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Epidemiology and the medical causes of miscarriage

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Human reproduction is extraordinarily wasteful. The reasons for this have taxed all of the contributors to this book. As we move into the 21st century it is sobering to reflect on the fact that we have failed to harness the power of the evolving revolution in molecular medical biology to answer the fundamental question: why is the fate of a fertilized egg so hazardous and so unsuccessful? The following account summarizes our limited knowledge of the epidemiology of miscarriage and then moves on to consider some of the medical causes of miscarriage. The contribution of genetic abnormalities to the problem of pregnancy wastage is discussed elsewhere in this volume.

Key words: miscarriage; fetal loss; thrombophilia in pregnancy; recurrent abortion.

EPIDEMIOLOGY OF MISCARRIAGE

A miscarriage is a pregnancy that ends spontaneously before the fetus has reached a viable gestational age. This definition currently equates both clinically and legally to a human pregnancy that ends before 24 weeks of gestation. The latest edition of the Oxford English Dictionary defines epidemiology as 'that branch of medical science which treats of epidemics' and an epidemic as a disorder 'prevalent among a people or community at a special time, and produced by some special causes not generally present in the affected locality'. But as long ago as 1745 an epidemic was defined as a disorder that is 'widely prevalent, universal'. Some 250 years later this description remains a more fitting term of reference for the magnitude of human reproductive loss.

In 1975, Roberts and Lowe published their paper[1] entitled 'Where have all the conceptions gone?'. Using a mathematical model they suggested that 78% of fertilized eggs fail to result in a live birth and that the vast majority of these losses occur before the clinical diagnosis of pregnancy. Epidemiological studies conducted in communities where no contraception is practised have demonstrated that fecundity – the

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probability of achieving a successful pregnancy per menstrual cycle – is only 25% in humans and that the unrecognized loss of fertilized eggs makes a major contribution to this low fecundity.[1a,2]

Sporadic miscarriage

Sporadic miscarriage is the most common complication of pregnancy, and one in four of all women who become pregnant will experience pregnancy loss. The vast majority are early, occurring well before 12 weeks of gestation. Sporadic miscarriage after this time complicates no more than 1–2% of pregnancies. The incidence of clinically recognizable miscarriage in general population studies has been consistently reported as 12–15%[3,4] but this figure is just the tip of the iceberg of total reproductive loss. The development of highly sensitive assays of beta human chorionic gonadotrophin (β-hCG), to detect the presence of an embryo, and their application initially as a research tool and more recently as 'over-the-counter' pregnancy testing, has confirmed that the magnitude of pregnancy loss between implantation and the clinical identification of pregnancy is in the region of 60%.[5] The most recent study of sub-clinical pregnancy loss has further demonstrated that, in most successful human pregnancies, the conceptus implants in the uterine cavity 8–10 days after ovulation, and that when implantation occurs on later dates in the conception cycle the incidence of very early miscarriage is increased.[6]

The risks of recurrence

Many studies have been published which attempt to quantify the risk of miscarriage after a woman's first, second, third or further pregnancy loss. Following three previous pregnancy losses the risk of a further miscarriage ranges from 20 to 70%, reflecting the different populations studied and the methods of data analysis employed (reviewed by Regan[7,8]). Retrospective and prospective hospital-based studies of miscarriage that recruit patients who are already pregnant tend to either (1) underestimate the incidence by (a) excluding those early miscarriages that do not require medical intervention or (b) including only those women who appear on a labour ward register having achieved a live birth after repeated miscarriages, or (2) exaggerate the incidence by recruiting women who present with symptoms of threatened miscarriage.[9]

In summary, there are very few studies available documenting the incidence of miscarriage in a normal, representative population of pregnant women. In order to avoid the most important types of selection bias the study design needs to be prospective, recruiting subjects from the community prior to pregnancy. The early pregnancy loss study conducted in Cambridge, UK, was designed to minimize these biases by recruiting non-pregnant women and prospectively observing their subsequent pregnancies. This study concluded that a woman's risk of miscarriage can be quantified by examining her past obstetric history, the single most important predictive factor being a previous miscarriage. Primigravidae and women with a history of live births had a low incidence of miscarriage of 5%. Women with only unsuccessful histories had a significantly greater risk, even when their only pregnancy had ended in miscarriage (20%) and the risk increased cumulatively as the number of previous miscarriages rose to two (28%) and three or more (43%).[4]

Similar data were subsequently reported from a large unselected Danish population of 300 500 pregnancies. The risks of a further miscarriage following 0 to 4 consecutive miscarriages were 16, 25, 45 and 54% respectively.[10] Importantly, similar miscarriage

rates were noted in both young and older women after they had experienced repeated losses, suggesting that in women with recurrent pregnancy failure an additional risk factor is present which is not age-related.

The association between rising maternal age and the incidence of miscarriage has been well documented in cross-sectional studies and has long been accepted as a reflection of the increased risk of some fetal chromosomal abnormalities (trisomies) and neural tube defects with rising maternal age. As with any study of early fetal loss, the data relate only to those miscarriages which are both recognized and reported. All the caveats concerning study design and bias mentioned earlier apply to this important variable, particularly at the earliest gestational ages, where the available data are known to be incomplete

The factors which influence maternal age at reproduction are complex and include age at menarche and menopause, desired family size, pregnancy order (a variable inextricably linked to maternal age) and pregnancy spacing (both very close spacing and involuntary infertility), all of which may be affected by cultural and socio-economic circumstances. What is not clearly understood is whether it is these factors, rather than maternal age alone, which determine the risk of fetal loss. The risk of miscarriage increases with maternal age after the mid-30s and has been most convincingly demonstrated in first pregnancies, before the picture has been confused by attempts at reproductive compensation which results in women entering higher gravidity groupings because their previous pregnancy outcome was unsuccessful.

In summary, from all the available literature, we may conclude that maternal age and the previous reproductive history are the two major epidemiological determinants of future pregnancy outcome for women with a history of miscarriage. The increased rate of miscarriage with advancing maternal age secondary to fetal chromosomal abnormalities is well referenced in the literature and is addressed by Drs Goddijn and Leschot in Chapter 9.

Environmental and occupational risks for miscarriage

Although miscarriage is one of the adverse reproductive outcomes presumed after exposure to potentially teratogenic or mutagenic agents, epidemiological evidence for such an association is sparse. Numerous drugs and environmental chemicals have been shown to cause chromosomal damage in in vitro animal studies, but data directly implicating an effect on the human species are scarce. Furthermore, environmental exposures which recur during a couple's reproductive life-span may reasonably be considered to contribute to the aetiology of recurrent miscarriage. The most recently published studies have suggested that maternal exposure to organic solvents increases the risk of fetal malformation[11] and that coffee consumption of more than four cups per day in early pregnancy is associated with miscarriage.[12]

A review of the effect of nicotine on ovarian, uterine and placental function suggests that cigarette smoking has an adverse effect on trophoblast invasion and proliferation.[13] Cigarette smoking in the first trimester of pregnancy has been reported to increase the risk of miscarriage significantly[14] although pre-conceptual smoking was not associated with pregnancy loss. Mothers who use cocaine in pregnancy are invariably cigarette smokers, hence the data implicating cocaine as a specific cause of early pregnancy loss are confounded. Nonetheless, a recent study has suggested that a cocaine habit is a significant risk for miscarriage.[15] There are numerous reports in the literature documenting the adverse effects of alcohol on fertility, pregnancy loss and fetal development but a recent prospective cohort study has reported that moderate

maternal alcohol consumption in the first 10 weeks of pregnancy (3 or more units per week) is associated with an increased risk of miscarriage.[16]

Recurrent miscarriage

In contrast to sporadic miscarriage, recurrent miscarriage is relatively uncommon. The incidence of recurrent miscarriage has never been reliably determined, primarily because of differing opinions as to whether two or three pregnancy losses should constitute the definition. When defined as the loss of three or more consecutive pregnancies, recurrent miscarriage affects 1% of all couples.[17] When women with two or more consecutive pregnancy losses are included, the scale of the problem increases to include more than 3% of all couples trying to achieve a live birth.

The term 'recurrent miscarriage' implies that recurrent episodes of early pregnancy loss have a systematic underlying cause, but this is probable in a proportion of women only because the incidence of sporadic miscarriage is so high. If miscarriage is always a random event and the incidence of clinical pregnancy loss is 15%, the theoretical risk of experiencing three successive miscarriages should be 0.34%. The frequency of women having a term delivery following three previous miscarriages has been reported as 0.7%[18], and because only those women eventually achieving a successful pregnancy were included in this figure it is likely to be an underestimate. This figure is significantly higher than the theoretical estimate of losing three or more pregnancies, and suggests that recurrent miscarriage cannot always be explained by consecutive episodes of bad luck.

There are two strands of evidence which support the view that, in addition to random causes, some couples are at increased risk of repeated loss.[19] First are the data mentioned earlier in this chapter which demonstrate that the risk of miscarriage increases with the number of previous miscarriages, or with characteristics of the index pregnancy loss such as karyotype, gestation or morphology. The second piece of evidence comes from studies demonstrating that women with a history of repeated pregnancy losses have reproductive characteristics which are associated with a poor prognosis for future pregnancy outcome and that distinguish them from women suffering sporadic miscarriage. In a large study of 500 consecutive couples referred to a specialist miscarriage clinic, a history of previous stillbirth or neonatal death was noted in 6%, termination of pregnancy for fetal abnormality in 2%, and 5% had suffered a previous ectopic pregnancy. Among the 45% of couples with a living child, a history of premature delivery and low-birth-weight infants was common. Approximately one-third of this population gave a history of conception delays and previous gynaecological investigations for subfertility.[20]

The relative importance of genetic, anatomical, infective, endocrine, immune and idiopathic abnormalities in the aetiology of recurrent miscarriages have proved difficult to establish. In most series, small numbers of patients preclude statistical analysis and frequently reflect the research interests of the clinicians concerned. In the following account we have attempted to critically evaluate the contribution of recognized medical disorders to the clinical problem of recurrent miscarriage.

MEDICAL CAUSES OF MISCARRIAGE

Endocrine, autoimmune and thrombotic abnormalities are the major recognized medical causes of recurrent miscarriage.

Endocrine

A variety of endocrinopathies, including luteal phase defect, progesterone deficiency, polycystic ovaries (PCO) and hypersecretion of luteinizing hormone (LH) have traditionally been cited as having a causal role in the aetiology of recurrent miscarriage. More recent evidence challenges these concepts, and attention is now focused on the relationship between hyperandrogenaemia, hyperprolactinaemia and recurrent miscarriage.

Luteal phase defect and progesterone deficiency

Interest that an endometrial defect leading to abnormal implantation may be a cause of recurrent miscarriage has led to the concept of a luteal phase defect (LPD). Jones, using basal body temperature charts, urinary pregnanediol levels and endometrial biopsies, first defined the LPD as a defective corpus luteum with insufficient progesterone production, whether in amount or duration.[21] This defect was correlated with an inadequate endometrial maturation, the standard diagnostic criteria for which were described by Noyes et al.[22] The last 50 years has witnessed considerable controversy concerning the role of LPD in the aetiology of both infertility and recurrent miscarriage. This controversy has arisen for two main reasons. First, the lack of consensus as to how an LPD is best diagnosed, and second, whether correction of the LPD leads to an improved pregnancy outcome among women with recurrent miscarriage. These issues remain unresolved. Serum progesterone levels are not predictive of pregnancy outcome[23] and there is no evidence to support the use of exogenous progesterone supplementation in early pregnancy.[24]

Polycystic ovaries, hypersecretion of LH and hyperandrogenaemia

Polycystic ovaries (PCO) are significantly more common among women with recurrent miscarriage compared with parous controls. However, ovarian morphology does not correlate with pregnancy outcome, and a specific endocrine defect associated with PCO which is causative of pregnancy loss remains to be established. Original studies reported that women who either hypersecrete luteinizing hormone (LH) or who are hyperandrogenaemic, two classical endocrinopathies associated with PCO, are at increased risk of miscarriage following either spontaneous or assisted conception.[25–28] However, a prospective randomized placebo-controlled study reported that pre-pregnancy pituitary suppression of high endogenous LH does not improve the live birth rate of women with recurrent miscarriage and PCO who hypersecrete LH.[29] In a re-appraisal of the association between PCO and miscarriage we reported that, among over 2000 consecutive women with recurrent miscarriage, the prevalence of PCO is 40.7% compared to 22% among a historic control group.[30] The future live birth rate in untreated pregnancies was similar among women with PCO (60.9%) compared to that among women with normal ovarian morphology (58.5%), and neither an elevated serum LH level (>10 IU/l) nor an elevated serum testosterone level (>3 nmol/l) was associated with an increased miscarriage rate. While testosterone levels do not appear to correlate with pregnancy outcome, it has been reported that women with recurrent miscarriage have increased levels of androstenedione compared with controls.[31] The authors of this study suggest that high levels of androgens are associated with retardation of the endometrium in the luteal phase of the cycle.

Hyperprolactinaemia

A recent Japanese study has reported that 18% of women with recurrent miscarriage have an elevated prolactin level which could not be explained by other ovarian or endocrine abnormalities.[32] In a prospective randomized study, these authors reported that correction of the hyperprolactinaemia with bromocriptine led to a significantly higher live birth rate (85%) compared to that among those in whom the hyperprolactinaemia was not corrected (52%, $P < 0.05$).

Autoimmune

Diabetes

Well controlled insulin-dependent diabetes mellitus (IDDM) is not a risk factor for miscarriage. In a well designed prospective study in which 386 women with IDDM and 432 women without diabetes were recruited before or within 21 days after conception, and followed prospectively, there was no significant difference in the miscarriage rate between the two groups.[33] This finding has been supported by other retrospective studies reporting a similar miscarriage rate among women with IDDM compared with the expected population prevalence.[34,35] Many studies have reported the importance of close glycaemic control in the peri-conceptual period and for there to be a direct correlation between glycaemic control, assessed by the levels of glycosylated haemoglobin (HbAlc), and the incidence of miscarriage.[33,36–38]

Animal models have provided an insight into the underlying scientific basis for these observations. In rodent pregnancies, maternal diabetes adversely affects pre-implantation embryo development. This is characterized by an increase in the number of fragmented embryos and a reduction in the number of cells in the inner cell mass of the blastocyst.[39] More recently, hyperglycaemic conditions both in vivo and in vitro have been reported to lead to an over-expression of *Bax*, a death-promoting member of the Bc1-2 family of proteins, in murine pre-implantation embryos. This over-expression of *Bax* correlates with an increase in apoptotic morphological changes, assessed on TUNEL labelling, which is reversed by insulin.[40]

Thyroid dysfunction and thyroid autoantibodies

Thyroid dysfunction has previously been cited as a cause of recurrent miscarriage.[41] However, direct evidence for a causal role is lacking and thyroid function tests are rarely abnormal in women with recurrent miscarriage.[20] Attention has instead focused on the relationship between thyroid autoantibodies and pregnancy loss. However, because of conflicting data, this relationship remains to be defined. Recent studies have reported the prevalence of thyroid antibodies to be either similar to[42] or increased among women with recurrent miscarriage, compared with controls.[43] Prospective studies have variously reported that pregnancy outcome is unaffected by these antibodies[44,45] or that they are associated with an adverse outcome.[46,47] All of these studies have included only small numbers of women, and, clearly, what is needed is a large prospective study into which women are recruited only after comprehensive evaluation.

Antiphospholipid antibodies

Antiphospholipid antibodies (aPL), the two most studied of which are the lupus anticoagulant (LA) and the anticardiolipin antibodies (aCL), are a family of

autoantibodies that are directed against phospholipid-binding plasma proteins. Recently revised criteria for the diagnosis of the antiphospholipid syndrome recognized the importance of the obstetric manifestations of aPL. These guidelines, which were agreed at the 8th International Symposium on aPL, define women with persistently positive tests for aPL and (1) a history of at least three consecutive first-trimester miscarriages, or (2) one unexplained second- or third-trimester loss, or (3) severe pregnancy induced hypertension before 34 weeks' gestation as having the antiphospholipid syndrome.[48]

Over the last decade, it has been established that aPL are found significantly more often among women with recurrent miscarriage compared with the general population (Table 1). Furthermore, women with aPL and a history of recurrent pregnancy loss have a miscarriage rate as high as 90% in future pregnancies in which no pharmacological treatment is given.[49]

The mechanism of pregnancy loss in women with aPL remains unclear. There are remarkably few histological reports on the nature of the placental lesions found in miscarriages complicated by aPL. Investigators have also failed to differentiate between miscarriages that have occurred in the first 8 weeks of pregnancy (embryonic period) and those that have occurred at later gestations. While spiral artery vasculopathy and placental infarction have been noted more often among aPL-positive compared with aPL-negative pregnancies that miscarried in the second trimester[50], these findings were not seen in the only published histological description of 11 aPL-positive pregnancies lost in the first trimester.[51] This suggests that first- and second-trimester miscarriage among aPL-positive women have different aetiologies. One can postulate that the former is a consequence of defective implantation and the latter secondary to thrombosis of the utero-placental vasculature.

Defective implantation

Evidence in favour of defective implantation comes from murine models which suggest that aCL inhibit embryonic implantation[52] and that aCL can directly bind to trophoblast and inhibit its formation and function.[53,54] Further support for the concept that aPL cause defective implantation, and hence pregnancy failure, comes from prevalence studies which have reported that aPL are found significantly more often among women who have undergone a failed in vitro fertilization cycle compared with those who have had a successful cycle.[55] However, these same authors, and our own group, have reported that there is no difference in the implantation rate between aPL-positive and aPL-negative women undergoing in vitro fertilization.[56] A possible explanation for this is that among women with infertility, aPL are merely an epiphenomenon and are representative of a disturbed autoimmune response that is itself the cause of the infertility.

Annexin V and thrombosis

Despite the low frequency of systemic thrombosis among women with recurrent miscarriage and aPL[57] the most commonly held view is that pregnancy loss associated with aPL is secondary to thrombosis of the utero-placental vasculature. The levels of Annexin V, a potent anticoagulant which has a high affinity for anionic phospholipids, are decreased on the placental villi of women with aPL.[58] It has further been reported that aPL reduce the levels of Annexin V and accelerate the coagulation of plasma on cultured trophoblast and human umbilical vein endothelial cells.[59]

However, thrombosis of the utero-placental vasculature is neither a universal nor a specific feature of aPL pregnancy loss. Evidence for other mechanisms of action for aPL in causing pregnancy loss have been sought. Attention is focused on three areas of aPL-mediated damage to trophoblast function – inter-trophoblastic fusion, hormone secretion and invasion.

Inter-trophoblastic fusion. Adler et al tested three monoclonal aPL in an assay for inter-trophoblastic fusion.[60] A JAR choriocarcinoma cell line was induced to undergo intercellular fusion by forskolin in the presence or absence of monoclonal aPL. Inter-trophoblastic fusion was assessed by staining membrane tight junctions with fluorescein-conjugated anti-desmosome antibody and counter-staining the nuclei with propidium iodide. After forskolin treatment, 80% of the nuclei were in multinucleate cells. When performed in the presence of the phosphatidylserine-reactive monoclonal antibody, inter-trophoblastic fusion was completely prevented. These data suggest that aPL can affect placental development by interfering with the normal formation of syncytio-trophoblast.

Defective trophoblast invasion. Adequate trophoblast invasion of the decidua is an essential prerequisite for the successful establishment and maintenance of pregnancy. Cytotrophoblast invasion has been investigated in an in vitro system using first-trimester trophoblast and choriocarcinoma cells on filters coated with Matrigel®.[61] Trophoblast or choriocarcinoma exposed to phosphatidylserine-reactive monoclonal antibodies were blocked from traversing the filters.

Treatment of aPL-associated pregnancy losses

A variety of treatments, including steroids, aspirin and heparin, have been used either as single agents or in combination, in attempts to improve the live birth rate among women with aPL. Steroids have fallen into disfavour. In a prospective randomized controlled study it was concluded that treating pregnant women with autoantibodies (including aCL) does not improve the live birth rate and, indeed, is associated with an excess risk of prematurity and the development of gestational hypertension and gestational diabetes.[62]

Both a European randomized controlled trial[63] and a North American study[64] in which women were alternately assigned to treatment, reported that combination therapy with low-dose aspirin and heparin significantly improves the livebirth rate among women with aPL to 70% compared to 40% achieved with aspirin alone. The safety of heparin in pregnancy has been confirmed in a prospective pregnancy study of 150 treated women with the antiphospholipid syndrome.[65,66] It is important to note, however, that despite treatment, pregnancies among women with aPL remain at high risk for pre-term delivery, fetal growth retardation and the development of pregnancy-induced hypertension.[65]

The use of intravenous immunoglobulin (IVIG) to treat women with either unexplained or aPL-associated recurrent miscarriage has recently been investigated. All studies have included small numbers of women and, apart from one[67], have been unable to demonstrate any significant beneficial effect from this treatment.[68–72] Aspirin together with heparin remains the treatment of choice for pregnant women with the antiphospholipid syndrome.

Thrombophilic defects

Acceptance of aPL as an important and treatable cause of recurrent miscarriage has prompted investigators to examine the potential role that other thrombophilic abnormalities may play in the aetiology of pregnancy loss at all gestations. This has led to the development of the hypothesis that some cases of recurrent miscarriage are due to an exaggerated haemostatic response to pregnancy, leading to placental thrombosis, placental infarction and subsequent miscarriage.

Women with recurrent miscarriage are in a pro-thrombotic state outside pregnancy

A subgroup of women with recurrent miscarriage are in a pro-thrombotic state outside pregnancy. We measured the levels of thrombin anti-thrombin (TAT) complexes, a global marker of thrombin generation, in 86 non-pregnant women with recurrent miscarriage and a control group of 34 age-matched, fertile parous women with no previous history of pregnancy loss.[73] TAT levels were significantly higher among women with recurrent miscarriage compared to the control group. This relationship was independent of the gestation of previous miscarriages and also of antiphospholipid antibody status. Using different markers of thrombin generation, it has also been reported that women with recurrent miscarriage are in a chronic state of endothelial stimulation which is associated with activation of the coagulation system.[74] These findings are supported by in vitro data reporting that, in a co-culture system, sera from 63% of women with recurrent miscarriage induced monocyte procoagulant activity.[75]

Coagulation changes precede pregnancy loss

There are few prospective longitudinal studies documenting changes in haemostatic variables in pregnant women with a history of recurrent miscarriage. Two studies do, however, provide evidence of abnormalities in the haemostatic pathways preceding fetal loss. Tulpalla et al reported that women with a history of recurrent miscarriage (RM) in weeks 4–7 of gestation have an excess of thromboxane production, and between weeks 8 and 11 they are relatively prostacyclin-deficient, compared with women with no previous history of pregnancy loss.[76] These changes were greatest among those whose pregnancy ended in abortion. The shift in the thromboxane : prostacyclin ratio in favour of the prothrombotic agent thromboxane may lead to vasospasm and platelet aggregation in the trophoblast, causing the development of microthrombi and placental necrosis.

Woodhams et al also reported that changes in the haemostatic system preceded spontaneous abortion.[77] They reported the cases of two women in whom a significant decrease in the level of protein C and a shortening in the rate of fibrinopeptide A generation (indicating activation of coagulation) could be detected several weeks in advance of the miscarriage. In one of these two women, similar haematological changes were documented in the early weeks of her second pregnancy. These were reversed by the administration of heparin. The patient went on to deliver at term.

PREVALENCE OF SPECIFIC COAGULATION DEFECTS IN WOMEN WITH RECURRENT MISCARRIAGE

Over the last 6 years the genetic basis for some of the commonest coagulation defects – Factor V Leiden, the prothrombin (factor II) G20210A mutation and the C677T mutation in the methylene tetrahydrofolate reductase (MTHFR) gene – have been established. All prevalence studies have included relatively small numbers of women and consequently have reported conflicting results.

Factor V Leiden. Activated protein C resistance, which is most commonly due to a single point mutation (G → A at nucleotide position 1691) in the Factor V gene, is an established risk factor for systemic venous thrombosis. Placental thrombosis in association with Factor V Leiden has also been reported.[78–79] The prevalence of Factor V Leiden among women with recurrent miscarriage has been variably reported to be either similar to that or increased compared to parous controls (Table I).[80–88] Previous studies have included (a) only small numbers of women, (b) have been prone to selection bias, and (c) some have not divided women into those with recurrent first-trimester miscarriage and those with later pregnancy loss. Our own data, based on 1000 consecutive Caucasian women, reports that the Factor V Leiden allele frequency is similar among (a) women with recurrent early miscarriage (3.4%; 56/1632, all heterozygotes); (b) those with a history of late miscarriage (3.4%; 13/388, 11 heterozygotes and one homozygote) and (c) parous controls group (4.0%; 12/300, all heterozygotes).[89]

Table I. Prevalence of the Factor V Leiden allele among women with recurrent miscarriage.

Authors	Trimester of miscarriages	Prevalence of Factor V Leiden allele		*P* value
		Recurrent miscarriage	Controls	
Balasch et al, 1997[80]	1st	1/110	1/100	0.95
Brenner et al, 1997[81]	1st and 2nd	22/78	2/80	<0.001
Grandone et al, 1997[82]	1st	2/54	5/236	0.49
	2nd	5/32		<0.001
Dizon-Townson et al, 1997[83]	1st	0/80	0/50	1.0
Metz et al, 1997[84]	1st and 2nd	6/200	3/170	0.44
Ridker et al, 1998[85]	1st and 2nd	9/226	16/874	0.05
Kutteh et al, 1998[86]	1st	1/100	0/100	0.99
Souza et al, 1999[87]	Not stated	4/122	6/768	<0.001
Tal et al, 1999[88]	Not stated	18/250	7/250	0.02

Prothrombin G20210A mutation and the C677T mutation in MTHFR gene. The prevalence of these mutations among women with recurrent miscarriage has been variously reported to be either similar to, or increased, compared with their prevalence among controls.[90]

Pregnancy outcome among women with thrombophilic defects

Several retrospective studies have reported a strong relationship between maternal thrombophilic defects and adverse late pregnancy outcome.[91,92] However, apart from

the inherent weakness of retrospective data, the results of these studies may have been prone to selection bias and should be interpreted with caution.

Sanson et al[93] studied the previous pregnancy outcome of 129 women who were relatives of individuals with a proven venous thromboembolism. Among those with a proven thrombophilic defect, 22% of their previous pregnancies had miscarried compared to only 11% among those with no haemostatic defect (odds ratio 2.0; 95% confidence intervals 1.2–3.3). The differences were most marked among those with an anti-thrombin III (ATIII) or protein C deficiency. Factor V Leiden was not tested for in this study.

Preston et al[91] also studied the outcome of previous pregnancies among 843 women with a thrombophilic defect who were participating in the European Prospective Cohort on Thrombophilia. Women with thrombophilia were at increased risk of fetal loss compared with controls (odds ratio 1.35; 95% confidence intervals 1.01–1.82). The risk was higher for stillbirth than for miscarriage and greatest among those women with combined thromophilic defects.

Kupferminc et al[92] screened 110 Jewish women whose pregnancies were complicated by severe pre-eclampsia, placental abruption, intra-uterine growth restriction or stillbirth for the three common thrombophilic mutations. The control group consisted of ethnically matched women with uncomplicated pregnancies. One or more of the thrombophilic mutations (Factor V Leiden, the C677T mutation in the MTHFR gene or the prothrombin G20210A mutation) was found in 52% of women with obstetric complications and, surprisingly, in as many as 17% of those with normal pregnancies. In subgroup analyses the prevalence of these mutations among those with (a) pre-eclampsia was 53%, (b) placental abruption 60%, (c) intra-uterine growth restriction 50%, and (d) stillbirth 42%.

These retrospective data, while supporting the hypothesis that maternal thrombophilic defects are strongly associated with adverse pregnancy outcome, have to be interpreted with caution.[94] The late-pregnancy problems cited by Kupferminc and colleagues affect no more than 5% of pregnancies, 95% of pregnant women enjoying uncomplicated pregnancies. Since 17% of women with a normal pregnancy outcome had a thrombophilic defect, the true risk of serious obstetric complications in women with either genetic or acquired thrombophilic defects is uncertain. Currently, there are no published data on the prospective outcome of untreated pregnancies among women with recurrent miscarriage and thrombophilic defects.

SUMMARY AND CONCLUSIONS

The effective management of women with recurrent miscarriage has been hindered by (a) the lack of epidemiological data on the incidence and risks of recurrence, and (b) the incorrect presumption that all cases must have a systematic and demonstrable underlying cause. We can conclude that at least 50% of women who experience recurrent miscarriage do so by chance. However, it is often difficult for the patient and her doctor to accept that three or more consecutive pregnancy losses are due to bad luck alone, and the search for an abnormal test result often leads to extensive investigations of doubtful practical use and the implementation of empirical treatment.

It is important for clinicians to remember that women who have miscarried recurrently from an established recurrent cause are not protected from a future sporadic miscarriage secondary to fetal aneuploidy. Furthermore, the likelihood of a successful pregnancy following three previous miscarriages is in the region of 60%, even

when no medical investigations are available, which further emphasizes the importance of randomized controlled trials to assess the efficacy of any potential new treatment options.

The introduction of evidence-based medical practice into the investigation and treatment of women with recurrent miscarriage has started and now needs to be firmly established. Advances in our understanding of the causes of repeated pregnancy failure have been made over the last decade. For example, the importance of detecting the presence of antiphospholipid antibodies during pregnancy has led to the introduction of treatment regimens which significantly improve the live birth rate. Furthermore, the potential role that other thrombophilic defects may play in the pathogenesis of recurrent miscarriage is currently being investigated. Future research needs to be directed towards understanding the molecular genetic abnormalities which predispose the mother, father and/or their fetus to succumb to infective, hormonal, immune or environmental factors resulting in pregnancy loss.

A dedicated miscarriage clinic has four purposes. First, to identify those women with an underlying cause for their pregnancy losses. Second, to conduct randomized prospective controlled studies of sufficient power to determine the optimal treatment of women with an identified cause for their pregnancy losses. Third, to practice evidence-based medicine and avoid subjecting those women with no identifiable cause for their miscarriages to treatments of no proven benefit. Fourth, to identify those women whose miscarriages remain unexplained despite detailed investigation, because this group can be reassured that they have a 75% chance of a successful outcome to their next pregnancy with psychological support and tender loving care alone.[95] This high success rate with supportive care alone emphasizes the fact that the use of empirical therapy in women with no recognizable aetiological factors for their miscarriages is unnecessary, potentially harmful and should be resisted. Furthermore, the clinical evaluation of future treatments for recurrent miscarriage should be performed only in the context of randomized controlled trials.

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