

# Unexplained recurrent miscarriage: how can we explain it?

Sotirios H. Saravelos\* and Tin-Chiu Li

Reproductive Medicine and Surgery Unit, University of Sheffield, Sheffield Teaching Hospitals, Jessop Wing, Tree Root Walk, Sheffield S10 2SF, UK

\*Correspondence address. Tel: +44-7840034710; E-mail: sotirios.saravelos@gmail.com

**ABSTRACT:** Unexplained recurrent miscarriage (RM) can be a challenging and frustrating condition for both patients and clinicians. For the former, there is no diagnosis available for consolation, while for the latter there is little evidence-based treatment to offer. However, the majority of these patients have an excellent prognosis without the need for any treatment. Epidemiological associations suggest that the reason for this is that the majority of women with unexplained RM are in fact healthy individuals, with no underlying pathology, who have suffered three miscarriages purely by chance. Nevertheless, a certain proportion of women with unexplained RM will continue to miscarry, and preliminary studies suggest the presence of pathology in some women of this group. As a result, two types of unexplained RM can be described: Type I unexplained RM, which occurs by chance in women who have no underlying pathology and has a good prognosis; and Type II unexplained RM, which occurs due to an underlying pathology that is currently not yet identified by routine clinical investigations and has a poorer prognosis. Distinguishing between Types I and II unexplained RM can be achieved by considering several factors: the age of the woman, the definition used for RM (i.e. whether biochemical pregnancy losses are considered as miscarriages), the number of previous miscarriages suffered and the karyotype of the products of conception, where available. A better understanding of the two types of unexplained RM could lead to more targeted referrals, investigations and treatments, which would improve cost-effectiveness and overall clinical care.

**Key words:** idiopathic / sporadic miscarriage / recurrent miscarriage / unexplained

## Introduction

Recurrent miscarriage (RM) is defined by most clinicians as three or more consecutive miscarriages (Stirrat, 1990). It can be emotionally and physically traumatizing for any couple, who experience the repeated loss of their offspring, but also live with the anxiety of a further miscarriage when they conceive. It is also very challenging and frustrating for the clinician, as approximately half of the patients will remain without a diagnosis, and are classified as having idiopathic or unexplained RM (Li *et al.*, 2002). The main relief comes from the fact that women with unexplained RM, and receiving no treatment, have a remarkably good prognosis, with a live birth rate in the region of 75% following referral to a specialized clinic (Clifford *et al.*, 1997). However, despite this good prognosis, many women will commonly continue to seek treatments, while clinicians may feel under pressure to provide therapies that remain unproven. To date, the reasons why the prognosis for these women is so good have not been fully understood, and the role of psychological supportive care, also known as tender loving care, has been thought to play a primary role. In this article, epidemiological associations between sporadic miscarriage (SM) and RM are reviewed, with an aim to help further explain the nature of unexplained RM and its favourable prognosis, and describe ways in which

investigations and treatments can be targeted and researched more effectively.

## Defining miscarriage: clinical versus biochemical loss

A miscarriage can be defined as a pregnancy that ends spontaneously before the fetus has reached a viable gestational age (Regan and Rai, 2000). Miscarriage is often classified as either a clinical or a biochemical pregnancy loss. Clinical pregnancies are the ones that can be identified by ultrasound or histological evidence, while biochemical pregnancies occur earlier and can only be identified by a raised bHCG. In practice, the majority of biochemical pregnancy losses may go unnoticed. In fact, evidence suggests that the actual biochemical loss rate in the general population may even reach 60% (Chard, 1991). Since this is so high, the relevance of biochemical pregnancy losses becomes questionable. This is reflected in the recent revised definitions of the American Society for Reproductive Medicine (ASRM, 2008), where clinicians are advised not to consider biochemical pregnancy losses as miscarriages when assessing women with RM.

The inclusion or exclusion of biochemical pregnancy losses can also cause great inconsistencies when estimating the incidence of miscarriage. For example, women of the general population would not

have their bHCG routinely measured and their biochemical loss rate would be under-estimated. On the other hand, women with RM often have closer monitoring and therefore biochemical pregnancies are less likely to be missed. In women undergoing IVF treatment, serial bHCG monitoring starting 2 weeks after oocyte retrieval would detect practically all cases of biochemical pregnancy losses. This assumption is supported by data from our centre that shows that women undergoing IVF ( $n = 3165$ ) have significantly higher reported biochemical pregnancy losses compared with women with RM ( $n = 954$ ) (18.4 versus 7.9%;  $P < 0.001$ ) (unpublished data). Although to some extent this may reflect a different underlying pathology, it shows how much the incidence of miscarriage can vary in different populations when taking into account the variation in the sensitivity of detecting biochemical pregnancy losses.

In order to eliminate this bias, in this article, we consider only clinical pregnancy losses as part of the definition of miscarriage, in accordance with the most recent ASRM guidelines. In addition, we do not include ectopic pregnancies as part of the definition of SM and RM as this would also affect the incidence.

## The incidence of SM

The incidence of SM is difficult to estimate as it varies significantly with age. Most authors would accept that the overall SM rate of clinical pregnancies is in the vicinity of 15% (Christiansen, 1996; Quenby et al., 2002; Rai and Regan, 2006). The most accurate way to investigate this further, is to consider SM rates with regards to different patient age groups. A prospective register linkage study has examined such data from over 1.2 million pregnancies in Denmark (Nybo Andersen et al., 2000). The investigators found the SM rate to increase significantly with age from 11% at ages 20–24 to 51% at ages 40–44 (Table I). They also adjusted their analysis to account for miscarriages that would not have been registered with the hospitals.

## Incidence of RM

In practice, the true incidence of RM is difficult to estimate for two main reasons. Firstly, authors may consider different pregnancies as part of the definition. For example, some may include and others

may exclude biochemical pregnancy losses. Secondly, there may be a bias towards an increase in reporting biochemical miscarriages following repeated loss, as women become vigilant after one or two miscarriages and use over-the-counter pregnancy tests, which may identify biochemical pregnancies that otherwise would have gone unnoticed. If these biochemical losses were to be considered true miscarriages, this would lead to an increase in the incidence of RM as the background rate of biochemical pregnancy losses in the general population is as high as 60% (Chard, 1991). To put this into context, it can be estimated that over 20% ( $0.6^3$ ) of women in the general population may suffer three biochemical pregnancy losses due to chance alone.

To our knowledge, the incidence of RM of clinical pregnancies has not been clearly documented in a large-scale population-based epidemiological study. Consequently, the current knowledge stems from widely accepted estimates, which indicate that RM affects ~1% of the general population (Stirrat, 1990; Jauniaux et al., 2006; Rai and Regan, 2006). Other estimates range between 0.4 and 3% (Christiansen, 1996; Li et al., 2002; Quenby et al., 2002; Stephenson et al., 2002), and it can be assumed that this variation in estimates is due to the reporting from different age groups.

## Incidence of RM occurring by chance

Using the incidence of SM in the general population, the incidence of patients suffering RM due to chance alone can be estimated. Specifically, if the incidence of SM equals to  $\mu$ , then the incidence of RM occurring due to chance alone would equal to  $\mu^3$ . Using this calculation, it can be shown that the incidence of RM occurring by chance varies significantly with age, ranging from 0.13 to 13.3% for ages 20–24 and 40–44, respectively (Table I). This means that women in their 40s are a hundred times more likely to suffer RM due to chance alone compared with women in their 20s.

For women of the general population aged 30–34, the SM rate is estimated to be ~15% (Nybo Andersen et al., 2000). As a result, the percentage of women in this age group suffering RM by chance alone is in the order of 0.34% ( $0.15^3$ ) (Christiansen, 1996; Quenby et al., 2002; Rai and Regan, 2006). This is an important figure, when keeping in mind that the incidence of RM is ~1%, as among those with RM, about half (i.e. ~0.5%) would, upon investigations, be found to have an underlying cause, while the remaining half (i.e. ~0.5%) would continue to be unexplained (Li et al., 2002). If 0.34% of the latter unexplained cases are attributable to chance alone, it would mean that the majority ( $0.34/0.5 = 68\%$ ) of women with unexplained RM would not be expected to have any pathology. If this is the case, then the majority, around 2 of 3, of women with untreated, unexplained RM would also be expected to show pregnancy outcomes similar to those of the general population in their next pregnancy.

## Favourable outcomes in women with unexplained RM: time to challenge tender loving care?

In women aged 25–39 of the general population, the SM rate is in the region of 12–25% (Nybo Andersen et al., 2000). For these miscarriages, there is often no obvious explanation or underlying pathology, other than fetal aneuploidy. If one assumes that women with RM have

**Table I** Incidence of SM or RM occurring by chance and of RM in total, in women of different age groups.

Age group (years)	Sporadic miscarriage (%) <sup>a</sup>	RM occurring by chance <sup>b</sup> , % (CI)	RM occurring in total (%)
20–24	11	0.13 (0.129–0.131)	—
25–29	12	0.17 (0.169–0.171)	~0.4
30–34	15	0.34 (0.338–0.342)	~1
35–39	25	1.56 (1.557–1.564)	~3
40–44	51	13.3 (13.29–13.31)	—

CI, confidence intervals for binomial proportions.

<sup>a</sup>Data from Nybo Andersen et al. (2000).

<sup>b</sup>Calculated based on the assumption that if sporadic miscarriage rate =  $\mu$ , recurrent miscarriage rate occurring by chance =  $\mu^3$ .

**Table II Miscarriage rates in women with untreated, unexplained RM (receiving supportive care alone) versus women in the general population.**

Study	Cases	Miscarriage rate (%)
Unexplained RM population <sup>a</sup>		
Stray-Pedersen and Stray-Pedersen (1984)	37	14
Liddell <i>et al.</i> (1991)	44	14
Vlaanderen and Treffers (1987)	20	20
Sheffield data (2011)	361	25
Brigham <i>et al.</i> (1999)	222	25
Clifford <i>et al.</i> (1997)	160	26
Total	844	14–26
General population		
Nybo Andersen <i>et al.</i> (2000)	513 832	12–25 <sup>b</sup>

RM, recurrent miscarriage.

<sup>a</sup>Data from cohort studies where no treatment was given.

<sup>b</sup>Sporadic miscarriage rate for women aged 25–39 years.

a specific pathology, the probability of a further miscarriage in a subsequent pregnancy would be expected to be higher than the SM rate. A number of cohort studies have assessed the pregnancy outcomes of women with, untreated unexplained RM, who received supportive care alone (Table II), and have reported the miscarriage rate in subsequent pregnancies to be between 14 and 26%. This is almost identical to the 12–25% SM rate of women in the general population, raising the question of whether women with unexplained RM have in fact any underlying pathology at all.

Traditionally, the excellent prognosis of women with unexplained RM has been attributed to psychological supportive care (also known as tender loving care) offered in specialist clinics. However, this has been based only on level three evidence of three small non-randomized trials. These studies have compared groups of women with and without exposure to supportive care, reporting increases in live birth rates of up to 50% (Stray-Pedersen and Stray-Pedersen, 1984; Liddell *et al.*, 1991; Clifford *et al.*, 1997). However, the conclusions that can be drawn for the groups of women who did not receive supportive care are significantly limited, as they were small in number and there was a lack of control over confounding variables. Liddell *et al.* (1991) reported on only nine women who did not receive supportive care. Stray-Pedersen and Stray-Pedersen (1984), at a time when antiphospholipid syndrome was not routinely tested for, analysed pregnancies of 24 women who were geographically further away and received care at a local antenatal centre instead of their dedicated clinic. Finally, Clifford *et al.* (1997) reported on 41 women who failed to return to the clinic and had to be contacted by telephone or letter to document the subsequent pregnancy outcomes. It is therefore evident, that the data concerning supportive care are very limited and one cannot really say with confidence that psychological supportive care is superior to standard antenatal care. In light of the epidemiological associations discussed, it may be time to question the traditional notion of tender loving care and consider whether the majority of patients with unexplained RM are in fact

healthy individuals who are merely unlucky in their pursuit of a successful pregnancy.

### Could all RMs be chance occurrences?

The simple answer is no. Overall, the incidence of women suffering RM by chance alone appears to be significantly less than the overall incidence of women with RM (0.34 versus 1%). This has been noted consistently by several authors as a strong indication that there is an underlying pathology in most women with RM (Christiansen, 1996; Quenby *et al.*, 2002; Rai and Regan, 2006). In addition, studies have reliably shown that the risk of miscarriage is related to women's previous pregnancy outcomes (Parazzini *et al.*, 1988; Regan *et al.*, 1989; Knudsen *et al.*, 1991; Quenby and Farquharson, 1993). This implies that the miscarriage rate is not simply 'reset' after each pregnancy as would be expected if it occurred purely by chance. Finally, there is strong evidence linking various pathological factors to RM, most notably antiphospholipid syndrome, which if treated have been shown to significantly improve pregnancy outcomes in women who would otherwise have a poor prognosis (Rai *et al.*, 1997).

### Could all unexplained RMs be chance occurrences?

The answer is probably not. Although the majority of unexplained RM may occur by chance, a certain proportion of women will go on to suffer a higher number of miscarriages, which statistically would be unlikely to occur due to chance alone. For example, the incidence of women suffering six miscarriages due to chance alone is in the order of 1 in 100 000 (0.15<sup>6</sup>). It is therefore reasonable to assume that a proportion of women with unexplained RM (around one of three) may have significant environmental risk factors or endogenous pathologies, not detected by current routine investigations, which increase the chance of miscarriage.

Several studies have suggested that factors such as obesity, smoking, alcohol, caffeine and exposure to certain occupational hazards may increase the chance of RM (Saravolos and Regan, 2011), and this could predominantly concern the unexplained RM group. Other experimental studies have shown increased numbers of uterine natural killer cells in women with unexplained RM (Clifford *et al.*, 1999; Quenby *et al.*, 1999; Tuckerman *et al.*, 2007), suggesting an immunological pathology. However, so far, these associations and their related treatments remain unsubstantiated (Rai *et al.*, 2005; Tang *et al.*, 2011). Endocrinological and endometrial abnormalities in a significant proportion of women with unexplained RM have also been demonstrated (Li *et al.*, 2000; Tuckerman *et al.*, 2004), although this has not been reproduced in larger-scale cohorts. Interestingly, a recent preliminary study demonstrated impaired decidualization of the endometrium in women with RM, suggesting that this causes 'superfertility' in these women, with implantation of non-optimum embryos which are then inevitably miscarried (Salker *et al.*, 2010). Novel findings such as these could concern some women with otherwise unexplained RM.

### Types I and II unexplained RM

From the above, we can conclude that there are two distinct types of unexplained RM, Types I and II.

Type I unexplained RM: refers to the RM that has occurred predominantly by chance, in women who have no specific underlying pathology. This type has a relatively good prognosis compared with women of a similar age and there is no need for any intervention.

Type II unexplained RM: refers to the RM that occurs due to an underlying pathology that is not currently identified by routine clinical investigations or due to significant environmental and lifestyle risk factors. This type has a poorer prognosis compared with women of a similar age.

## How to distinguish between Types I and II unexplained RM

Although it seems likely that the majority of unexplained RM will be Type I unexplained RM (i.e. RM occurring by chance), the question remains: how can we identify Type II unexplained RM that has occurred due to an underlying pathology that cannot be as yet be detected by current investigations? Several clinical features are useful in this respect:

- (1) **Age:** The younger the woman is, the less likely it is that the RM is occurring due to chance, as women aged 40–44 are a hundred times more likely to suffer RM due to chance alone compared with women aged 20–24 (13.3 versus 0.13%, respectively).
- (2) **Definition of RM:** If only clinical pregnancy losses (and not biochemical pregnancy losses) are considered as miscarriages, then the RM is less likely to be due to chance. This is because the incidence of biochemical pregnancy loss in the general population may be as high as 60% (Chard, 1991), while the incidence of pregnancy losses at a later stage, for example, after the detection of fetal heart activity, is significantly lower (Bricker and Farquharson, 2002).
- (3) **Number of previous miscarriages:** The higher the number of previous miscarriages, the less likely it is that the RM is due to chance, because statistical consideration shows that the likelihood of having four or more miscarriages due to chance alone is rather small.
- (4) **Karyotype of products of conception:** If the karyotype of the products of conception is normal, then the RM is less likely to occur as a consequence of chance. In women with RM, the finding of a normal karyotype in the products of conception is associated with a worse prognosis for a future pregnancy (Carp *et al.*, 2001) and a higher number of miscarriages (Ogasawara *et al.*, 2000). In contrast, RM occurring due to chance is most commonly associated with sporadic fetal aneuploidy, and an abnormal karyotype of the products of conception (Rai and Regan, 2006).

A typical case of Type I unexplained RM is an older woman (e.g. over 40 years) with three biochemical or early losses, in whom the products of conception of the most recent miscarriage showed aneuploidy. On the other hand, a typical case of Type II unexplained RM is a young woman (e.g. under 30 years), with four or more losses, all occurring after fetal heart beats had been visualized and in whom the products of conception of the most recent miscarriage showed a normal result.

## Implications for clinical practice

Firstly, the fact that the majority of unexplained RM may be a chance occurrence could be difficult to fathom, but stresses the need to

withhold any non-evidence-based treatment for most cases of unexplained RM, as it may cause more harm than good. This is demonstrated in a recent randomized controlled trial (RCT) of the relatively safe combined aspirin/heparin treatment versus placebo in women with unexplained RM. Although no differences were shown for live birth rates, the women in the treatment group reported significant bruising, swelling and itching at their injection sites (Kaandorp *et al.*, 2010).

Secondly, the fact that younger women are much less likely to suffer RM purely by chance means that they should be investigated earlier in search of an underlying cause, while older women may not necessarily benefit from exhaustive investigations and interventions. Consequently, it may be appropriate to consider adjusting guidelines for specialist referral, to include women of a younger age who have suffered just two miscarriages. The reasoning behind this is that for women aged 20–29 years, the probability of two miscarriages occurring due to chance alone is 1.2–1.4% ( $0.11^2-0.12^2$ ), which is less than the 1.6–13.3% ( $0.25^3-0.51^3$ ) probability of three miscarriages occurring by chance alone in women aged 35–44 years. It does mean that women under the age of 30 years presenting with two miscarriages are more likely to have an underlying pathology compared with women over the age of 35 years presenting with three miscarriages. Of course, other factors such as lifestyle and when the miscarriages exactly occurred would also have to be considered. It may therefore be reasonable to offer investigations for women of a younger age (e.g. <30 years) who have suffered just two miscarriages, especially if they occur after the demonstration of fetal heart beats.

Finally, the fact that biochemical pregnancy losses may be so common in the general population, stresses the need to consider only clinical pregnancy losses as miscarriages when making a diagnosis of RM. This would help reduce unnecessary referrals, investigations and treatments.

With the above in mind, it may be time to reconsider the criteria for referral and investigation of RM, which would necessarily take into consideration maternal age and type of pregnancy losses suffered.

## Implications for research

In the context of clinical research and cost-effectiveness, it may be exceedingly difficult to conduct meaningful multicentre RCTs on women with unexplained RM. This is because the majority of women with unexplained RM will have no underlying pathology, and their favourable outcomes will overshadow the adverse outcomes of women with an underlying pathology, albeit as yet not clearly identified. For this reason, any non-RCTs assessing the effect of certain treatments on women with three unexplained RMs should be interpreted with care, as the improvement may simply be a consequence of ‘chance’ and the expected good prognosis, regardless of the intervention, in women with Type I unexplained RM. As a result, continuing research efforts are required to identify and distinguish women with Type II unexplained RM from women with Type I unexplained RM (that occurs due to chance). Initial efforts may be focused on young women with high order RM (e.g. five or more) as there is a strong likelihood of a specific underlying pathology. It is also of interest to examine whether age has a significant impact on the prevalence of known causes of RM, such as anti-phospholipid syndrome, which is currently the main treatable cause of RM.

## Conclusion

Epidemiological associations suggest that the majority of older women with unexplained RM do not have any underlying pathology, which would explain the overall good prognosis for this group of women. However, there is another group of women, often younger, who do have a specific underlying pathology, that is as yet unidentified, as a cause for their repeated losses. A better understanding of these separate subgroups of women with unexplained RM would lead to different treatment pathways and management strategies.

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Both authors were responsible for the conception and scope of the report. S.H.S. performed the literature search, analysis and writing of the report. T.-C.L. commented on the report and contributed amendments and additional writing.

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