Miscarriage 1

Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss

Siobhan Quenby, Ioannis D Gallos, Rima K Dhillon-Smith, Marcelina Podesek, Mary D Stephenson, Joanne Fisher, Jan J Brosens, Jane Brewin, Rosanna Ramhorst, Emma S Lucas, Rajiv C McCoy, Robert Anderson, Shahd Daher, Lesley Regan, Maya Al-Memar, Tom Bourne, David A MacIntyre, Raj Rai, Ole B Christiansen, Mayumi Sugiura-Ogasawara, Joshua Odendaal, Adam J Devall, Phillip R Bennett, Stavros Petrou, Arri Coomarasamy

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This is the first in a Series of three papers about miscarriage

Division of Biomedical Sciences, Warwick Medical School (Prof S Quenby MD, Prof J J Brosens PhD, E S Lucas PhD, J Odendaal MBBS) **and Warwick Clinical Trials Unit** (J Fisher PhD), **University of Warwick, Warwick, UK; Tommy's National Centre for Miscarriage Research, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK** (Prof S Quenby, Prof J J Brosens, E S Lucas, J Odendaal)**; Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK** (I D Gallos MD, R K Dhillon-Smith PhD, M Podesek MSc, A J Devall PhD, Prof A Coomarasamy MD)**; University of Illinois Recurrent Pregnancy Loss Program, Department of Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, IL, USA** (Prof M D Stephenson MD)**; Tommy's Charity, Laurence Pountney Hill, London, UK** (J Brewin BSc)**; CONICET, Universidad de Buenos Aires, Instituto de Química Biológica de la Facultad de Ciencias Exactas y Naturales IQUIBICEN, Buenos Aires, Argentina** (R Ramhorst PhD)**; Department of Biology, Johns Hopkins University, Baltimore, MD, USA** (R C McCoy PhD)**; Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK** (R Anderson MA, S Daher PhD, Prof S Petrou PhD)**; Tommy's**

Miscarriage is generally defined as the loss of a pregnancy before viability. An estimated 23 million miscarriages occur every year worldwide, translating to 44 pregnancy losses each minute. The pooled risk of miscarriage is 15·3% (95% CI 12·5–18·7%) of all recognised pregnancies. The population prevalence of women who have had one miscarriage is 10·8% (10·3–11·4%), two miscarriages is 1·9% (1·8–2·1%), and three or more miscarriages is 0·7% (0·5–0·8%). Risk factors for miscarriage include very young or older female age (younger than 20 years and older than 35 years), older male age (older than 40 years), very low or very high body-mass index, Black ethnicity, previous miscarriages, smoking, alcohol, stress, working night shifts, air pollution, and exposure to pesticides. The consequences of miscarriage are both physical, such as bleeding or infection, and psychological. Psychological consequences include increases in the risk of anxiety, depression, post-traumatic stress disorder, and suicide. Miscarriage, and especially recurrent miscarriage, is also a sentinel risk marker for obstetric complications, including preterm birth, fetal growth restriction, placental abruption, and stillbirth in future pregnancies, and a predictor of longer-term health problems, such as cardiovascular disease and venous thromboembolism. The costs of miscarriage affect individuals, health-care systems, and society. The short-term national economic cost of miscarriage is estimated to be £471 million per year in the UK. As recurrent miscarriage is a sentinel marker for various obstetric risks in future pregnancies, women should receive care in preconception and obstetric clinics specialising in patients at high risk. As psychological morbidity is common after pregnancy loss, effective screening instruments and treatment options for mental health consequences of miscarriage need to be available. We recommend that miscarriage data are gathered and reported to facilitate comparison of rates among countries, to accelerate research, and to improve patient care and policy development.

Introduction

Miscarriage is often misunderstood by many women, men,[1] and health-care providers, and misconceptions about miscarriage are widespread.[1–3] For example, women might believe miscarriage is rare, that it could be caused by lifting heavy objects or previous contraceptive use, or that there are no effective treatments to prevent a miscarriage.[3] Such misconceptions can be damaging, leaving women and their partners feeling at fault and not seeking treatment and support.[1] Miscarriage can also lead to isolation, since many women might not tell their family, close friends, or even their partner about the loss of their pregnancy. Couples have voiced concerns over unsympathetic routine clinical care by health-care providers.[4–6]

Women and their partners who have had a miscarriage generally want to understand why the miscarriage occurred, what they can do to prevent miscarriage from happening again, what the chance is of a subsequent pregnancy resulting in a healthy baby, and how to deal with their grief surrounding their loss.[3] Couples might be given diverse opinions by different health-care professionals, which can exacerbate their distress. There are also debates over definitions, causes, consequences, and costs of miscarriage. This paper is the first of three in this Series on miscarriage in which we present the current knowledge, recommendations, need for further research, and a call to action on priorities. We discuss the epidemiology of sporadic and recurrent miscarriage, and present a literature review of the risk factors and consequences of miscarriage on future obstetric and maternal psychological and long-term health. We also evaluate the economic cost of miscarriage through a review of the literature.

Definitions and terminology

The definition of miscarriage varies among countries and international organisations, affecting estimations of the risk and prevalence of miscarriage. Miscarriage is generally defined as the loss of an intrauterine pregnancy before viability; however, challenges exist over the diagnosis of pregnancy, and the definitions of what is unequivocally an intrauterine pregnancy and what is viability. The limits of viability can be defined by gestational age or by fetal weight. The gestational threshold for viability can range from 20 weeks to 28 weeks of pregnancy depending on geographical region. WHO defines miscarriage as the expulsion or extraction of a fetus (embryo) weighing less than 500 g equivalent to approximately 22 weeks gestation.[7,8] In the UK, the limit of viability is determined legally as up to

Search strategy and selection criteria

We did a comprehensive literature search on MEDLINE (from database inception to May, 2020). The date of our last search was May 14, 2020. We searched for existing systematic reviews and primary studies on risk factors for miscarriage (demographic, lifestyle, clinical, and environmental factors). A separate search was conducted for observational studies of obstetric, perinatal, and long-term health risks associated with miscarriage. Free text search terms and Medical Subject Headings terms for miscarriage were combined with each risk factor, pregnancy consequences, and perinatal and long-term health outcomes. For each literature review, the raw aggregate data or adjusted odds ratios were presented, which are presented in the appendix pp 3–9.

Key messages

- Miscarriage risk: nine studies, consisting of 4 638 974 pregnancies, found the pooled risk of miscarriage was 15·3% (95% CI 12·5–18·7) of all recognised pregnancies. The risk of miscarriage is lowest in women with no history of miscarriage (11%), and then increases by about 10% for each additional miscarriage, reaching 42% in women with three or more previous miscarriages.
- Demographic risk factors: risk of miscarriage is lowest in women aged 20–29 years at 12%, increasing to 65% in women aged 45 years and older. Male age older than 40 years is also associated with an increased risk of miscarriage. Female body-mass index (BMI) is associated with miscarriage risk; the BMI associated with the least risk of miscarriage is 18·5–24·9 kg/m^2. Black ethnicity is associated with a high miscarriage risk.
- Lifestyle and environmental risk factors: both smoking and alcohol consumption during pregnancy are associated with an increased risk of miscarriage, as is exposure to air pollution and pesticides. Persistent stress and working night shifts are associated with an increased risk.
- Risks and complications of miscarriage: miscarriage, and especially recurrent miscarriage, is associated with future obstetric complications. The risk of preterm birth increases stepwise with each previous miscarriage, showing a biological gradient with the highest risk in women with three or more previous miscarriages. The risk of fetal growth restriction, placental abruption, and stillbirth in future pregnancies is also increased. A history of recurrent miscarriage is also a predictor of longer-term health problems, such as cardiovascular disease and venous thromboembolism, and mental health consequences.
- Economic costs of miscarriage: the costs of miscarriage affect individuals, health-care systems, and society. The short-term national economic cost of miscarriage is estimated to be £471 million per year in the UK. Further research is needed to understand the long-term economic costs, along with the gathering and reporting of miscarriage data to facilitate comparison of rates among countries, to accelerate research, and to improve patient care and policy development.

24 weeks and 0 days of gestation.[9] The American Society for Reproductive Medicine defines miscarriage as a clinical pregnancy loss of less than 20 weeks of gestation.[10] The European Society of Human Reproduction and Embryology defines miscarriage as the loss of pregnancy before 22 weeks of gestation.[11] The limit of viability is, in most nations, legally defined and, particularly as neonatal intensive care for preterm infants becomes more effective in high-income countries, often deviates from the medical limits of viability. Although embryologists define the first week of pregnancy as the week following implantation, historically, for clinical purposes, gestational age has referred to the length of pregnancy after the first day of the last menstrual period. That convention will be used in this Series.

A bewildering array of terminology for pregnancy loss before viability has developed on the basis of whether the pregnancy diagnosis was derived from serum or urinary β-human chorionic gonadotropin (hCG) concentrations, or from the visualisation of an intrauterine pregnancy by ultrasonography (panel).

Risk of miscarriage

The risk of miscarriage depends on the defined upper gestational age or fetal weight limit, and whether the denominator is all pregnancies identified by serum or urinary β-hCG concentrations or only pregnancies diagnosed by ultrasonography. Inclusion of preclinical losses, defined as the loss of a pregnancy before diagnosis by ultrasonography, will increase the miscarriage rate. The development of highly sensitive β-hCG assays has allowed detection of very early pregnancies (from 22 days since last menstrual period) and, therefore, diagnosis of very early miscarriages which otherwise might have been missed, again resulting in an increase in the miscarriage rate. Finally, demographic features of a population will affect the miscarriage risk, with the distribution of female age having a profound effect on the risk (appendix p 4).

Our literature search identified nine large cohort studies that reported on miscarriage risk in an aggregated total of 4638974 pregnancies (appendix p 3).[14–21] All studies were from Europe and North America. Six studies were prospective cohorts using self-reported pregnancy outcomes, and three used record linkage to ascertain the outcome of miscarriage. Our review of current evidence found that the pooled risk of miscarriage was 15·3% (95% CI 12·5–18·7%) of all recognised pregnancies (appendix p 3).

With an approximate 130 million births per year worldwide,[22] a 15% risk of miscarriage suggests approximately 23 million miscarriages per year, or 44 per min. In the UK, there were 40000–45000 hospital admissions in 2012–13 for the management of miscarriage[23] but, since miscarriages and preclinical pregnancy losses are commonly managed at home, the actual number of miscarriages is considerably higher than reported. Unfortunately, since 2013, the data for hospital admissions for miscarriage are no longer included in the UK maternity statistic report.[23] Only a few countries, such as Denmark, report an annual miscarriage rate, which makes international comparisons difficult. Based on the few cohort studies available, the incidence of miscarriage appears to be increasing in the USA,[20] China,[24] and Sweden[25], but decreasing in Finland.[18] The reasons for

National Centre for Miscarriage Research, Imperial College London, London, UK (Prof L Regan MD, M Al-Memar PhD, Prof T Bourne PhD, D A MacIntyre PhD, R Rai MD, Prof P R Bennett PhD); **Centre for Recurrent Pregnancy Loss of Western Denmark, Department of Obstetrics and Gynaecology, Aalborg University Hospital, Aalborg, Denmark** (Prof O B Christiansen PhD); **Department of Obstetrics and Gynecology, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan** (M Sugiura-Ogasawara MD)

Correspondence to: Prof Siobhan Quenby, Tommy's National Centre for Miscarriage Research, University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, UK **s.quenby@warwick.ac.uk**

See **Online** for appendix

Panel: Early pregnancy terminology

Pregnancy loss
Spontaneous pregnancy demise.

Early pregnancy loss
Spontaneous pregnancy demise before 10 weeks of gestational age.

Biochemical pregnancy loss
Spontaneous pregnancy demise based on a previous positive pregnancy test that then becomes negative without an ultrasound evaluation.

Preclinical pregnancy loss
Loss of a pregnancy before it could be identified on transvaginal ultrasound scan (TVS).

Clinical pregnancy loss
Loss of a pregnancy after it has been identified on TVS.

Pregnancy of unknown location (PUL)
Temporary classification to describe when no pregnancy can be visualised inside or outside the uterus on TVS in a woman with a positive pregnancy test.

Resolved pregnancy loss of unknown location (resolved PUL)
Following the finding of a PUL, the woman has a negative pregnancy test 2 weeks after her initial follow-up.

Persistent pregnancy of unknown location
Following the finding of a PUL, serial serum human chorionic gonadotropin concentrations taken 48 h apart plateau, whereas the location of the pregnancy is unclear with TVS.

Intrauterine pregnancy of unknown viability
TVS has shown the following, irrespective of the date of a woman's last menstrual period: intrauterine gestational sac seen with a mean sac diameter of less than 25 mm without a visible yolk sac or embryonic pole; intrauterine gestational sac with mean sac diameter of less than 25 mm with a yolk sac seen without a visible embryonic pole; intrauterine gestational sac with an embryo with a crown-rump length measuring less than 7 mm with no visible heartbeat.

Viable intrauterine pregnancy
Intrauterine gestational sac containing an embryo with a heartbeat that has been visualised with ultrasonography.

Miscarriage
Intrauterine pregnancy demise confirmed by TVS or histology of pregnancy tissue.

Missed miscarriage
An intrauterine pregnancy with an empty gestational sac with a mean sac diameter of 25 mm or more, or an embryo with an crown-rump length measuring more than 7 mm without an embryonic heartbeat.

Incomplete miscarriage
Irregular heterogeneous echoes within the endometrial cavity on TVS and the diagnosis is based on the subjective impression of the examiner and the clinical findings.

Complete miscarriage
History of a positive pregnancy test followed by vaginal bleeding (or a history of an ultrasound scan showing an intrauterine pregnancy) and then an ultrasound finding of an empty uterine cavity with no intrauterine pregnancy or extrauterine pregnancy visualised on TVS with a negative pregnancy test.

Panel adapted from Kolte and colleagues[12] and Doubilet and colleagues.[13]

these changes are not clear but might reflect increasing female age at the time of pregnancy (in the USA, China, and Sweden but not Finland). Female age and the number of previous miscarriages have a profound effect on the risk of miscarriage (appendix p 4). Risk of miscarriage is lowest in women aged 20–29 years at 12%, increasing steeply to 65% in women aged 45 years and older (appendix p 4). The risk of miscarriage is lowest in women with no history of miscarriage (11%), and then increases by about 10% for each additional miscarriage, reaching 42% in women with three or more previous miscarriages (appendix p 4).

Recurrent miscarriage

Whether miscarriage should be defined as recurrent after two or more or three or more pregnancy losses is an ongoing controversy. There is also no consensus on whether recurrent miscarriage should be restricted to clinical losses only, or include both clinical and preclinical losses (appendix p 5). The definitions are further complicated by whether the previous pregnancy losses need to be consecutive or be interspersed with livebirths. The UK Royal College of Obstetricians and Gynaecologists defines recurrent miscarriage as the loss of three or more consecutive pregnancies.[26] However, in this definition, the term miscarriage encompasses all pregnancy losses from the time of conception until 24 weeks, including biochemical pregnancy losses and pregnancy losses of unknown location (ie, no visualisation on transvaginal ultrasound scan). The German, Austrian, and Swiss Societies of Gynaecology and Obstetrics offer similar guidance.[27] The American Society for Reproductive Medicine has defined recurrent miscarriage as two or more failed clinical pregnancies.[10] Since the diagnosis of pregnancy in this definition requires ultrasound or histological confirmation, it excludes biochemical pregnancy losses and pregnancy losses of unknown location. In 2018, the European Society of Human Reproduction and Embryology redefined recurrent pregnancy loss as two or more pregnancy losses without the stipulation that these losses need to be consecutive.[11] This definition would therefore apply even if there had been a livebirth in between pregnancy losses.

These variations in the definition of recurrent miscarriage or recurrent pregnancy loss have important implications on the reported prevalence and on the prognosis in any future pregnancy. The average population prevalence of women who have had one previous miscarriage is 10·8%, two miscarriages is 1·9%, and three or more miscarriages is 0·7% (appendix p 5).[28–35] If two or more pregnancy losses is used as the definition of recurrent miscarriage, the population prevalence of recurrent miscarriage equates to 2·6%. The chance of a future successful subsequent pregnancy ranges from 50% to 90%, depending on the recurrent miscarriage definition used and population characteristics.

The current definitions of recurrent miscarriage do not go beyond the inclusion or exclusion of preclinical pregnancy losses and the setting of an arbitrary number of previous pregnancy losses. However, the risk of miscarriage increases independently with maternal age and with the number of previous losses (appendix p 4). A definition of recurrent miscarriage that is based on individualised risk assessment, which takes into account maternal age, reproductive history, and other clinical variables, is likely to facilitate better stratification, targeted care, and research.

Risk factors for miscarriage

Embryonic chromosomal errors

Chromosomal abnormalities are found in 60% of miscarried tissue,[36] but less than 1% of livebirths when prenatal diagnosis is not used.[37] Among miscarriages, autosomal trisomy is the most frequent abnormality followed by monosomy X and triploidy.[36] In addition, developmental abnormalities of embryos not seen in livebirths are found in miscarriages with normal chromosomes.[38,39]

Endometrial defects

Endometrium transforms into decidua during implantation to accommodate the invading placenta.[40] A defect in decidualisation can result from changes in immune cells,[41] foremost uterine natural killer cells,[42] or endometrial stem cells,[43,44] which could result in endometrial breakdown and miscarriage. Multiple risk factors of recurrent miscarriage, including metabolic (eg, obesity) and endocrine (eg, hypothyroidism) disorders (appendix p 6), have been shown to adversely affect the decidual process in the endometrium.[45,46]

Parental risk factors of miscarriage

There are demographic, lifestyle, clinical, and environmental risk factors for miscarriage (appendix p 6). The inferences about the risk factors are based on the strength of association (represented by the size of odds ratios [ORs]), consistency among the studies, biological gradient (whether the risk increases with increasing number of miscarriages), and the persistence of association after adjustments for key confounding variables, particularly female age.[47]

Demographic risk factors

Our literature review showed that the key demographic risk factors for miscarriage are female age, female body-mass index (BMI), female ethnicity, and male age (appendix p 6). There is a strong association between female age and miscarriage risk, with a powerful biological gradient, found consistently in several studies (appendix p 6). This association is attributed to an age-related increase in the frequency of embryonic trisomies, particularly trisomies on chromosomes 13, 14, 15, 16, 18, 20, 21, and 22.[48,49] The risk of trisomy 16, the most common cause of miscarriage, rises linearly from 20 years to 40 years of age, whereas the risks of other trisomies generally show a sharp upward inflection around the age of 35 years.[36] Our literature search found that female BMI is associated with miscarriage risk; the BMI associated with the least risk of miscarriage is 18·5–24·9 kg/m^2 (appendix p 6). Black ethnicity is associated with a higher risk of miscarriage when compared with White ethnicity, as is male age of 40 years or older, even after adjusting for confounders such as the age of his female partner (appendix p 6).

Lifestyle risk factors

Smoking is an important modifiable risk factor for miscarriage (appendix p 6). The risk is greater when smoking exposure occurs specifically during the pregnancy in which miscarriage risk was measured.[33] Miscarriage risk increases with the amount smoked (1% increase in relative risk per cigarette smoked per day).[33] Our literature review has shown that alcohol use is also an important modifiable risk factor as high alcohol consumption during the first trimester is associated with an increase in miscarriage risk (appendix p 6).[15,31,50–58] Our review has indicated that high caffeine intake might be associated with miscarriage (appendix p 6), although there was statistical uncertainty in the finding.[15,31,59] Furthermore, any association between caffeine and miscarriage is likely to be confounded as a healthy pregnancy is associated with nausea and vomiting (due to pregnancy hormones), which in turn might reduce caffeine consumption.[60] Night shift work is also associated with an increased risk of miscarriage (appendix p 6). This risk appeared to follow a dose–response relationship. Our review of the evidence also found that high stress is associated with miscarriage risk (appendix p 6);[54,59,60–65] however, there is no evidence that the association represents a causal link because, for example, preconception stress, as measured by basal salivary cortisol and α–amylase concentrations, did not predict subsequent pregnancy loss.[66]

Clinical risk factors

An important determinant of risk of miscarriage is the gestational age of a pregnancy. The risk of pregnancy loss decreases with advancing gestational age.[67–70] Once the pregnancy reaches 8 weeks, the risk of miscarriage decreases substantially; conversely, the likelihood of a livebirth approaches 97–98%.[70]

The number of previous miscarriages is a major determinant of miscarriage risk; the relationship is consistent across various studies, and shows a biological gradient according to the number of previous miscarriages.[71] Several maternal conditions, including antiphospholipid antibodies, thyroid autoantibodies, and subclinical hypothyroidism, are associated with miscarriage (appendix p 7). Uterine anomalies, in particular canalisation defects such as uterine septae, have been associated with both spontaneous and recurrent miscarriage.[72]

Bacterial (ie, bacterial vaginosis, brucellosis, *Chlamydia trachomatis*, and syphilis), viral (ie, herpes viruses: herpes simplex virus type 1 [HSV-1] and HSV-2, human cytomegalovirus, human papillomavirus, parvovirus, adeno-associated viruses, parvovirus B19, bocavirus, HIV, polyomavirus, dengue virus, hepatitis B, hepatitis C, rubella, and coronaviruses [SARS, MERS, and H1N1]), and protozoa (ie, malaria and toxoplasmosis) infections have all been linked to miscarriage.[73] In the era of bacterial community assessment with DNA sequencing, there is evolving evidence linking the composition of the vaginal microbiome to miscarriage.[74] Miscarriage is more commonly associated with a lactobacillus deplete microbiota, but whether it is cause or effect, or what the potential mechanisms are, remains unclear. These findings are supported by older data that used more traditional microbiology techniques, which showed an increase in the risk of miscarriage in women with bacterial vaginosis.[75] Sperm DNA fragmentation is also associated with miscarriage (appendix p 7).[76] Association between sperm DNA fragmentation and smoking, recreational drugs, obesity, and treatment with lifestyle changes and antioxidants are important research questions.

Environmental risk factors

Air pollution, composed of primary pollutants, pollutants emitted directly from the source, and secondary air pollutants formed from the interaction of primary pollutants within the atmosphere, has a large effect on human health. In the context of pregnancy, air pollution is linked to stillbirth, preterm delivery, and low birthweight.[77,78] A large study assessed the effect of exposure to air pollution on miscarriage rates in Beijing, China, showing a strong relationship with miscarriage (OR 1·51; 95% CI 1·33–1·69).[79] Similarly, a case-control study on women attending an emergency department in the state of Utah, USA,[80] found that a 10 parts per billion rise in nitrogen oxide concentrations was associated with an increased risk of miscarriage (1·16; 1·01–1·33). The Nurses' Health Study 2 showed a positive association between particulate air pollution and miscarriage.[81] Exposure to air pollution therefore appears to increase miscarriage risk and constitutes a modifiable risk factor (appendix p 7).

Pesticides have also been linked to recurrent miscarriage (appendix p 7). Exposure to sprayed pesticides in rural South Africa in the first 3 months of pregnancy was associated with an increased risk of miscarriage (2·8; 1·1–7·2).[82] This epidemiological study correlates with a clinical study showing higher concentrations of serum organochlorine pesticides in women with recurrent miscarriage than controls (ie, who have live term births).[83]

Risks and complications of miscarriage

Vaginal bleeding in early pregnancy and obstetric complications

Threatened miscarriage, defined as vaginal bleeding in early pregnancy (in the first 12 weeks of pregnancy), is among the most common reasons for women to seek medical care in early pregnancy.[84] Clearly, events in early pregnancy have a substantial effect on pregnancy outcomes.[85–88] A systematic review of 14 studies (n=64 365) found that women who have had a threatened miscarriage have a higher risk of antepartum haemorrhage due to placenta previa (OR 1·62; 95% CI 1·19–2·22) or antepartum haemorrhage of unknown origin (2·47; 1·52–4·02), compared with those with no bleeding in early pregnancy.[85] There is also an association with preterm prelabour rupture of membranes (1·78; 1·28–2·48), preterm delivery (2·05; 1·76–2·40), and fetal growth restriction (1·54; 1·18–2·00).[85] Significantly higher rates of perinatal mortality (2·15; 1·41–3·27) and low-birthweight neonates (1·83; 1·48–2·28) have also been reported compared with those women with no early pregnancy bleeding.[85] Ultrasound diagnosis of intrauterine haematoma is also associated with an increased risk of antenatal complications such as pre-eclampsia (relative risk 4·0; 2·4–6·7), placental abruption (5·6; 2·8–11·1), and preterm delivery (2·3; 1·6–3·2).[87]

Miscarriage and obstetric complications

Our literature review showed striking associations between a history of miscarriage and several adverse obstetric outcomes in subsequent pregnancies (appendix p 8). The risk of preterm birth increases stepwise with each previous miscarriage, showing a biological gradient; this association persists even with adjustment for confounding variables (appendix p 8). Adverse outcomes after miscarriage could possibly be at least partly attributable to the management of miscarriage. Repeated uterine curettage after cervical dilation might cause injury to the uterine cervix and endometrial cavity, or change the uterine microbiome, increasing the risk of preterm birth due to damage to the cervix or chronic endometritis. Injury to the uterine wall or endometrium can also cause abnormal placentation in subsequent pregnancies, resulting in increased risk of placental abruption and placenta praevia (appendix p 8).

A nationwide population-based birth cohort study in Japan found an increased risk of placental adhesions and uterine infection in women with recurrent pregnancy loss.[89] Abnormal placentation can also contribute to low birthweight (appendix p 8). However, plausibly, the increased frequency of low birthweight and perinatal complications is an inherent part of the recurrent miscarriage syndrome. Women who have had recurrent miscarriages are themselves born with a substantially reduced birthweight,[90] and a history of perinatal complications has been found in many women in their pregnancies before they acquire a recurrent miscarriage diagnosis.[91] An inadequate decidual response, if it does not lead to miscarriage, might lead to inadequate placentation causing placental dysfunction disorders, and so increasing the risk of placental abruption, fetal growth restriction, preterm birth, and perinatal death.

There is growing evidence that preterm infants born after spontaneous preterm labour have a lower mean birthweight than what would be expected for their gestation.[92–94] Therefore, the likelihood is that the association between miscarriage and adverse obstetric outcomes could partly be driven by a common cause, perhaps originating in suboptimal endometrial repair and decidualisation. The increasing incidence of perinatal complications with increasing number of previous pregnancy losses[95] suggests a need for heightened antenatal surveillance in patients with a history of multiple miscarriages. In addition, miscarriage could be a time to consider prophylactic interventions, such as lifestyle changes, before another pregnancy.

Miscarriage and long-term health risks

Recurrent miscarriage is associated with long-term health problems beyond pregnancy. Our literature review has shown that recurrent miscarriage is associated with an increased risk of cardiovascular disease and venous thromboembolism (appendix p 8). No association was identified between miscarriage and stroke diagnosis (appendix p 8). These findings are important because they add to the concept of a recurrent miscarriage syndrome, and could mean that a history of repeated miscarriage is an opportunity for reducing risks for cardiovascular and thromboembolic disease.

The psychological consequences of miscarriage involve both trauma and bereavement,[96] and these consequences might have little or no outward physical manifestation, so can go unrecognised by health-care professionals, family, and friends. This scenario occurs particularly in a society that views miscarriage as unimportant or shameful, thus leading to concealment of a pregnancy loss and its consequences.

Our literature review identified that anxiety, depression, and suicide are strongly associated with miscarriage (appendix p 9). A multicentre, prospective, cohort study of 537 women following a miscarriage found that 9 months after a pregnancy loss, 18% of women met the criteria for post-traumatic stress, 17% for moderate or severe anxiety, and 6% for moderate or severe depression.[97] Identifying women at risk of psychological distress following miscarriage and the development of optimal treatment strategies have been recognised as research priorities.[98]

Economic costs

We did a literature review with the goal of identifying and summarising evidence on the economic costs associated with miscarriage, the cost-effectiveness of prevention or management strategies, and preference-based outcomes associated with miscarriage, or its prevention or management derived with economic methods. A total of 30 articles were included: 15 articles reported costing studies, 12 articles reported economic evaluations, and three articles reported preference elicitation studies. Due to heterogeneity in study design, outcomes and intervention types, and variations in health-care practices and relative prices for resource inputs, a narrative synthesis of economic evidence is presented. All economic costs are presented in pounds sterling (GBP; 2018 prices) for comparative purposes.

Published evidence on the economic outcomes of miscarriage has focused largely on direct health service costs associated with miscarriage treatment procedures. Cost estimates vary by the nature of the intervention (eg, expectant, medical, or surgical management), location of care (inpatient or outpatient), and cost accounting methodology and jurisdiction. Most published studies have aimed to provide information about options that are less costly than current practice,[99–106] or to probe the value of adjuncts to current practice.[107] The emphasis is usually on cost comparisons for achieving a standard outcome, namely complete removal of pregnancy tissue from the uterus. The use of decision analysis is common,[99,106] mainly as a means of tracking cumulative costs over different treatment pathways, particularly in which additional treatment might be required following inadequate effects of initial therapy. Unit costs estimates have been derived from a number of sources, including primary research methods[101,103,104] and administrative tariffs.[108,109]

Published estimates of direct health service costs associated with miscarriage treatment procedures vary considerably between and within countries. However, a consistent pattern emerges with direct health service costs highest for surgical management and generally lowest for expectant management. Direct health service costs for expectant management ranged from £380 in a study from the USA[108] through to £1067 in a study from Hong Kong.[106] Direct health service costs for medical management ranged from £298 in a study from the USA[108] through to £1421 in a UK study.[101] Direct health service costs for surgical management, usually curettage, ranged from £455 in a study from Finland[110] through to £2242 in a study from Spain.[99]

In a comparison of outpatient versus inpatient treatment in the USA, the cost of manual vacuum aspiration as an outpatient (£852) was much lower than that for inpatient treatment (£1729).[109] Direct health service costs associated with surgical management of miscarriage procedures are generally lower in low-income countries than high-income countries. For example, in Pakistan, manual vacuum aspiration was estimated to cost on average £56,[111] curettage £146,[111] and electrical vacuum aspiration £193,[103,104] and in Eswatini, manual vacuum aspiration was estimated to cost on average £131 and dilation and curettage £201 for incomplete first trimester miscarriages.[112] Estimates of direct health service costs not differentiated by treatment method ranged from £401 in the Netherlands (care provided in an early pregnancy assessment unit)[105] to £973 in the UK (progesterone as a preventive therapy).[107]

A few studies have estimated the non-health-care costs associated with miscarriage or its management, in which the focus has largely been on the economic value of lost work productivity for women experiencing miscarriage. As part of the economic evaluation done alongside the MIST trial, the investigators asked study participants to estimate time taken off work as a consequence of their miscarriage at 10–14 days and 8 weeks following trial entry.[101] The mean value of work absences was estimated at £431 with no significant difference in values observed between the three management methods evaluated (expectant, management, and surgical). In a study in the Netherlands, the estimated value of lost productivity was ostensibly similar (£439), but its composition notably different, with most of it driven by lower productivity after women had returned to work rather than taking time off work.[113] A broadly similar estimate of £428–521 (depending on the treatment strategy) has emerged in another economic evaluation from the Netherlands[114] that compared misoprostol treatment and curettage in women who had been managed expectantly for at least 1 week. Among women allocated to the misoprostol group, the mean value of lost productivity exceeded mean direct costs to the health-care system.

The economic studies emerging from our literature review typically used a short-term timeframe, focusing on the initial treatment period. They do not cover long-lasting effects such as the economic consequences associated with increased risk of psychological morbidity.

Evidence generated by the literature review can act as data inputs into burden of illness calculations. For example, assuming that the economic outcomes of miscarriage are felt only over the short term, and combining national prevalence data for England with estimates of costs of hospital and community health and social services,[101] costs to patients,[115] and broader societal costs associated with lost productivity[101] generates an annual national estimate of economic cost of £471 million. Economic estimates such as these can contribute to clinical and budgetary service planning.

Discussion

Miscarriage is common, but its scale and effect are not fully understood by some women, family, care providers, policy makers, and health-care funders. There are multiple risk factors for miscarriage, most prominently female age and the number of previous losses. Some risk factors—eg, BMI, smoking, and alcohol—are modifiable. Environmental risk factors are an emerging concern. However, an association does not imply causation, and there is a need to better understand the nature, mechanisms, and implications of many of the associations highlighted in this Series paper. The physical consequences of miscarriage are well appreciated, but psychological sequelae less so. Even less well known are future reproductive, obstetric, and health consequences, particularly the risk of miscarriage recurrence, preterm birth, and placental disorders in future ongoing pregnancies, and cardiovascular disease and venous thromboembolism later in life.

Although there are data for the short-term costs of miscarriage, the long-term costs might be considerable and might outweigh short-term concerns; however, the data are insufficient. Newly emerging cohort studies with long-term follow-up, such as the Tommy's Net Cohort Study (ISRCTN17732518), and population-wide record linkage studies provide potential vehicles for ascertaining long-term economic outcomes such as downstream use of health and social care services, employment and occupational status, income, and receipt of social welfare benefits and reproductive health, which might in turn have economic consequences. Future research should use evidence from economic evaluations encompassing information on incremental costs and health gains associated with prevention and treatment strategies to inform decisions around the prioritisation of health-care resources in this area.

We recommend miscarriage data are gathered and reported to facilitate comparison of miscarriage rates among countries, to accelerate research, and to improve patient care and policy development. Key epidemiological research priorities include establishing how we can monitor miscarriage rates on a population basis; ascertaining if miscarriage risk and prevalence differ across nations and ethnic groups; whether miscarriage rate is increasing, and if so why; what the key outcomes are from women's point of view; and which risk factors for miscarriage are potentially causative and modifiable; and the effect of modification of the risk factor on clinical outcomes. Important clinical research questions include the role of sperm DNA damage on miscarriage, both diagnosis and the treatment; development of effective screening instruments to identify women with severe stress disorders and anxiety as a consequence of miscarriage, and the evaluation of therapies to treat these disorders; and a better understanding of the effect of air pollution on miscarriage. Concerted effort from both researchers and national policy makers is needed to address these issues.

The current evidence indicates that smoking cessation and stress management should be prioritised to improve general health and reduce the risk of miscarriage. Alcohol should be avoided in early pregnancy, fruit and vegetables should be thoroughly washed to avoid the risk of ingesting pesticides, and the possibility of reducing night shifts should be explored. Women with a history of miscarriage, particularly those with three or more miscarriages, are at an increased risk of obstetric complications including preterm birth. Therefore, these women should be treated as patients at high risk during antenatal and intrapartum care. We recommend that robust strategies are developed, evaluated, and scaled up to manage these risks associated with miscarriage, particularly psychological morbidity, and future obstetric consequences.

Contributors

All authors participated in the design of the review, literature searches, and assisted with the writing of all sections and agreed to submit the manuscript. The manuscript represents the view of named authors of this paper only.

Declaration of interests

We declare no competing interests.

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