurrent Pregnancy Loss are a High-Risk Population for Adverse Obstetrical Outcome: A Retrospective Cohort Study. J. Clin. Med. 2021;10:179). This could be taken into account in the introduction section.

- We thank the reviewer for suggesting relevant literature. We have added the suggested references in the introduction, mentioning that obstetric complications are not part of current prediction models.

Study outcomes

The pregnancy complications since intake should be reported in detail

- We have described that we will report and study the pregnancy complications under study outcomes.

Tab. 1, RPL examination: did the authors consider to include TSH assay, that is strongly recommended by ESHRE 2019 Guidelines?

- Indeed, this is part of regular examination. We thank the reviewer for this remark. We have added this to the table.

The study population to be included in the research protocol will be composed by women with known causes of RPL (“explained RPL”) and by women with unexplained RPL. Did the authors plan to stratify the outcomes according these two major diagnostic categories?

- We agree with the reviewer that it is important to distinguish between these groups. For this reason, the predictor “identification of an associated RPL factor” is included in our prediction model. See under header “study outcomes”.

Some of the study women underwent or will undergo treatments, whose impact should be taken into account in a predictive model.

- We definitely agree that treatments might impact study results. However, treatments for unexplained RPL have not been shown to improve live birth rates. In the new ESHRE guideline, progesterone treatment in women with three or more pregnancy losses that present with vaginal blood loss in early pregnancy might be started. If future studies confirm this treatment regimen or show that certain treatments improve the outcome in women with unexplained RPL, we will update the prediction model with that treatment as predictor.

Reviewer: 2

Dr. Frederic Blavier, UZ Brussel, Centre hospitalier Orange

Comments to the Author:

The article is well written. The objective, the method and the discussion are clear and relevant. But some important predicting or prognostic factors are forgotten. After minor revisions, this manuscript could be accepted.

Some previously published predicting/prognostic factors are missing. They should be studied or at least discussed. Serum progesteron levels, serum uric acid levels, corpus luteum aspect or corpus luteum score (Doppler) and eventually endometrial microbiotome should be considered.

- We thank the reviewer for the compliments and suggestions. As predictor finding studies in recurrent pregnancy loss are not widely available, it is unknown whether the suggested predictors/prognostic factors qualify for inclusion in this prediction model. Furthermore, we have decided to adhere to the latest ESHRE guidelines, and all the suggested factors by the reviewer are not recommended to be performed by these guidelines and therefore will not be studied in this study. In addition, we have performed a literature search to include those predictors that are shown to have a prognostic role in RPL.

VERSION 2 – REVIEW

REVIEWER	Carlo Ticconi University of Rome Tor Vergata
REVIEW RETURNED	10-Aug-2022

GENERAL COMMENTS	All the questions raised have been properly met.
-------------------------	--

REVIEWER	Frederic Blavier UZ Brussel
REVIEW RETURNED	26-Aug-2022
GENERAL COMMENTS	Congratulations for your great work! It could be improved by including other predictors of miscarriage, at least serum progesterone levels and treatments, and potentially US aspect of corpus luteum (which secretes progesterone), endometrial microbiome (presented in ESHRE congress 2022).