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

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CHAPTER 10

SUMMARY AND GENERAL DISCUSSION

Although RPL has been studied for almost a century, it is still a poorly understood condition that has a large impact on couples, which is intensified with each further loss experienced. Ideally, all underlying mechanisms of RPL are known and effective therapies targeted at these mechanisms are available. In the majority of RPL patients, the cause for RPL is aneuploidy, which lacks therapeutic options. In women with higher number of pregnancy losses, the proportion of aneuploid embryos could possibly be lower (1). It leaves the clinician to guide couples without having targeted therapeutic options, in which counselling towards future pregnancies is key. In this thesis we therefore aimed to identify current RPL practice to get a better understanding of the different concepts of definition, investigations and treatments in RPL, to appraise existing evidence that could impact counselling of RPL couples in order to individualize RPL care and management.

In summary, in this thesis we conclude that practice variation in clinical management of couples with RPL is present, both on local, national level as well as on international scale. Several barriers exist for RPL guideline implementation in the Netherlands; we identified possibilities to focus on implementation strategies. We found that currently existing prediction models, that estimate the chance of future live birth in women with RPL are not accurate, and should not be used in daily clinical practice. These results opened up various new research questions to be explored, one of which is the development of a new prediction model for which the study protocol is included in this thesis.

IDENTIFYING

Practice variation is present between various countries (2). This is particularly the case for medical conditions for which evidence regarding investigations and treatments are not based on undeniable evidence. On the other hand, little was known on practice variation that exists within a country, even in the presence of a national guideline. **Chapter 2** shows a comparison of seven local Dutch RPL protocols that have been compared to each other and to the Dutch NVOG guideline (3). Although the differences found between protocols were merely in the details of performing investigations, it reflects that practice variation is even present on a local, national level. It could leave couples with questions why different strategies

are available in different hospitals, which might lead to cross-border reproductive care (CBRC). Some practice variation is justified, for example because of varying patient characteristics such as ethnicity and accompanied risk profiles for certain diseases, and varying access to health care. Unwarranted practice variation however could impact various stakeholders, as effective care could potentially be underused and ineffective care could be overused. This could push healthcare costs up, while patient outcomes remain the same or even worse (4, 5). The emphasis should therefore not lie on clinicians' opinions, but rather on patient preferences after careful consideration of all medical evidence.

In **chapter 3** we analysed practice variation on an international level. We aimed to describe a methodology assessment (AGREE II) (6), summarize and compare the recommended definitions, risk factors, investigations and therapies of three prominent guidelines considering RPL. We found discrepancies between the guidelines across all aforementioned domains. Risk factors and investigations are generally similar between the compared guidelines, and the found discrepancies can be explained partly by their methods of development and the time of their publication, as well as the lack of strong evidence on some clinical aspects of RPL. This lack of evidence could also explain differences in treatment recommendation for uterine malformations and hereditary thrombophilia, for example. In general, the differences found in investigations and treatment recommendations create practice variation that could lead to CBRC. RPL couples are very much aware of investigations and treatments that are performed in other countries, and often seek these as a way of last resort, as they are in great distress of not being able to carry a pregnancy to term. Of course, psychological counselling, to support these couples in their distress and frustration, plays an essential role here. Additionally however is a universal, evidence-based RPL guideline derived from large associations such as the European Society for Human Reproduction and Embryology (ESHRE), Royal College of Obstetricians and Gynaecologists (RCOG) and American Society for Reproductive Medicine (ASRM) to ensure that couples with RPL all over the world receive comparable and evidence-based investigations and treatment options (7-10). In fact, only one guideline is needed, as all societies aim to develop an evidence-based guideline. A lot of work is being put into the development of these guidelines, which if bundled together might achieve

this universal guideline which will improve PRL practice variation across many countries. Of course, not all the recommendations are applicable to all populations worldwide, but if countries are similar in terms of medical services and populations, guidelines could be unified and tweaked according to local healthcare structures and organizations. One of the major hurdles in the universal application of one guideline is the inconsistency of the definition criteria of RPL, which appears to be a discussion based on opinions rather than evidence. If not internationally consistent, it will inherently lead to discrepancies in therapy of RPL. The definition will also have significant resource implications, as it will define when and when not to start performing investigations.

The previous chapters have shown that guidelines differ on both a national as well as international level. As the Dutch RPL guideline is currently being adapted from the ESHRE guideline, we aimed to detect possible barriers of implementing a new evidence-based guideline. **Chapter 4** describes a questionnaire study conducted across all gynaecology and obstetrics clinics in the Netherlands that identifies current clinicians' management and views on RPL practice. We observed that Dutch clinicians generally adhere to evidence-based investigations and therapeutic interventions in RPL care, but there is room for improvement. The main differences in guideline recommendation and clinician's RPL practice lies in the investigations performed and treatments considered, such as couple karyotyping, hereditary thrombophilia screening, thyroid function and auto-immunity testing and β2-glycoprotein antibodies testing in the context of APS. Differences were also found in APS treatment, where the starting order of LMWH and aspirin is based on expert opinion in the absence of evidence. The most frequently described non-evidence-based treatments were progesterone and aspirin in unexplained RPL. The use of aspirin or LMWH is not recommended in patients with unexplained RPL, as no significant benefits for any – or combination - of these anticoagulants was shown in comparison to placebo (11). The use of progesterone has been extensively studied for patients with unexplained RPL. The recommendation of the ESHRE guideline to not recommend progesterone treatment is based on the most recent and high-quality trial (12). In this chapter however, we were not able to examine the reason behind the differences in RPL practice in

this chapter. Future interview studies could be conducted to clarify why clinicians choose to offer non-evidence-based care.

As stated, and based on the present practice variation on local, national and international level, the development of one evidence-based RPL guideline is needed, that might be tweaked according to local healthcare structures and organizations. However, the existence of such an ideally available guideline is not enough, as dissemination of new guidelines is found to be insufficient to achieve proper guideline adherence. Implementation strategies are necessary to ensure guideline adherence (13, 14). The objective of **chapter 5** was to test a multi-faceted implementation strategy to improve healthcare professional's adherence to the RPL guideline. We found that four elements were directly related to higher adherence; the specified medical chart file, patient questionnaire, pocket card and electronic decision program. Adherence was significantly higher on most indicators on diagnostics and counselling. Prior to the strategy, 9 out of 21 measurable indicators showed an adherence below 50%, and after using implementation strategies, adherence was below 50% for just three out of 21 indicators. The highest increase was measured for selective screening for thrombophilia (+37%, Odd Ratio (OR) 5.2, 95% Confidence Interval (CI) 3.6-7.6). For counselling, the highest increase was measured for advising patient and partner to quit smoking (+50%, OR 13, 95% CI 4.8- 33). These strategies resulted in health care costs reduction of 206,916 euros annually in the four participating centres. This cost reduction, when extrapolated to all RPL clinics in the Netherlands, would potentially be even higher.

In the previous chapters we have identified several lessons in translating theoretical RPL guidelines to daily RPL practice. Both literature and clinical experience teaches that RPL is a frustrating condition with significant negative psychological impact on the patient. Many patients may feel the need to explore alternative care in other centres, both nationally and internationally. Organizing RPL care in a unified way may therefore also diminish this necessity felt by patients to turn to multiple, cross border opinions. This idea is supported by a comparable study to **chapter 4**, where Manning et al. showed equivalent results regarding practice variation (15). Their arguments revolve around the fact that in many practices no dedicated RPL specialists are present. A lead RPL clinician within each hospital or clinic could reduce variation and could result in a consistent approach of

managing RPL couples. Continuing onwards, differences exist between countries as well, which is probably the largest incentive for CBRC in RPL couples. Where options for investigations and treatments may be limited in one country, couples could travel to other countries in hope to increase their chances of a successful pregnancy. It is important for clinicians to realize that differences in RPL guidelines exist, increasing the number of investigations and treatments offered to couples attending RPL clinics. Knowledge of these differences should then be turned into counselling couples, assuring them that even though other clinics might provide other options, that current clinical practice is the best care possible. As mentioned earlier, a universal guideline should negate this issue of national healthcare societies recommending different strategies. Moreover, when obstetrics and gynaecology societies develop such a guideline together, this could ultimately be more cost-efficient, compared to these societies developing a guideline separately. In this way, societies could collectively present the same evidence-based guideline, adapted to the facilities of each country.

In chapter 5 we have also identified that implementation strategies for new guidelines are effective in increasing guideline adherence. Literature has shown that dissemination of guidelines alone is not enough for proper adherence, but no gold standards exist for developing strategies aiding implementation of updated or new guidelines. Lack of adherence to guidelines could result in under, as well as over diagnostics and treatments, which in turn leads to increasing health care costs. This is not only a theory, but the efficacy of implementation strategies is proven in chapter 5.

Overarching societies like the ESRHE could play a central role in implementation strategies. Next to the development of a unified evidence-based guidelines, every guideline should contain an implementation section. The efficacy of selected implementation strategies could be studied and adapted in the future for updated versions of the guideline. The ESHRE as overarching European society could work more closely with local societies to translate guidelines, and finetune implementation strategies according to the need of a specific obstetrics and gynaecology society. Working together will eventually lead to less practice variation, higher guideline adherence and therefore cost reduction and higher quality of care.

APPRAISING

Through the years, RPL definition and associated risk factors have been discussed extensively. There is no pathophysiological prove that distinguishes between women with two and women with three or more pregnancy losses, however there is some evidence that the probability of having certain associated factors such as APS and carrier status of structural chromosomal abnormalities are not different (16, 17). Chapter 6 provides insight in the occurrence of RPL associated risk factors, as well as a comparison in those with two pregnancy losses, and those with three or more pregnancy losses. We found that RPL associated factors occur with equal frequency in those two groups. Appraising this cohort provides evidence towards choosing two pregnancy losses as definition of RPL. Having established that the known risk factors are comparable across the two groups, one could argue that women with two pregnancy losses in their obstetric history should be eligible for RPL investigations and counselling, especially knowing that RPL couples carry a deep burden of not being able to successfully reproduce. By presenting at an early stage in their reproductive path with two failed pregnancies in hindsight, supportive care could be initiated at an early time point.

One of the most asked questions of RPL couples relates to their future: "will we carry a pregnancy successfully resulting in a live birth? And if so, how high is our chance of doing so?"

In chapter 6 we described that chances of having a future ongoing pregnancy are relatively high even though this chance decreases with an increasing number of pregnancy losses. In 83.5% of women included in the study, an ongoing pregnancy was reported). It is important to note that an ongoing pregnancy was defined as a pregnancy continuing after the 12th week of gestation. This high chance of a future ongoing pregnancy could be a comforting thought for couples suffering from RPL, however it does not indicate the chance of having a live birth, which is the ultimate goal for RPL couples. Furthermore, this prediction is for the whole cohort, and could not be applied on individual couples. To be able to finetune this, a prediction model is needed. Prediction models combine characteristics of individual patients to provide information about the likelihood of uncertain outcomes. Predicting live birth rate of subsequent pregnancies in RPL is an essential

part of supportive care, as information manages the expectations of the couple and improves their ability to make an informed decision regarding further pregnancy attempts.

Before using prediction models in clinical practice, it is of utmost importance that these models have been developed accurately, and have been validated internally and externally. Several prediction models for RPL exist and used in clinical practice, however they have never been critically appraised. Therefore, in **chapter 7** a systematic review has been conducted, aiming to find existing RPL prediction models and critically appraise them. As knowledge on development and validation of prediction models has increased throughout the years, tools have been published aiming to provide guidance for reporting all necessary prediction study items and for critically appraising risk of bias in prediction studies (18, 19). We showed that the seven included prediction models did not follow the recommended steps for prediction model development, including internal validation for the prevention of overfitting. None of the studies performed a sample size calculation, and retrospective sample size calculation showed that three studies were too small for the included number of prediction parameters (20-26). It is especially noteworthy that the preferred prediction models by the ESHRE for clinical use, Brigham et al. and Lund et al. (21, 24), were both shown to be at high risk of bias, reasons thereof including insufficient sample size and categorization of predictors. Other limitations include not reporting missing data, which in case of systematic reasons could lead to selection bias, and the inclusion of patients that have been treated with various therapeutics, which could impact the prognostic effect of selected predictors.

Besides limitations based on reporting of data, there are also limitations concerning the statistical validity and applicability of prediction models. Usually, predictive performance of prediction models is described using discrimination and calibration. Only two studies reported a c-statistic, a measure of the prediction model's discriminative ability, namely 0.642 for subsequent pregnancy risk calculation in Sugiura-Ogasawara's study and 0.62 in Bashiri's study, both considered moderately discriminative (20, 26). None of the included study in this chapter performed calibration of their model, which is arguably more important than assessing its discriminative ability as calibration assesses the fitness of data to the developed model.

Before using clinical prediction models in clinical practice both internal as external validation should be performed. Internal validation is important as the model is expected to perform well on its own data, since, the model was designed to fit the development data. Without internally validating a prediction model, overfitting could exist, meaning that the model will be less accurate when tested in a new RPL population. External validation is similar to internal validation, but performed in an unrelated cohort. It is needed to confirm that the developed prediction model is able to predict the outcome well enough in unrelated individuals to those of the development cohort. If external validation is performed, and the prediction model was found to perform well, implementation of the model could be considered.

In short, based on the results of this systematic review, at this moment we cannot recommend any prediction model in clinical practice. Though the use of prediction models is recommended by various guidelines, it is important to perform external validation to make sure that couples are counselled correctly.

Based on the conclusions and advices we formulated in **chapter 7**; an external validation study was performed on the most widely used and recommended RPL prediction models. In **chapter 8** we aimed to validate the prediction models of Brigham et al. and Lund et al. We learned from **chapter 7** that the prediction model of Lund et al. was not intended for individual risk assessment and did not calculate the chance of future pregnancy success individually. We therefore decided to only externally validate the prediction model as described by Brigham et al. In a cohort consisting of 739 women, with similar characteristics compared to Brigham's cohort (mean age of 33.1 years and a median of three pregnancy losses at intake), we showed that the mean predicted pregnancy success rate was 9.8 percentage points higher in the Brigham model than the observed pregnancy success rate in the dataset (73.9% vs 64.0% (CI 95% for the 9.8% difference 6.3% – 13.3%)) (21). Performance was measured using calibration and discrimination, with calibration showing overestimation of the model and too extreme predictions (negative calibration intercept of -0.46 (CI 95% -0.62 – -0.31) and calibration slope of 0.42 (CI 95% 0.11 – 0.73)). This calibration slope of < 1 suggests that the estimated risks are too extreme, which translates to a stronger effect of the

predictors used by Brigham compared to the validation dataset. The c-statistic, describing the discriminative ability of the model was 0.55 (CI 95% 0.51 – 0.59). This value ranges from 0.5 to 1.0, with 0.5 indicating prediction based on pure chance and 1.0 indicating perfect prediction. In short; the model overestimates, has too extreme predictions and has a poor discriminative ability.

The results of the external validation of the prediction model as developed by Brigham et al. could be regarded as a consequence of the high risk of bias discovered in **chapter 7**. The accuracy of prediction models is often lower in an unrelated cohort (27) and this also relates to for Brigham's model. A small cohort of RPL patients, the lack of internal and external validation probably resulted in the poor performance of this model. Even after model updating using recalibration, which re-estimates all used coefficients, no improvement was possible. The results of this study suggest that the currently most widely used prediction model for couples with RPL leads to a model that cannot discriminate between patients with or without a successful future pregnancy.

The current model's base prognosis on only two predictors: the number of previous pregnancy losses and maternal age. This leads to the following question whether the predictive ability of the model will improve when taking additional candidate predictors into account. Actually, which predictors should be included in future RPL prediction models, and how well the RPL prediction model should be able to discriminate between those with and without the desired outcome? Regarding the first question, the answer is that predictor finding studies in RPL are scarce, and that selecting predictors for inclusion in RPL prediction models is often done on theoretical grounds, rather than on grounds of a scientifically proven predictive association. Of course, in the absence of such predictor finding studies, this is the next best solution for now.

Next, the question is how good the predictive ability of the model should be to be used in clinical practice. The second question could be answered in two ways, either based on the values a c-statistic can hold or based on the multifactorial process that leads to pregnancy, and eventually the success or failure of pregnancy. Ideally, the higher the c-statistic, the better. However, prediction studies in pregnancy often find c-statistics lower than

0.65. It is known that pregnancy is indeed a multifactorial process, that is still not fully understood in terms of what leads to pregnancy success and what leads to failure. One can therefore discuss whether a prediction model could ever have a discriminative ability much higher than those described in current day literature.

Besides these performance measures, differences in cohort characteristics are important to take in mind, including differences in definitions and cohort populations. This will remain present as prediction models are time-dependent owing to scientific advances and population changes. It is therefore important that future prediction studies take this into account and allow for updating.

INDIVIDUALIZE

Having identified clinical RPL practice and having appraised prediction models aimed at improving counselling, it is time to take a look at the future and pave a pathway for individualization of RPL counselling. **Chapter 9** combines all lessons learned from both clinical practice and prediction studies, presenting a protocol for the development and validation of a new RPL prediction model, aiming to precisely and accurately predict future chances of live birth in couples with RPL, in the group with and without underlying risk factors.

The primary objective of this model is to predict the chance of a live birth within three years after first consultation in couples with unexplained RPL. This outcome was defined as more clinically relevant for patients than just knowing the outcome of the first pregnancy after intake. Secondly, the aim of the model is to dynamically predict the chance of a live birth given any outcome of pregnancy after intake.

In our protocol we carefully considered development and reporting according to the TRIPOD statement in order to ensure a scientifically valid model (18). In addition, the PROBAST-tool will be used to ensure risk of bias across the various domains of the study is minimized as much as possible (28). By involving all stakeholders including clinicians and patient organizations for couples with fertility problems, we aim to create a supporting base for the use of this model in the future. A well designed and

easy to use tool caters to the likelihood of this model being implemented in daily RPL care.

For model development, we selected variables found in the systematic literature search described in **chapter 7**. We are however limited regarding the inclusion of predictors due to sample size requirements. Various factors associated to RPL could possibly improve model performance (such as sperm DNA fragmentation), but data backing these factors are currently lacking (29). As mentioned previously, it is important to keep scientific and population changes throughout time in mind, and update this model when needed.

The ultimate goal of this study is to accurately predict chances for future successful pregnancies, by using as much predictive information as possible from both male and female partner, 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. Over time, this model should be a living, dynamically changing tool that is updated through time according to the latest evidence identified, and should be continuously appraised to keep providing the best possible individualized counselling.

SUPPORTIVE CARE

Supportive care is central to the management of RPL, especially in those couples without an identifiable factor (30-32). Specialised RPL unites could arrange supportive care perfectly, consisting of both psychological and medical help. Part of medical supportive care consists of counselling on the prognosis and live birth rate in future pregnancies. This is important information for couples, as it could help manage expectations and aid couples into making informed decisions regarding future pregnancy attempts. Based on the findings in this thesis, after having appraised various prediction models, a few items follow to consider in RPL prediction studies.

First of all, the predictors considered should be extensively reviewed. Up till now, mainly age and previous pregnancy losses are included. Although predictor findings studies are lacking, there are several known factors influencing spontaneous pregnancy loss, which are often lifestyle related (smoking, high BMI (33, 34)). As half of the product of conception is derived

from the male partner, male predictor parameters should be considered as well (29).

Besides predictors, it is also important to reconsider the outcome that is being predicted. Clinical experience tells that couples are not just interested in the first pregnancy after intake, but want to know their perspective in a time range of 3 to 5 years. Live birth in 3-5 years would therefore be more relevant as outcome for RPL prediction models. This could also help the clinician in adjusting supportive care strategies according to the predicted chances and couples' preferences for supportive care (35).

The findings of chapters 6, 7 and 8 pave a path towards individualized RPL care, in which counselling should be adapted to the individual needs of each couple. This concept of individualized RPL care could shift current practices to a more value-based organization of RPL care, in which matters that patients value the most are more closely incorporated in RPL practice. Value-based healthcare is a healthcare system in which (multidisciplinary) care is organized around a patient's medical condition. It targets the outcomes that make the biggest difference to patients, while driving cost efficiencies within health services. RPL care could benefit from this system as patient outcomes and values are central to the provided care. By analysing current practices and interviewing RPL couples, a set of high priority values could be selected, to which RPL care could be adapted. By continuously evaluating patient outcomes, this system allows for improvements over time in this RPL care path.

CONCLUSIONS AND A LOOK TOWARDS THE FUTURE OF RPL CARE

This thesis has shed light on RPL practice and the management of RPL couples in need of counselling towards future pregnancies. Both clinical practice research and prediction research indicate that there is room for improvements in RPL practice and RPL counselling. We studied quality of care by diving into clinical practice variation and quality of counselling by diving into prediction research.

It could be defeating to know that a large proportion of couples with RPL seem to not have any identifiable risk factor. It is understandable that both clinicians and patients seek options outside of guideline recommendation, being desperate in grasping every bit of hope that might lead to a live birth. Acknowledging practice variation and reasons hereto might shift the focus of research to study subjects that will improve effective, evidence-based care and above all maintain one of the most important principles in medicine: first, do no harm. This could be applied to investigations and treatments performed in RPL couples, but is also on RPL research in which low quality research harms the way our medical society perceives new evidence. Research output should focus on quality instead of quantity, and be focused on those questions that are most urgently waiting to be discovered.

In the absence of effective treatment options that increase live birth rates in RPL couples, counselling towards future pregnancies plays a key role and enables couples to make an informed decision regarding further pregnancy attempts. This key role for prediction models will still be present when future treatment options are investigated or discovered, as these models could then evaluate the effects of these treatments on performance of the model. It is therefore of utmost importance that prediction models are well-developed and validated for use in clinical practice.

In an era of technological advancement at high rates, bringing societies, researchers and clinicians from all over the world more closely together than ever, it is time to step up and work together, to unify RPL care and to create collaborations that hugely impact RPL research which can lead to high impact publications that can unravel the mysteries of RPL.

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