Opinion

Miscarriage in contemporary maternal–fetal medicine: targeting clinical dilemmas

Defining miscarriage

Miscarriage is the most common adverse outcome in maternal–fetal medicine, occurring in 10–20% of clinical pregnancies. However, the total rate of pregnancy loss is difficult to estimate if cases of peri-implantation failure are taken into account. These cases are diagnosed only by urinary human chorionic gonadotropin levels greater than 0.025 ng/mL on 3 consecutive days, and their rate could be as high as 60% in the population at reproductive age. Recently, Silver et al. suggested replacing the more generic medical term of ‘early pregnancy loss’ with terminology based on developmental biology such as peri-implantational loss (<5 weeks), pre-embryonic loss (5 weeks), embryonic loss (6–9 weeks) and fetal demise (10–19 weeks). Yet, the Royal College of Obstetricians and Gynaecologists (RCOG) considers 24 weeks as the upper limit for miscarriage, given that this gestational age is nowadays regarded as the limit of viability.

Miscarriage, otherwise referred to as spontaneous abortion, should be considered a clinical event, consisting of all losses beyond 5 weeks of gestational age. In this commentary, given that we deal with clinically diagnosed pregnancy, our preference is to use the term ‘miscarriage’. Regarding a woman’s total number of miscarriages, a distinction is made between sporadic (one) and recurrent (at least two) miscarriage.

Predisposing factors for miscarriage

Risk factors for miscarriage have been described extensively. Data extracted from national Danish registries encompassing 15 years established that risk of miscarriage increases with maternal age. Taking into account only miscarriages leading to hospital admissions, an overall rate of 11% was observed, ranging from 9% at 22 years to 84% by 48 years. The risk of miscarriage, as well as being age-dependent, is reported to depend on previous reproductive history and parity in the preceding 10 years. It appears that in women with no previous history of miscarriage, there is a slightly higher risk among parous, as compared to nulliparous, women. Conversely, in women with a history of miscarriage, this tendency is reversed, with a higher risk among nulliparous women. In relation to paternal age, the effect is unclear due to a multitude of confounding factors. It seems, however, that advanced paternal age over 50 years accounts for double the risk of late fetal loss.

Recently, prediction of miscarriage at 6–10 weeks and 11–13 weeks has been attempted using maternal and pregnancy characteristics. At 6–10 weeks, miscarriage can be predicted using a combination of maternal characteristics (advanced age, African racial origin, and cigarette smoking), pregnancy complications (vaginal bleeding) and ultrasound findings (increased yolk sac diameter and decreased gestational sac diameter, fetal heart rate and crown–rump length (CRL)). The same group also investigated several models combining risk factors at 11–13 weeks to determine the risk of miscarriage. The risk increased with certain maternal factors (higher age and weight, African racial origin, previous miscarriages or stillbirths, pre-existing diabetes mellitus and conception with ovulation induction) and with abnormal first-trimester screening markers (low pregnancy-associated plasma protein-A levels, increased nuchal translucency thickness and reversed ductus venous A-wave).

A novel approach for the prediction of miscarriage, presented in the current issue of this Journal, is based on the timely recognition of failed placentation in pregnancies without potential to evolve. Reduced trophoblast volume and growth during the first trimester (6–12 weeks), assessed by three-dimensional volumetric ultrasound, is particularly evident at 6–8 weeks. These findings are anticipated in autosomal trisomies except for trisomy 21, given that a small placental volume has been reported for trisomies 13 and 18 at 11–13 weeks. However, the extent of failed placentation in euploid pregnancy loss remains unknown.

Interestingly, when a first pregnancy is complicated by miscarriage, there is an independent increased risk of adverse perinatal outcome in the subsequent pregnancy. Specifically, there is increased risk of premature rupture of membranes, preterm delivery, growth restriction, pre-eclampsia and delivery by Cesarean section.

The challenge of diagnosing miscarriage

Ultrasound is the method of choice for the diagnosis of early embryo demise. A recent editorial by Thilaganathan summarizing the latest data urges clinicians to establish standard reference sonographic criteria for accurate diagnosis of miscarriage. The guidelines issued by RCOG in 2006 and by the American College of Radiology in 2009 had discordant recommendations regarding whether to consider diagnostic: a) an ‘empty sac’ diameter of 16 or 20 mm; and b) an embryonic CRL of 5 or 6 mm without cardiac activity. Abdallah et al. demonstrated that 4.4% and 0.5% of continuing pregnancies are misdiagnosed as miscarriages with an...
empty gestational sac diameter of 16 and 20 mm, respectively. Similarly, there is an 8.3% false-positive rate if miscarriage is diagnosed by a 5-mm CRL cut-off for embryos with an absent heart beat. Thus, the authors suggest using a 25-mm gestational sac and a 7-mm CRL as safer cut-offs. The same group also suggested that, at a follow-up scan a week later, failure to visualize a yolk sac or embryo, rather than slow growth of gestational sac or CRL, is associated with miscarriage. Furthermore, the range of interobserver limits of agreement in mean sac diameter and CRL evaluated by transvaginal ultrasound, as reported by Pexsters et al., revealed measurement discrepancies and possible diagnostic error. Thus, there is a chance of accidental termination of desired pregnancies when measurements approach the decision-making cut-offs. Immediately following this evidence, the RCOG/National Institute for Health and Clinical Excellence (NICE) guidance for early pregnancy loss was revised; the new recommendations establish a diagnosis of miscarriage by transvaginal ultrasound if there is an empty gestational sac measuring ≥ 25 mm or a fetal pole with no heart beat measuring ≥ 7 mm. In addition, a second opinion or a repeat scan performed in a week’s time is strongly recommended. In any case, a cautious approach is advised to avoid misdiagnosis.

Underestimated psychological morbidity

The emotional impact of miscarriage, although generally underestimated by clinicians, can be as important as that experienced in second-trimester termination of pregnancy. Depressive and anxiety symptoms and disorders following miscarriage have been the focus of research in the last decade. Lee et al. assessed separately the frequency of anxiety and depressive symptoms occurring after spontaneous miscarriage and concluded that, of the two, the prevalence of anxiety is significantly higher. A recent longitudinal study by Lok et al. provided emerging evidence regarding depression symptomatology in women who experienced miscarriage. They demonstrated that although psychological morbidity decreases over time, a significant proportion of these women are still distressed after 1 year. Furthermore, delayed depression was also noted in the group of women who were initially less distressed. Women who have miscarried also appear to be at risk of anxiety stress disorders such as obsessive-compulsive disorder, acute-stress disorder or post-traumatic stress disorder, with reported prevalence ranging from 15% to 25% up to 4–6 months following miscarriage. Long-term psychological implications of first-trimester pregnancy loss have not been explored extensively in the literature and consequently reports are equivocal. The risk of a subsequent pregnancy complicated by psychological morbidity in women who have miscarried needs to be investigated further. Longitudinal studies are warranted to define if these patients are more likely to suffer from overt post-traumatic symptoms in need of treatment or postnatal depression.

In any case, timely diagnosis and follow-up of these cases will ensure delivery of appropriate care. Healthcare practitioners should be informed and trained in dealing with psychological morbidity following a miscarriage. The RCOG and the European Society for Human Reproduction Special Interest Group for Early Pregnancy are even encouraging a new revised terminology for events related to miscarriage in order to alleviate the negative impact some terms could exert on patients. For example, when counseling patients, inadvertent use of terms such as ‘abortion’ and ‘pregnancy failure’ should be avoided, and replaced by the term ‘miscarriage’, while ‘blighted ovum’ could be replaced by the term ‘delayed miscarriage’.

High-yield karyotyping

Several etiologies for first-trimester miscarriage have been described, including chromosomal abnormalities, hormonal imbalances, immunological disorders, uterine malformations and environmental exposures. Ultrasound has contributed mainly to diagnosis, adding little to establishing the etiology of miscarriage, either sporadic or recurrent. Recently, Angiolucci et al. attempted to identify ultrasound features suggestive of aneuploidy: miscarriage due to trisomy 22 was characterized mostly by an enlarged yolk sac and smaller embryos correlated with monosomy X, while normal ultrasound findings correlated with trisomy 21. Historically, histopathology has been the test available to evaluate a miscarriage. However, pathology studies of placental and embryonic tissue, beyond diagnosing molar and excluding ectopic pregnancies, are far from conclusive regarding the etiology of miscarriage.

Since more than half of miscarriages are due to chromosomal anomalies, and these differ in their recurrence patterns, chromosomal analysis should be offered as soon as miscarriage is diagnosed. The benefits of recognizing the pathology underlying pregnancy failure are obvious. Yet, despite the extensive work-up following stillbirth, only histopathology is commonly offered for evaluation of miscarriage. We recently published a study carried out in our center, in which all women miscarrying from 2007 onwards were offered placental karyotyping. The uptake was high, and we found a 65% rate of chromosomal anomaly in our series, with a similar spectrum between pre-embryonic (empty sac) and embryonic miscarriages. Pre-embryonic pregnancy losses occur at an earlier gestational age than do miscarriages due to viable trisomies (trisomies 13, 18 and 21) and monosomy X (Turner syndrome), i.e. neither viable trisomies nor monosomy X are responsible for pre-embryonic miscarriages. The information provided by cytogenetic studies was valuable for parental and future reproductive counseling, since different types of chromosomal anomalies have different recurrence patterns. For instance, inherited unbalanced structural

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anomalies have the highest risk of recurrence, autosomal trisomies also carry some risk, but other types are unlikely to recur\textsuperscript{30}. Thus, chromosomal analysis may provide an answer to common questions such as ‘Why did it happen to me?’ and ‘Will it happen again?’. These answers helped to reduce our patients’ anxiety and enabled them to deal better with bereavement and grieving following pregnancy loss\textsuperscript{32}.

Testing villi before evacuation rather than products of conception

As already mentioned, chromosomal anomalies account for the vast majority of early pregnancy losses\textsuperscript{29–31}. When compared with analysis of products of conception, chorionic villus sampling (CVS) is more successful in achieving a cytogenetic result. It is therefore crucial to obtain placental tissue before any treatment commences. Inaccuracy of cytogenetic analysis or failure to deliver results may be due to unsuccessful culture growth, microbial contamination or maternal cell contamination\textsuperscript{33}. The semi-direct method for chorionic villi overcomes these limitations, since omitting culture eliminates the potential for maternal contamination. Occasionally, metaphase samples cannot be obtained, and it is for this reason that other cytogenetic and molecular tests have been introduced. Fluorescence in-situ hybridization (FISH) is a rapid test of uncultured material that allows determination of ploidy status and chromosomal reorganizations, but the obtained information is limited by the choice of probe used\textsuperscript{34}. Quantitative fluorescent polymerase chain reaction (QF-PCR) is a rapid molecular test that diagnoses mosaicism, maternal cell contamination and partial or complete hydatidiform mole (coupled with a maternal sample), but again the number of analyzed chromosomes is limited to between five and ten\textsuperscript{35}. Non-invasive prenatal testing (NIPT), using cell-free fetal DNA (cffDNA) in maternal blood, does not appear to have a role in pregnancy loss, although some trophoblast activity may persist after fetal demise. Besides NIPT testing only five chromosomes, cffDNA (originally from placental tissue) is expected to present a low ‘fetal fraction’ in miscarriages before 10 weeks\textsuperscript{36}. Another new method of chromosomal analysis covering the whole genome is array comparative genomic hybridization (array-CGH), with or without single nucleotide polymorphism (SNP) testing. Array-CGH detects aneuploidy and unbalanced structural rearrangements, as well as DNA gains and losses less than 10 Mbp in size, which go undetected by karyotyping. However, balanced translocations and many polyploidy remain undetected\textsuperscript{37,38}. When applied to products of conception, array-CGH has been shown to detect \textit{de-novo} copy number changes in 13% of cases in which cytogenetic testing (i.e. karyotype) was normal or not available\textsuperscript{39}. SNP microarrays differ from array-CGH in their ability to identify maternal contamination and uniparental disomy\textsuperscript{38}. Although costs may still be higher and laboratory experience lower compared with conventional karyotyping, there is evidence that, nowadays, array-CGH with SNP is the method of choice, after maternal cell contamination, polyploidy and partial/complete hydatidiform mole have been ruled out by a normal QF-PCR result\textsuperscript{40}.

Present strategies in invasive procedure training are not based on a general consensus. The current requirements for increasing numbers of clinicians performing invasive procedures in prenatal diagnosis have compromised training standards\textsuperscript{41}. Furthermore, both the necessity to acquire these technical skills in real patients and the consideration that in some cases these diagnostic procedures could be the last chance for a patient to make crucial decisions make training even more complicated. This is certainly the case regarding CVS training. The introduction of CVS before evacuation in the management of miscarriage may prove valuable to the training process. Trainees will acquire more experience by increasing the number of procedures performed without the extra psychological pressure of interfering with a viable pregnancy.

Once an anomaly, always a procedure?

Historically, use of the simplistic 1% approach (‘once an anomaly, always an invasive procedure’) to estimate the recurrence risk was widespread after a chromosomal anomaly diagnosed in a viable pregnancy. In reality, a more refined definition of the recurrence risk in subsequent pregnancies can be attempted, estimating the excess risk for both homo- (same) and hetero- (different) trisomy in women with a previous pregnancy affected by autosomal chromosomal abnormality. Earlier studies presented various statistical models to calculate the recurrence risk for aneuploidies, such as relative risk (RR), standardized morbidity ratio (SMR) and excess risk. RR and SMR were both calculated as the ratio between observed and expected risk\textsuperscript{42,43}. The statistical implication of excess risk is that it describes the component of risk due to the previous affected pregnancy, independent of the background risk of maternal age\textsuperscript{44}.

Data from the National Down’s Syndrome Cytogenetics Register of England and Wales demonstrate that the excess risk for a subsequent trisomy 21 pregnancy decreases with increased maternal age at the time of the previously affected trisomy 21 pregnancy, from 0.62% at 20 years to 0.01% at 46 years\textsuperscript{45}. Data from the same group encompassing three Australian registers reported the increased recurrence risk for both the same and different trisomies, when the previous pregnancy was affected by trisomy 13, 18 or 21\textsuperscript{42}. Trisomies 13 and 18 are more likely to recur (RR = 3.8) than is trisomy 21 (RR = 2.2). If maternal age is taken into account, the increased risk is greater for younger women\textsuperscript{42}. Interestingly, Warburton \textit{et al.}\textsuperscript{43}, who analyzed data from Canada and United States registries, reported similar results. Specifically, if trisomy 21 affects a previous (index) pregnancy before 30 years of age, the SMR is 4.7 for trisomy 21 and 2.4 for heterotrisomy. Conversely, if the maternal age is 30 years or more, SMR is 1.6 for all viable trisomies. Overall, index pregnancies with trisomies 13 or 18
increase the recurrence risk by 2.5 for trisomy 21 and 1.6 for other trisomies. Finally, a previous pregnancy with a non-viable trisomy increases the risk by 1.8 for all subsequent viable trisomies. It is generally accepted that the association of young maternal age and increased recurrence risk is probably due to disjunction errors during meiosis. These results are in line with reports from the field of preimplantation genetic screening (PGS). Munne et al.\textsuperscript{46} demonstrated that a previous trisomic pregnancy, irrespective of viability, is associated with an increased risk of future aneuploidy. Similarly, Al Asmar et al.\textsuperscript{57} reported a two-fold increase in number of aneuploid embryos after a preceding autosomal anomaly.

**A simpler work-up for recurrent miscarriage**

Recurrent miscarriage affects 1% of couples of reproductive age\textsuperscript{48} and historically has been attributed to genetic, anatomical, immunological and endocrinological factors\textsuperscript{49}. More than half of recurrent miscarriage cases are considered idiopathic after extensive work-up in the couple, including maternal pelvic ultrasound, hysterosalpingography, thrombophilia screening (particularly for antiphospholipid antibodies) and thyroid hormone assessment, and parental karyotyping\textsuperscript{50}.

In our center during the last decade, to all women with recurrent miscarriage we have offered routinely transcervical CVS before evacuation of the products of conception. In our recently published series, no differences in the chromosomal anomaly rate were found between sporadic (first) (66%) and recurrent (third or more) (60%) miscarriage\textsuperscript{51}. Maternal age was found to be the only statistically significant predictor for aneuploidy; specifically, the chromosomal anomaly rate increased with increased maternal age, being 54% for women below 35 years of age and 74% for those aged 35 years or more. However, within both age groups, no differences were observed between those with sporadic and those with recurrent miscarriage, these chromosomal anomaly rates being 56% vs 44% in younger women and 78% vs 69% in older women. Regarding differences in the chromosomal anomaly spectrum, in the younger group, there were more chromosomal structural anomalies in cases of recurrent compared with sporadic miscarriage (29% vs 5%). In the older group, the autosomal trisomy pattern was different, given that viable trisomies (trisomies 13, 18 and 21) and non-viable ones (other autosomal trisomies) had a similar distribution in sporadic miscarriage (37% vs 38%, respectively), while in recurrent miscarriage there were more non-viable (37%) than viable (11%) trisomies, possibly due to a higher proportion of pre-embryonic miscarriages in this group\textsuperscript{51}.

Our findings are in agreement with a recent commentary of Saravelos and Li\textsuperscript{52}, which argues that the majority of women with unexplained recurrent miscarriage are in fact healthy individuals, with no underlying pathology, who have suffered three miscarriages purely by chance. A typical case in this group of unexplained miscarriage would be a 40-year-old woman with three early losses and with a finding of aneuploidy in the most recent miscarriage. This group may account for two-thirds of unexplained recurrent and one third of all recurrent miscarriages at 30–34 years of age. The authors recommend karyotyping to identify those cases of recurrent miscarriage occurring by chance. In line with this recommendation, Robberecht et al. highlighted the benefit of applying SNP arrays in cases of euploid recurrent miscarriage\textsuperscript{53}. They identified uncommon de-novo copy number variants and regions of loss of heterozygosity of more than 5 Mb in half of their sample size of unexplained recurrent miscarriage.

Furthermore, PGS has shed more light on the etiology of this entity. Higher rates of chromosomal abnormalities at PGS in patients with recurrent pregnancy loss are documented by many authors\textsuperscript{54–56}. Specifically, a two-fold incidence of aneuploid pregnancy is reported after a previous trisomic conception, irrespective of whether the index aneuploidy follows spontaneous conception or assisted reproductive technology\textsuperscript{57}. Two recent reviews\textsuperscript{57,58} and a study by Hodes-Wertz et al.\textsuperscript{54}, expressing concerns about the efficiency of PGS by FISH analysis, due to the poor livebirth rate, have led research groups to develop new PGS methods such as polar body or blastocyst sampling in combination with the use of array-CGH, which is able to interrogate all chromosomes.

Therefore, chromosomal analysis could contribute to select cases of recurrent miscarriage due to chromosomal abnormalities, avoiding unnecessary and costly investigations and treatments. Similarly, exclusion of chromosomal structural rearrangements means that there is no need for parental karyotyping. Indeed, the cost-effectiveness of parental karyotyping in England has been seriously questioned as only 1% of couples with balanced translocation will produce an affected offspring\textsuperscript{59}.

**Still seeking optimal management**

Historically, dilatation and curettage has been the cornerstone in the treatment of first-trimester pregnancy loss. Medical management is gaining acceptability, while 7–14 days’ expectant management has been suggested by NICE as a first-line therapeutic option, aiming at a non-invasive resolution of the failed pregnancy\textsuperscript{19}. There is considerable heterogeneity between reported series and efficacy of treatment alternatives. Recent data comparing surgical with expectant treatment do not support the superiority of surgical treatment, because of similar rates of infection and future reproductive and psychological outcomes\textsuperscript{60}. While cost-effectiveness analysis mostly shows expectant treatment to be preferable, this modality results in higher blood transfusion rates and pain scores\textsuperscript{60}. NICE guidance in fact recommends avoiding expectant management in cases with increased risk of bleeding, infection or a previous traumatic obstetric experience\textsuperscript{59}. Identification of predictors for expectant management success, such as lower values of inhibin-A and inhibin proα-CRI and higher level of insulin-like growth factor-binding protein-1 (IGFBP-1), could increase up to 69% the
resolution rate of missed and incomplete miscarriage. As an alternative to both surgical and expectant management, medical management is suggested as a safe second-line option. The available literature suggests that misoprostol, a prostaglandin E1 analog, administered either orally or vaginally, is a successful treatment for early pregnancy loss. Regarding dosage, it is reported that regimens of 600 or 800 µg of intravaginal misoprostol are equally effective in achieving complete uterine evacuation in up to 85% of patients, without serious side effects. It is noteworthy that the aforementioned high success rates occur in selected cases, i.e. nulliparous women or in those with lower abdominal pain and active bleeding. Immediate medical treatment, compared with delayed medical treatment following a period of expectant management, reduces the need for surgical intervention. In accordance with this evidence, NICE recommends the use of preferably 800 µg of intravaginal misoprostol together with pain relief and antiemetics. Finally, surgical treatment is suggested in cases of failure of previous management or when clinically appropriate.

Efficacy of the different treatment options could possibly be improved by accurate classification of each case, according to biological criteria, into pre-embryonic, embryonic or fetal subgroup. Yet, there is still room for improvement regarding the optimal management of miscarriage through evidence-based standards and anticipation at all times of patients’ needs.

Conclusion

In conclusion, miscarriage is a life event that can cause mental distress with potentially long-term consequences. The paucity of guidelines for clinical practice is surprising not only because of the emotional impact of miscarriage, but also because of its common occurrence during reproductive age. High rates of spontaneous first-trimester miscarriage and continuing discrepancies in diagnosis and treatment have prompted clinicians to focus on improving the delivery of care and introducing more strict protocols. The recently issued RCOG and NICE (2012) guidelines have extended miscarriage diagnostic criteria to an empty gestational sac ≥ 25 mm or a fetal pole ≥ 7 mm with no heart beat. Emphasis is given to ascertain diagnosis through a second opinion and/or a repeat scan in a week’s time. Once miscarriage is confirmed, clinicians should base management on 7–14 days of expectant management as the first-line treatment, but other options should be explored when indicated.

Traditionally, because of the high prevalence of chromosomal anomalies in first-trimester loss, karyotyping was considered redundant. However, chromosomal studies provide valuable information about the cause of miscarriage, as well as a recurrence risk estimate for the couple. Thus, CVS could be offered routinely to reduce the high rates of unsuccessful karyotyping, particularly when array-CGH is not used. Of note, distinct recurrence risk can be obtained for both homotrisomy and heterotrisomy according to maternal age. Individualizing recurrence risk should be regarded as the recommended clinical practice, instead of suggesting an invasive procedure after any viable chromosomal anomaly in a previous pregnancy. In the event of recurrent miscarriage, chromosomal studies of the miscarried pregnancy itself, rather than of the parents, are more relevant and may eliminate further costly testing. High-resolution advances in genetics technology might help to identify subtle genetic alterations as a cause of unexplained recurrent miscarriage. The time has come to consider first-trimester miscarriage not as a trivial incident but as a profound adverse life event. Building on evidence-based approaches in management and counseling, future research will allow a more comprehensive treatment of women who experience miscarriage.

REFERENCES


