Obtaining the Relevant History

Ole B. Christiansen^{1,2}

 ¹Unit for Recurrent Miscarriage, Fertility Clinic 4071, Rigshospitalet, Copenhagen, Denmark
²Department of Obstetrics and Gynaecology, Aalborg University Hospital, Aalborg, Denmark

Introduction

In most clinics, patients referred with a diagnosis of recurrent miscarriage (RM) will normally come to a first consultation with a physician where information about the reproductive history and other medical information are collected, blood samples are taken, and other relevant investigations are carried out or planned.

Whereas authors in the area of RM often spend plenty of space in their articles to list the abundance of investigations undertaken in their clinic: hysteroscopy, endometrial biopsy, parental or fetal karyotyping, screening for thrombophilia, autoantibodies and microbiobes in addition to endocrine investigations, they spend very little space (if any) to describe the stringency and accuracy through which information has been obtained from the patients themselves or their hospital records. This reflects the modest emphasis most authors lay on reproductive and disease history compared with information obtained from other kind of investigations.

In this chapter, I will review information that we aim to collect at the first consultation at my clinic because we (i) find it important for assessing the spontaneous prognosis for live birth and (ii) it can often point toward etiological factors before any results from ultrasonic and laboratory investigations are obtained.

The relevant information achievable from the patients themselves or their case records can be divided into demographic data, reproductive history, disease history, and family history. The information should be obtained from both partners but the information concerning the women must be considered the most important.

Demographic data

The most important demographic data are information about parental age, body mass index (BMI), lifestyle, social class, and occupational factors in addition to information about the partner.

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Parental Age

High maternal age is one of the strongest negative prognostic factors known. Maternal age over 41–42 years will be decisive for a conservative treatment approach since the dominant risk factor for miscarriage in this age group is embryonal aneuploidy (especially trisomies), which can only be actively treated by IVF with egg donation. The impact of high paternal age on risk of miscarriage and RM is difficult to study since parental ages are strongly correlated and the only couples that are really informative are those few comprising a young woman and an elderly male. The evidence provided so far suggests that high paternal age per se indeed increases the risk of miscarriage, although much less than high maternal age.

BMI

The patients should be weighted and the height measured at the first consultation to obtain a reliable BMI since both BMI below 20 and over 30 have in some studies been reported to decrease the prognosis for live birth in women in the background population and among RM patients. However, a recent study from my clinic showed that high BMI did not exhibit any impact on subsequent miscarriage rate in RM patients with regular menstrual cycles who can conceive spontaneously. BMI may therefore only have an impact on subsequent miscarriage rate in patients with polycystic ovary syndrome who normally only can conceive after ovulation induction. Whether normalization of an abnormal BMI will improve the pregnancy prognosis in terms of miscarriage rate in these patients is still to be documented, but clearly, weight loss will decrease the risk of gestational diabetes and other late pregnancy complications.

Lifestyle Factors

The most important lifestyle factors of importance for RM are consumption of coffee, alcohol, and tobacco in addition to the extent of leisure-time exercise during pregnancy. Drug abuse is rare in RM women but should be monitored. Whereas information about coffee consumption is trustworthy, information about alcohol and tobacco use will probably be underestimated. In my clinic we tell patients that daily consumption of four or more cups of coffee (and tea and cola with an equivalent caffeine content) during pregnancy should be avoided since several studies have reported that this increases the risk of miscarriage in the general population.

Any use of alcohol at least in the first half of pregnancy should be strongly discouraged since just one to two drinks a week in the first trimester have been shown to double the miscarriage risk and there is also an increased risk of fetal alcohol syndrome.

Whereas there is no good proof that tobacco use increases the risk of early miscarriage, the patients should try to reduce smoking, primarily to diminish the risk of late pregnancy complications such as intrauterine growth retardation, preterm birth, and placental abruption – conditions strongly associated with both RM and smoking.

Information should be obtained about leisure-time exercise since recent research suggests that some kinds of high-impact exercise, defined as exercise more than 75 min a week, may increase miscarriage risk <14th week significantly with relative risks of 3.6–4.2 in pregnant women from the general population. Therefore, patients should be interviewed specifically about what kind of exercise they perform and for how many hours a week. If it is estimated that the patient practises too much "dangerous" exercise, she should be encouraged to reduce its intensity and duration.

Social Class

Low social class and low educational level are risk factors for perinatal complications such as preterm birth, which can only partly be explained by a more unhealthy lifestyle (high BMI, smoking, drinking) among low social class women. In my clinic, we ask the couples about their occupation and this information will in most instances provide a rough estimate of their social status. Whereas the social factors cannot be changed by interventions at the RM clinic, extra surveillance in the third trimester should be provided for some of these patients due to the higher risk of late pregnancy complications.

Occupational Factors

Patients should be interviewed in details about their working situation. Is their working situation very stressful? Are they standing many hours a day or are they lifting heavy burdens? Do they have changing working times including night work? Are they working with hazardous chemicals or radiation? Although the documentation that improvement of working conditions indeed improves perinatal outcome is poor, RM patients with risky work conditions should be encouraged to change the conditions and support be provided to implement the changes (letters to the employers, etc.). Patients with night work may be encouraged to only work by day time in the next pregnancy, diminish working load, or get pregnancy leave.

Partner

Patients with RM are almost always married or live in an established partnership. In my clinic, the husband is asked whether he has fathered pregnancies in previous relationships and about the outcome of these pregnancies. In addition, he is asked about health status with particular focus on congenital or testicular disorders and intake of medicine.

An increasing number of our RM couples are immigrants from the Middle East, with tradition for inter-cousin marriages. Therefore, it is important to obtain information about whether the couples are related. There may be an increased risk of miscarriage in first-cousin marriages and definitely an increased risk of malformations and autosomal recessive diseases in the offspring. This may be an indication for closer-than-normal ultrasonic fetal monitoring during pregnancy. If a first-cousin couple with RM continues to miscarry in spite of other treatments, the possibility of offering insemination with donor sperm should be mentioned to the couple, but due to culture and religion, this offer will rarely be accepted.

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CAUTION

Most published studies put little emphasis on lifestyle and occupational factors, although these may affect pregnancy outcome more than factors found by blood tests.

Too much emphasis should not be put on the importance of a moderately increased BMI since its impact on miscarriage risk in RM is unclear and the effect of weight loss on miscarriage risk is undocumented.

Many patients with RM seek an explanation for their miscarriages in some self-inflicted factor, for example, intake of a specific food ingredient, a stressful event, a jump, or a heavy lift. Such self-guilt can be enhanced if the importance of lifestyle factors for RM is over-exaggerated when talking with the patients.

Reproductive history

Clinical Appearance of Pregnancy Losses

In my clinic, considerable time is spent to get valid information about the patients' reproductive history, especially about the gestational ages at the time of previous fetal demise and the ultrasonographic and hormonal measurements undertaken in each pregnancy. This information is obtained from questionnaires sent to the patients before the first consultation in order to give them time to collect relevant data from hospital records and other documents and to recall events.

At the first consultation, every effort is done to integrate information from written records and the patients' own information in order to answer four main questions relating to each pregnancy: (i) was it confirmed by a urinary pregnancy test or serum-hCG measurement? (ii) were there signs of intrauterine pregnancy by ultrasound (intrauterine gestational sac, yolk sac, or embryonal echo with or without fetal heart action)? (iii) were chorionic villi detected by histology after uterine curettage? and (iv) at which gestational age had the fetal demise probably happened?

Other information relating to previous pregnancies is also thoroughly collected: mode of conception, results from karyotyping of miscarriages, identity of the partner for each pregnancy, and perinatal data relating to pregnancies progressing to the second/third trimester. Any treatment attempts in each pregnancy are also registered.

Our efforts to register detailed data from previous pregnancies are primary due to the fact that the number of previous pregnancy losses is the strongest prognostic factor for further miscarriage/live birth after RM. It is thus important to confirm that the patients had really had pregnancy losses by documenting a positive urine or serum-hCG measurement and not merely irregular cycles. It is also important to know whether a pregnancy has been documented by ultrasound or histology and not only by hCG detection since biochemical pregnancies (also called pregnancies of unknown location = PULs) may influence the prognosis after RM differently from clinical miscarriages. Some gynecologists and specialist societies such as the American Society of Reproductive Medicine do not recognize the importance of PULs in the RM diagnosis. However, my group has documented that PULs in the reproductive history indeed matter – in a multivariate analysis of variables of importance for subsequent pregnancy outcome in 499 RM patients, each PUL reduced the prognosis for subsequent live birth significantly and almost to the same degree as each clinical miscarriage.

We also found that primary RM patients with a history of exclusively PULs exhibit a very high (16%) frequency of clinical tubal pregnancy at some time point in their reproductive history. This may indicate that the pregnancy losses in many of these patients may be spontaneously resorbed ectopic pregnancies due to tubal damage rather than intrauterine losses. We suspect that these patients have a subtotal tubal damage and as a consequence, we offer them IVF treatment in the next pregnancy – providing them with a good chance for live birth (see Chapters 8 and 17).

SAUTION

Some patients exaggerate the number of pregnancy losses in order to qualify for being referred to a dedicated RM clinic and qualify for active treatment at the clinic. These patients can be identified by doing an extensive collection of information from files from hospitals and general practitioners.

Gestational Age of Pregnancy Losses

Information about time of fetal demise, not to confound with the time of discovery of fetal death, is important, especially when we are dealing with pregnancy losses in the early second trimester (13th–18th week gestation). It has been reported in several studies that when fetal death is documented to have happened after 13th week, it is associated with a much higher risk of new second trimester miscarriage or extreme early birth compared with an early miscarriage (see Chapter 5). Some miscarriages detected by ultrasound in the second trimester have, evaluated from the size of the dead fetus, probably happened in the first trimester. Since the impact of a "real" second trimester loss on the risk of new late loss or preterm birth seems to be much greater than the impact of a first trimester loss, in my clinic much efforts are done to collect relevant information in order to distinguish between "real" and "false" second trimester losses in the history.

★ TIPS AND TRICKS

Questionnaires requesting information about time and place for previous pregnancy losses and about investigations undertaken in each pregnancy should be mailed to new patients 3 weeks prior to initial consultation.

Perinatal Data

Information about outcome of previous births or stillbirths is important to obtain. Our studies have shown that in patients with secondary RM, the birth of a boy compared with a girl prior to RM decreases the prognosis for live birth in the first pregnancy after referral by 22% corresponding to an OR for birth of 0.37 (95% CI 0.2–0.7). If the firstborn boy was born preterm or had birth weight <2500 g, the prognosis seems to be reduced even more.



Figure 1.1 Pedigree showing the reproductive histories of a woman (proband) with secondary recurrent miscarriage after the birth of a slightly growth-retarded boy and her mother. Information about autoimmune diseases and screening for risk factors for recurrent miscarriage are also given. MBL, mannose-binding lectin.

The patient database at my clinic indicates that women with secondary RM significantly more often than expected had given birth to a firstborn child with some congenital disorder or malformation. In these cases, many efforts are done to achieve information about the exact diagnosis of the child and together with experts in genetics and ultrasound to make a plan for surveillance in the next pregnancy, including prenatal screening and, if possible, offer treatment with IVF combined with preimplantation genetic diagnosis (see Chapter 6).

Information about perinatal complications when the patients themselves were born can provide information about the prognosis for birth since women being born with a low own birth weight (<2900 g) will have a high risk of experiencing multiple (\geq 5) miscarriages in their later reproductive life (Figure 1.1).

🛞 SCIENCE REVISITED

In the majority of published studies in RM, little emphasis is put on getting a comprehensive reproductive history with documentation of pregnancy losses being biochemical, early clinical miscarriages, or "real" second trimester miscarriages.

Detailed information about the time of fetal demise in previous pregnancy losses and perinatal outcome in previous ongoing pregnancies is important for assessing the risk of new miscarriage and late pregnancy complications.

Disease history

A thorough history of disease must be obtained. We focus in particular on autoimmune diseases, which are clearly overrepresented in RM women. The endocrine and metabolic changes associated with some autoimmune diseases such as type I diabetes and hypothyreosis may in theory directly interfere with trophoblast invasion and growth; alternatively, the increased inflammatory cytokine response and breakage of immunological tolerance characterizing autoimmune disease is predisposing to miscarriage and RM. Whatever autoimmune disease a patient has, its presence strengthens the belief that immunological disturbances are causing the miscarriages also in patients negative for the limited panel of autoantibodies investigated in most RM clinics. The patients should also be asked about previous thromboembolic episodes; presence of such will strengthen the suspicion that the patient has a thrombophilic disorder even though the routine screening for thrombophilic factors is normal.

Family history

Collecting a family history, especially from RM women, has high priority in my clinic. During a period of 20 years, we have asked our patients for information about the reproductive histories of siblings and mothers and we found that also in families of patients with normal karyotypes, sisters, brothers' wives and mothers all displayed miscarriage rates that were almost doubled compared with the background population. In addition, we found that first-degree relatives had an increased prevalence of a series of autoimmune diseases. A high frequency of miscarriages, perinatal complications, and autoimmune disease among first-degree relatives may suggest that the patient origins from a family carrying genes for poor trophoblast development and genes predisposing to breakage of immunological tolerance and proinflammatory responses (Figure 1.1). Carriage of such genetic factors is probably associated with a diminished prognosis for live birth. An accumulation of miscarriage and autoimmune disease among the first-degree relatives should alert the general practitioner or nonspecialized gynecologist and lead to referral to a specialized RM clinic already after two or three miscarriages. A burdened family history should lead the physicians of the RM clinic to monitor the patients more closely during early and late pregnancy since the risk of miscarriage and perinatal complications in the patients' next pregnancy may be increased. A family history of early onset autoimmune or thromboembolic disease should alert the physician in the RM clinic about a possible immunological or thrombophilic etiology in spite of normal routine blood screening and this may warrant extended blood testing.

Information about repeated miscarriages among first-degree siblings or their mothers increases the chance that the patients carry a balanced translocation and based on this finding it has been proposed only to investigate karyotypes in younger RM patients with a family history of repeated miscarriages to save costs (see Chapter 2).

However, it must be emphasized that no study has so far attempted to quantify the impact of a family history of miscarriage, perinatal complications, or early onset autoimmune and thromboembolic disease for the risk of new miscarriage in patients with RM. When such a study has been undertaken, it will hopefully be possible to include family information in a more exact way when estimating the prognosis in patients with RM.

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PEARLS TO TAKE HOME

A family history of repeated miscarriages or autoimmune or early onset thromboembolic disease should alert the physician of a diminished spontaneous prognosis, which should lead to referral to a dedicated RM clinic already after few (2–3) miscarriages.

Conclusions

As reviewed earlier, it is rewarding to spend efforts and time to get a comprehensive history from the patients. I think that a thorough reproductive history with detailed knowledge about whether the pregnancy loses had been PULs or clinical miscarriages, whether miscarriages had been before or after gestational week 13, and whether there had been perinatal complications associated with previous births is paramount for estimating the prognosis as exact as possible and thus will help in the decision taking regarding whether to treat or not. A reliable estimate of the number of previous pregnancy losses and their gestational ages is also important for assessing the risk of perinatal complications in subsequent ongoing pregnancies, which will influence the level of monitoring that should be offered in late pregnancy. Sometimes the reproductive history per se can be decisive for offering the patients IVF treatment or other kinds of assisted reproduction.

Clearly, if risk factors for miscarriages in the patients' lifestyle or occupation are identified, this should result in improvement of lifestyle and working conditions.

Information about autoimmune or thromboembolic disease among the patients themselves or their first-degree family members can often raise suspicion about a possible immunological or thrombophilic etiology of miscarriages in spite of normal routine blood screening, and this may lead to extended biochemical testing.

Figure 1.1 illustrates the value of obtaining a thorough disease and reproductive history concerning a RM patient and her first-degree family members. The patient was referred to our clinic after having experienced six early miscarriages after the birth of a growth-retarded boy. It was planned to offer her treatment with intravenous immunoglobulin (IvIg) in her next pregnancy but unfortunately 3 years after referral, she had not yet managed to conceive in spite of assisted reproductive technology (ART), probably due to advanced age (now 42 years). Her history with own low-birth weight, the birth of a growth-retarded boy in the first pregnancy, symptoms of autoimmune disease (ulcerous colitis), and her mother's history of several unexplained stillbirths (of growth-retarded boys), RM and autoimmune disease (hyperthyreosis) suggest that the family carries genetic variants that predispose both to autoimmunity and impaired trophoblast growth or function and points to a poor prognosis. We found that both the patient and her mother had very low plasma levels of mannosebinding lectin (MBL), which is determined by genetic polymorphisms on chromosome 10. Low MBL levels predispose to RM with reduced prognosis, late fetal death, and low-birth weight. The clinical information about the patient and her family was not very useful at the time when the patient was finally referred to our clinic because at that time she had become candidate for our most extensive therapy (IvIg), exclusively due to the high number of miscarriages. However, she did not get the chance to benefit from this treatment due to advanced age. If the information regarding the patient and her mother had been collected and taken seriously already when she had suffered her third miscarriage, she would have been referred at a time when she was still able to conceive and benefit from the possible effect of IvIg treatment (see Chapter 6).

Overall, a valid and detailed information about all the relevant factors that can be achieved from talking with the patients and reading their hospital records will, in conjunction with results from blood tests and investigations of uterine anatomy, provide the best basis for assessing the patients' prognosis, in terms of chance of life birth and risk of perinatal complications, and will help taking the decision about when and how to treat.

PATIENT ADVICE

If a risk factor for RM is identified in a patient, it is important to tell her that this is probably not the full explanation for the disorder but a piece in the jig jaw puzzle and eliminating or treating this factor is no guaranty for pregnancy success.

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