Identify, appraise and individualize: clinical practice and prediction models in recurrent pregnancy loss

Youssef, A.

9

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

A. Youssef, M.L.P. van der Hoorn, R. van Eekelen, N. van Geloven, M. van Wely, M.A.J. Smits, A.G.M.G.J. Mulders, J.M.M. van Lith, M. Goddijn and E.E.L.O. Lashley

ABSTRACT

INTRODUCTION

Recurrent pregnancy loss (RPL) is defined as the loss of two or more conceptions before 24 weeks gestation. Despite extensive diagnostic workup, in only 25%–40% an underlying cause is identified. Several factors may increase the risk for miscarriage, but the chance of a successful pregnancy is still high. Prognostic counselling plays a significant role in supportive care. The main limitation in current prediction models is the lack of a sufficiently large cohort, adjustment for relevant risk factors, and separation between cumulative live birth rate and the success chance in the next conception. In this project, we aim to make an individualised prognosis for the future chance of pregnancy success, which could lead to improved well-being and the ability managing reproductive choices.

METHODS AND ANALYSIS

In this multicentre study, we will include both a prospective and a retrospective cohort of at least 931 and 1000 couples with RPL, respectively. Couples who have visited one of three participating university hospitals in the Netherlands for intake are eligible for study participation, with a follow-up duration of 5 years. General medical and obstetric history and reports of pregnancies after the initial consultation will be collected. Multiple imputation will be performed to cope for missing data. A Cox proportional hazards model for time to pregnancy will be developed to estimate the cumulative chance of a live birth within 3 years after intake. To dynamically estimate the chance of an ongoing pregnancy, given the outcome of earlier pregnancies after intake, a logistic regression model will be developed.

ETHICS AND DISSEMINATION

The Medical Ethical Research Committee of the Leiden University Medical Centre approved this study protocol (N22.025). There are no risks or burden associated with this study. Participant written informed consent is required for both cohorts. Findings will be published in peer-reviewed journals and presentations at international conferences.

TRIAL REGISTRATION NUMBER

NCT05167812

INTRODUCTION

Recurrent pregnancy loss (RPL) is defined as the loss of two or more conceptions before 24 weeks of gestation (1). This condition affects approximately 1-3% of all fertile couples (2, 3). RPL is a highly heterogeneous condition with multiple known maternal risk factors, varying from auto-immune diseases (antiphospholipid syndrome (APS), antithyroid antibodies), parental balanced chromosomal translocations and congenital uterine abnormalities to advanced maternal age, maternal smoking and alcohol consumption. Besides these maternal factors, a potential contribution of paternal factors (such as male age, lifestyle factors and DNA fragmentation) has been recognized to add to the risk for miscarriages (4, 5, 6).

Despite extensive diagnostic work-up offered to couples with RPL, underlying risk factors can be identified in only 25-40% of couples (7, 8). Limited understanding of mechanisms underlying RPL has the consequence that effective treatment options are often lacking. When no evidence-based therapeutic options are available for couples with RPL, clinical management is primarily focused on providing supportive care. Supportive care and intensive pregnancy surveillance in the first weeks of gestation are assumed to be of influence in the prevention of new pregnancy loss (9).

Part of this supportive care is counselling on the prognosis and live birth rate of subsequent pregnancies in couples with RPL. Recently we conducted a systematic search to identify and assess the methodological quality of existing prediction models [Youssef et al, submitted for Fertility and Sterility 2021]. This review included the two most frequently used models which provide an estimate of subsequent chance of ongoing pregnancy/live birth in couples with unexplained RPL (10, 11). The model of Lund, et al. is actually not suitable for individual risk assessment, as stated by the authors themselves (11). The model of Brigham, et al. has been implemented in RPL care in the Netherlands and the United Kingdom, (10, 12, 13). These studies however did not follow the nowadays recommended TRIPOD guideline in the development and reporting of the model (14). For example, neither of the studies were internally nor externally validated and this could influence the validity and performance of the model. Recently, we showed that the

Brigham prediction model has poor performance in a Dutch RPL cohort, possibly due to a low number of patients included and a substantial change of the RPL population since 1999, in light of changes in defining unexplained RPL (15).

Most studies only concentrate on the first pregnancy after intake as primary outcome of the model, which lacks future perspective for couples with RPL. In addition, all earlier prediction models focused on the unexplained RPL population and on maternal predictors. None of them incorporated different causes for RPL, nor did they include paternal factors to establish a prediction specific to individual couples (16).

Individual couples with RPL now have an unclear prognosis of future success in terms of having a live birth. The aim of the current project is therefore to develop a prediction model that is able to provide tailormade estimations of pregnancy success in couples with both unexplained and explained RPL, and secondarily to develop a dynamic model that adjusts future chances based on pregnancies after intake.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

To predict the chance of a live birth within three years after intake in couples with unexplained RPL.

SECONDARY OBJECTIVES

- To predict the chance of an ongoing pregnancy (>12 weeks) in the next pregnancy in couples with unexplained RPL.

- To predict the chance of a complicated pregnancy in couples with unexplained RPL (preeclampsia, HELLP, eclampsia, gestational diabetes, gestational hypertension, preterm birth, low birth weight).

- To predict the chance dynamically of a live birth given the outcome of a pregnancy after intake.

- To predict the chance of above outcomes in couples with a known cause for RPL.

METHODS AND ANALYSIS

STUDY DESIGN

A multicenter hospital-based prospective and retrospective cohort study to develop a prediction model. This study has a total expected duration of 5 years (Figure 1).

ELIGIBILITY CRITERIA

Couples with the following criteria at intake visit will be included:

1. RPL in the current relationship: defined as the loss of ≥ 2 preceding pregnancies. These pregnancy losses include:

    - All pregnancy losses before the 24th week of gestation verified by ultrasonography or uterine curettage and histology

    - Non-visualized pregnancies (including biochemical pregnancy losses and/or resolved and treated pregnancies of unknown location), verified by positive urine or serum human chorionic gonadotropin (hCG)

    - Both consecutive and non-consecutive pregnancy losses

2. Dutch or English speaking by either the male or the female of the couple

3. Couples with females aged ≤42 years

Couples will be excluded in case of mental or legal incapability of either male or female, or in case of < 2 pregnancies in current relationship.

Table 1	Collection of clinical characteristics
Female	Date of birth, female age, alcohol consumption, smoking, caffeine intake, drugs intake, exercise pattern, education, BMI, blood pressure, general medical history (hypertension, diabetes mellitus, surgeries, earlier blood transfusions), use of medication, ethnicity and family history.
Male	Date of birth, male age, alcohol consumption, smoking, caffeine intake, drugs intake, exercise pattern, education, BMI, general medical history (hypertension, diabetes mellitus, surgeries etc.), use of medication, ethnicity and family history.
Obstetric history	Parity, number of miscarriages, ectopic pregnancies or induced abortions, mode of conception, mode of delivery of previous births, gestational age at previous births, birth weight of children of previous births.
RPL examination	Presence of APL (anticardiolipin IgG and IgM, β2 glycoprotein I antibodies IgG and IgM, and lupus anticoagulant), presence of thyroid antibodies, parental chromosomal abnormalities and presence of congenital uterine anomalies.

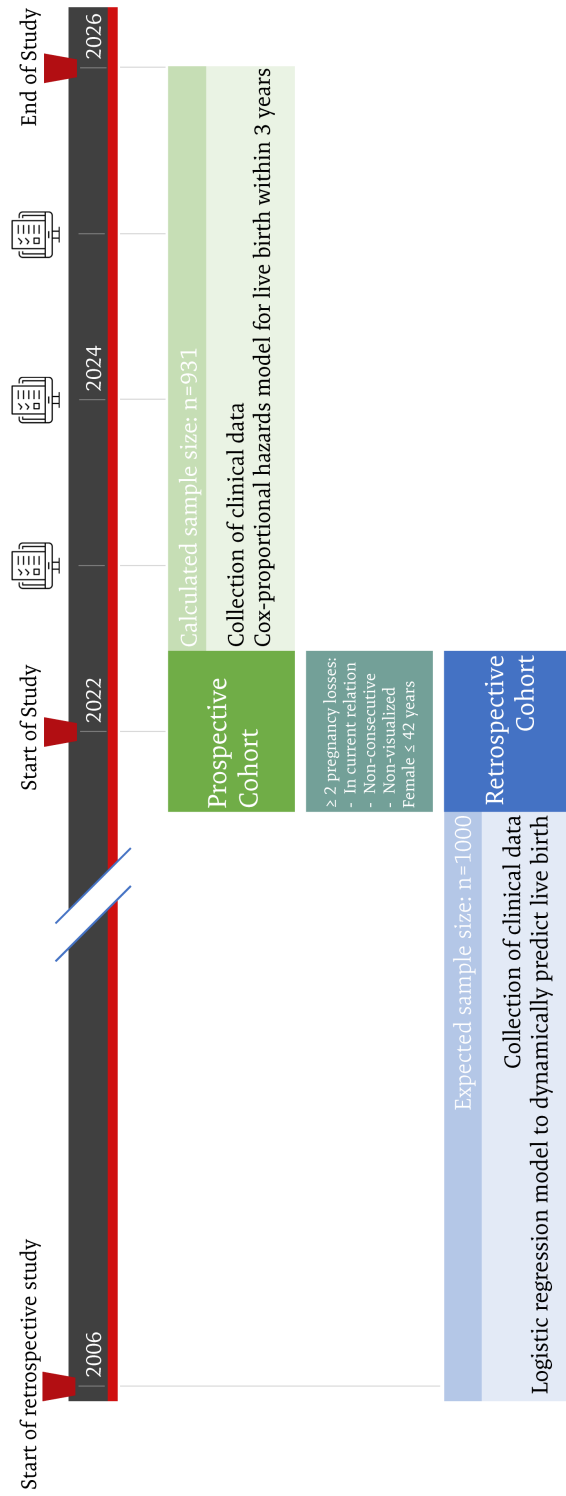BMI: body mass index; RPL: recurrent pregnancy loss.

Figure 1: Schematic diagram of study design

STUDY POPULATION AND RECRUITMENT

RPL couples that visit the RPL outpatient clinic of the Leiden University Medical Centre (LUMC), or early pregnancy unit of the Erasmus University Medical Centre (Erasmus MC) or Amsterdam University Medical Centre (AUMC) will be assessed for eligibility. The LUMC is the coordinating centre. After referral, couples will have an intake at one of the aforementioned centres, where they will be invited to participate in this study. If eligibility criteria are met, and in case of consent, couples will be selected for inclusion. In addition to this prospective inclusion of patients, couples that have visited the aforementioned clinics between 2006 and 2021 will be included retrospectively.

Couples will receive written information about both the prospective and retrospective cohort, and a concomitant informed consent form. The informed consent consists of a request to obtain data from their medical records for this study, together with a request to obtain data from other medical professionals in case pregnancies were monitored in other centres. Study information underlines that participation is voluntary, and that couples are free to withdraw from the study at any time point without any consequences.

STUDY PROCEDURES

General medical history, lifestyle data and obstetric history will be collected for all couples (see table 1). Data will be collected during the initial intake visit. Uniformity in data collection between the participating centres will be ensured through templates. Digital surveys will be sent to participating couples to obtain additional data. All information will be stored in the electronic data capture software Castor EDC.

Couples participating in the prospective cohort will be followed for a total of 5 years after initial visit. Annual questionnaires will be digitally sent to obtain data of new pregnancies and/or changes in health or lifestyle. If follow up has taken place in one of the participating centres, couples will not have to fill in these questionnaires, but data will rather be obtained during consultation. Couples participating in the retrospective cohort will receive an online questionnaire in case of missing data.

CONTROL OF BIAS

According to the PROBAST-tool (17), risk of bias in prediction model development studies can be divided into four domains: participants, predictors, outcome and analysis. Study population is clearly defined, minimizing selection bias in the participants domain. As clinicians in the participating centres perform intakes in a semi-standardized manner, predictors will be assessed in a similar way for all participants. The outcome is clearly defined and determined: urine or serum hCG

measurement or heartbeat on ultrasound determine an ongoing pregnancy. To ensure that the analysis domain is not at risk of bias, the PROBAST-items of that domain will be followed. For the retrospective cohort, there is a risk of recall bias. Since intake visits are semi-structured, information at baseline is moderately similar across all inclusions. For additional information that has to be collected retrospectively, we aim to minimize recall bias by avoiding recall periods longer than five years.

SAMPLE SIZE CALCULATION

The method of Riley et al. for the sample size calculation in prediction models is used (18). This method consists of four steps and four different sample sizes, after which the largest one is selected as the study sample size. The four steps ensure a precise estimate of the overall outcome risk, predicted values with a small mean error across all individuals, a small required shrinkage of predictor effects and a small optimism in apparent model fit. Using an anticipated outcome proportion of 0.65 (live birth), 12 predictor parameters, a shrinkage of 0.9 and an anticipated R2cs of 0.1089, the largest sample size and thus this study's sample size is 931.

STUDY OUTCOMES

The following predictors were selected based on current literature, and will be assessed at intake (8, 10, 11, 19, 20, 21):

- Female age as a continuous variable

- Male age as a continuous variable

- Female BMI as a continuous variable

- Male BMI as a continuous variable

- Current female smoking as a categorical variable

- Current male smoking as a categorical variable

- Number of pregnancy losses as a categorical variable (2, 3, 4 and 5 or more)

- Heartbeat on ultrasound in obstetrical history as a binary variable

- ART in previous pregnancies as a binary variable

- Identification of an associated RPL factor as a binary variable

The following outcomes will be studied:

- Live birth within three years after initial intake visit (defined as the birth of a living child after 24 weeks gestation)

- Pregnancy outcomes since intake

- Time to pregnancy since intake

- Time between pregnancies since intake

- Pregnancy complications since intake

STATISTICAL ANALYSIS PLAN

For the primary outcome (live birth within three years after intake), we will develop a Cox proportional hazards model for time to pregnancy, including couples without full 3- or 5-year outcome information. For the secondary outcome, a logistic regression model for the binary outcome live birth in couples who conceived after their RPL intake will be developed. This will be used to dynamically predict live birth, given the outcome of pregnancies after intake

We will consider both simple linear and non-linear (restricted cubic splines) functions for continuous variables. The best fitting model is selected based on the Akaike Information Criterion which reflects the trade-off between information and model complexity (variable selection). Measurement of the AUC, the Brier score, the Brier skill score, and calibration of the model will be performed (Model performance). Internal validation will be performed using the bootstrapping method.

To cope with analysis of missing values (missing at random, missing completely at random), multiple imputation will be performed. Once the dataset is complete, cross validation of the previously selected variables will be performed, variables with a low predictive strength will be excluded.

External validation will be performed using data of Dutch academic hospitals which have not participated in this study.

PATIENT AND PUBLIC INVOLVEMENT

The Dutch association for patients with fertility problems (Freya) was consulted during the development of the study protocol. Study information will be published on their website, and information on progress and results will be presented to patients during meetings organized by Freya.

ETHICS AND DISSEMINATION

This study will be conducted according to the principles of the Declaration of Helsinki. The Medical Research Ethics Committee of the Leiden University Medical Centre provided ethical approval for this study (N22.025). There are no risks or burden involved in this study. All data will be collected during regular hospital visits or via questionnaires. Eligible couples will have sufficient time to decide on participating in this study, after having received written information. The Castor

EDC database of the OPAL study will contain all clinical and survey data. This database will not include directly traceable patient data. The findings of this study will be disseminated via peer reviewed publications and presentations at international conferences.

DISCUSSION

The perspective of a live birth is one of the most important aspects of RPL. Prognostic counselling plays a very important role in the RPL clinical practice, especially in the absence of an underlying risk factor and with the lack of treatment options. Different prognostic tools exist and are implicated in RPL care in the Netherlands and the United Kingdom, but these tools often are often of low quality [Youssef et al, submitted for Fertility and Sterility 2021].

In order to enable prediction of a live birth within three years or longer after initial intake visit, or to dynamically predict the chance of a live birth, a longer follow-up period is necessary. In this study proposal we will therefore include our patients not only prospectively, but also retrospectively. Retrospective inclusion is however known for recall bias. The initial intake visit is according to a semi-structured interview, thus minimizing differences between inclusion data across the retrospective cohort. In case of missing data, we will aim to minimize recall bias by avoiding recall periods longer than five years.

Another limitation of this study regards the predictors included in the model. There are various factors that are associated to RPL (such as sperm DNA fragmentation), that could possibly improve model performance, but we currently lack data to include these factors in a prediction model (22). Secondly, the predictor "identification of an associated RPL factor" does not specify the associated factor, something that would help counselling RPL couples. Of course, as there are several factors that could be categorized, the sample size needed for the inclusion of these factors would be much higher.

The ultimate goal of this study is therefore to accurately predict chances for future successful pregnancies, in order to aid expectation management, and provide a perspective for RPL couples. The outcomes of this study will provide tailormade and individual prognostic assessments of live birth in couples with RPL, and will have to be externally validated to ensure generalizability.

REFERENCES

1. Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, et al. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open. 2018;2018(2):hoy004.

2. Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Human reproduction (Oxford, England). 2006;21(9):2216-22.

3. Rai R, Regan L. Recurrent miscarriage. Lancet. 2006;368(9535):601-11.

4. McQueen DB, Zhang J, Robins JC. Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis. Fertility and sterility. 2019.

5. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ (Clinical research ed). 2000;320(7251):1708-12.

6. Venners SA, Wang X, Chen C, Wang L, Chen D, Guang W, et al. Paternal smoking and pregnancy loss: a prospective study using a biomarker of pregnancy. American journal of epidemiology. 2004;159(10):993-1001.

7. Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy losses. Fertility and sterility. 2010;93(4):1234-43.

8. Youssef A, Lashley L, Dieben S, Verburg H, van der Hoorn ML. Defining recurrent pregnancy loss: associated factors and prognosis in couples with two versus three or more pregnancy losses. Reproductive biomedicine online. 2020;41(4):679-85.

9. Liddell HS, Pattison NS, Zanderigo A. Recurrent miscarriage--outcome after supportive care in early pregnancy. The Australian & New Zealand journal of obstetrics & gynaecology. 1991;31(4):320-2.

10. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Human reproduction (Oxford, England). 1999;14(11):2868-71.

11. Lund M, Kamper-Jorgensen M, Nielsen HS, Lidegaard O, Andersen AM, Christiansen OB. Prognosis for live birth in women with recurrent miscarriage: what is the best measure of success? Obstetrics and gynecology. 2012;119(1):37-43.

12. NVOG. Herhaalde Miskraam 2007 [08/06/2007:[Available from: www.nvog-documenten.nl/richtlijn/doc/download.php?id=750.

13. RCOG. The Investigation and Treatment of Couples with Recurrent Firsttrimester and Second-trimester Miscarriage. 2011.

14. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. BMC Med. 2015;13:1.

15.   Youssef A, van der Hoorn MLP, Dongen M, Visser J, Bloemenkamp K, van Lith J, et al. External validation of a frequently used prediction model for ongoing pregnancy in couples with unexplained recurrent pregnancy loss. Human reproduction (Oxford, England). 2021.

16.   du Fosse NA, van der Hoorn MP, de Koning R, Mulders A, van Lith JMM, le Cessie S, et al. Toward more accurate prediction of future pregnancy outcome in couples with unexplained recurrent pregnancy loss: taking both partners into account. Fertility and sterility. 2022;117(1):144-52.

17.   Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med. 2019;170(1):W1-W33.

18.   Riley RD, Ensor J, Snell KIE, Harrell FE, Jr., Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. BMJ (Clinical research ed). 2020;368:m441.

19.   du Fosse NA, Lashley E, van Beelen E, Meuleman T, le Cessie S, van Lith JMM, et al. Identification of distinct seminal plasma cytokine profiles associated with male age and lifestyle characteristics in unexplained recurrent pregnancy loss. Journal of reproductive immunology. 2021;147:103349.

20.   Sugiura-Ogasawara M, Ozaki Y, Kitaori T, Suzumori N, Obayashi S, Suzuki S. Live birth rate according to maternal age and previous number of recurrent miscarriages. American Journal of Reproductive Immunology. 2009;62(5):314-9.

21.   Kling C, Magez J, Hedderich J, von Otte S, Kabelitz D. Two-year outcome after recurrent first trimester miscarriages: prognostic value of the past obstetric history. Archives of gynecology and obstetrics. 2016;293(5):1113-23.

22.   du Fosse NA, van der Hoorn MP, van Lith JMM, le Cessie S, Lashley E. Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis. Human reproduction update. 2020;26(5):650-69.