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

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Summary

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 with one miscarriage is 10·8% (95% CI 10·3% – 11·4%), two miscarriages is 1·9% (95% CI 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, older male age, very low or very high body mass index, black ethnicity, previous miscarriages, smoking, alcohol, stress levels, night shift working, 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, healthcare systems and society at large. The short-term national economic cost of miscarriage is estimated to be £471 million per year in the United Kingdom. As recurrent miscarriage is a sentinel marker for various obstetric risks in future pregnancies, women should receive care in pre-conception and high-risk obstetric clinics. 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 amongst countries, to accelerate research, and to improve patient care and policy development.

Keywords: miscarriage, epidemiology, risk, prevalence, economic burden, literature review

Introduction

Miscarriage is often misunderstood by women, men,[1] and healthcare providers. Misconceptions about miscarriage are widespread.[1-3] For example, women may believe miscarriage is rare, 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 may also lead to isolation, since many women may not tell their family, close friends, or even their partner about the loss. Couples complain of unsympathetic 'routine' clinical care by healthcare providers.[4-6]

Women and their partners who suffer 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 may be given diverse opinions by different healthcare professionals, which can exacerbate their distress. There are debates over definitions, causes, consequences and costs of miscarriage. This is the first of three articles in which we present the current knowledge, recommendations, need for further research and a call to action on priorities. Here 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 burden of miscarriage through a review of the literature.

Box 1: Methods for literature searches for miscarriage risk, prevalence, risk factors and consequences

We performed a comprehensive literature search on MEDLINE (database inception to May 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 (MeSH) terms for miscarriage were combined with each risk factor, pregnancy sequelae, perinatal and long-term health outcome. For each literature review, the raw aggregate data or adjusted odds ratios were presented.

Definitions and terminology

The definition of miscarriage varies amongst countries, and international organisations, impacting upon 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 viability. The limits of viability may be defined by gestational age or by fetal weight. The gestational threshold for viability can range from 20 to 28 weeks of pregnancy depending on geographical region. The World Health Organization defines miscarriage as the expulsion of a fetus (embryo) weighing less than 500 grams, equivalent to approximately 22 weeks of gestation.[19] In the UK the limit of viability is determined legally as up to 24+0 weeks.[18] The American Society for Reproductive Medicine (ASRM) defines miscarriage as a clinical pregnancy loss of less than 20 weeks of gestation.[20] The European Society for Human Reproduction and Embryology (ESHRE) defines miscarriage as the loss of pregnancy before 22 weeks of gestation.[21] 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. Whilst 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 review.

A bewildering array of terminology for pregnancy failure before viability has developed based upon whether the pregnancy diagnosis was based on serum or urinary β-hCG levels, or on the visualisation of an intrauterine pregnancy by ultrasonography (Table 1).

Table 1. Early pregnancy terminology

Term	Description
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
Pre-clinical pregnancy loss	Loss of a pregnancy before it could be identified on 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 (PPUL)	Following the finding of a PUL, serial serum human chorionic gonadotropin (hCG) levels taken 48 hours apart plateau, while the location of the pregnancy remains unclear using TVS.
Intrauterine pregnancy of unknown viability (IPUV)	TVS has shown the following, irrespective of the date of a woman's last menstrual period: - intrauterine gestational sac seen with an MSD of <25 mm without a visible yolk sac or embryonic pole - intrauterine gestational sac with MSD of <25 mm with a yolk sac seen without a visible embryonic pole - intrauterine gestational sac with an embryo with a CRL measuring <7 mm with no visible heartbeat
Viable intrauterine pregnancy (VIUP)	Intrauterine gestational sac containing an embryo with a heartbeat that has been visualised using ultrasonography
Miscarriage	Intrauterine pregnancy demise confirmed by TVS or histology of pregnancy tissue
Missed miscarriage	An intrauterine pregnancy with an empty gestational sac of ≥MSD 25 mm, or an embryo with an embryo CRL measurement of >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 demonstrating an IUP) and then an ultrasound finding of an empty uterine cavity with no intra or extra-uterine pregnancy visualised on TVS with a negative pregnancy test

TVS: transvaginal ultrasound scan; IU(P): intrauterine (pregnancy); MSD: mean sac diameter; CRL: crown-rump length. Table adapted from 'Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group'[22] and Doubilet et al, 2013.[23]

Risk of miscarriage

The risk of miscarriage depends both upon the defined upper gestational age or fetal weight limit, and upon whether the denominator is all pregnancies identified by serum or urinary β-hCG levels or only pregnancies diagnosed by ultrasonography. Inclusion of pre-clinical losses, defined as the loss of a pregnancy before it could be identified on ultrasonography, will increase the miscarriage rate. The development of highly sensitive β-hCG assays has allowed detection of very early pregnancies, and therefore diagnosis of very early miscarriages which otherwise may 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. Our literature search identified nine large cohort studies that reported on miscarriage risk in an aggregated total of 4,638,974 pregnancies (Table 2).[24-31] All the 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 miscarriage risk was 15·3% (95% CI: 12·5% – 18·7%) of all recognised pregnancies (Table 2).

Table 2. Risk of miscarriage in pregnant women

Study	Source population	Definition of miscarriage	Miscarriages / pregnancies	Miscarriage risk (%) (95% CI)
Himmelberger et al, 1978	Survey of operating room personnel in the USA from 1972 to 1974	Self-reported pregnancy outcomes	2,157 / 12,914	16·7 (16·0, 17·4)
Armstrong et al, 1992	Women with a reproductive outcome at 11 hospitals in Montreal, Canada from 1982 to 1984	Self-reported pregnancy outcomes	10,191 / 47,146	21·6 (21·2, 22·0)
Andersen et al, 2000	Women with a reproductive outcome in Denmark from 1978 to 1992	Record linkage using a National Hospital Discharge Registry and excluding ectopic pregnancies. Induced abortions were excluded through linkage with an induced abortion register	85,838 / 936,524	9·2 (9·1, 9·2)
Adolfsson and Larsson, 2006	Women with a reproductive outcome in Sweden from 1983 and 2003	Self-reported pregnancy outcomes for all women who delivered a child	366,796 / 2,136,809	17·2 (17·1, 17·2)
Maconochie et al, 2006	Survey of reproductive histories of women randomly sampled from the UK electoral register in 2001	Self-reported pregnancy outcomes	1,322 / 8,523	15·5 (14·7, 16·5)
Linnakaari et al, 2019	Nationwide retrospective cohort study of women that had experienced a miscarriage in Finland between 1998 and 2016	Record linkage using ICD codes in National Hospital Discharge Registry database and excluding codes of ectopic pregnancy, molar pregnancy, induced abortions or continuing pregnancy	128,381 / 1,096,916	11·7 (11·6, 11·8)
Magnus et al, 2019	Women with a reproductive outcome in Norway from 2009 to 2013	Record linkage using ICD codes in National Birth Registry and patient register excluding ectopic pregnancies. Induced abortions were excluded through linkage with an induced abortion register	43,803 / 344,906	12·7 (12·6, 12·8)
Rossen et al, 2019	National survey of women who reported at least one pregnancy that was conceived in the USA between 1990 and 2011	Self-reported pregnancy outcomes	8,378 / 42,526	19·7 (19·3, 20·1)
Nguyen et al, 2019	National survey of women who reported pregnancy outcomes that was conceived in the USA between 2011 and 2015	Self-reported pregnancy outcomes	2,300 / 12,710	18·1 (17·4, 18·9)

Pooled risk	15·3 (12·5, 18·7)

With approximate 130 million births per year worldwide[32], a 15% miscarriage risk suggests approximately 23 million miscarriages per year, or 44 per minute. In the UK, there were 40-45,000 hospital admissions in 2012-2013 for miscarriage management,[33] but since miscarriages and preclinical pregnancy losses are commonly managed at home, the actual number of miscarriages is considerably higher. Unfortunately, since 2013 the data on hospital admissions for miscarriage are no longer included in the UK maternity statistic report.[33] Only a few countries, for example Denmark, report an annual miscarriage rate, which makes international comparisons difficult. Based on limited cohort studies, the incidence of miscarriage appears to be increasing in the USA,[30] China[34] and Sweden[35], but decreasing in Finland.[28] The reasons for these changes are not clear but may reflect increasing female age at the time of pregnancy. Female age and the number of previous miscarriages have a profound effect on miscarriage risk (Table 3). Miscarriage risk is the lowest in women aged 20 – 29 years at 12%, increasing steeply to 65% in women aged 45 years and over (Table 3). The miscarriage risk is the lowest women with no history of miscarriage (11%), and then increases by about 10% for each additional miscarriage, reaching 42% in women with 3 or more previous miscarriages (Table 3).

Table 3. Miscarriage risk according to female age and number of previous miscarriages

	Number of studies	Miscarriages / pregnancies	Miscarriage risk (%) (95% CI)
Age category (years)			
<20	4	9,165 / 71,763	15·9 (11·3, 22·4)
20-24	3	32,326 / 337,995	12·1 (8·5, 17·2)
25-29	6	47,266 / 481,112	11·9 (10·0, 14·3)
30-34	6	37,015 / 309,328	14·4 (11·4, 18·2)
35-39	4	21,607 / 118,771	17·9 (15·8, 20·2)
40-44	2	8,635 / 23,783	36·8 (30·1, 45·0)
≥45	2	1,081 / 1,687	65·2 (49·8, 85·2)
Number of previous miscarriages			
0	3	23,233 / 172,405	11·3 (7·2, 17·6)
1	3	6,770 / 31,564	20·4 (13·8, 30·3)

2	3	1,276 / 4,221	28·3 (19·0, 42·1)
≥3	3	364 / 865	42·1 (38·0, 46·7)

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 pre-clinical losses (Table 4). The definitions are further complicated by whether the previous pregnancy losses need to be consecutive or may be interspersed with successful pregnancies. The UK Royal College of Obstetricians and Gynaecologists (RCOG) defines recurrent miscarriage as the loss of three or more consecutive pregnancies. However, in this definition, the term 'miscarriage' encompasses all pregnancy losses from the time of conception until 24 weeks, including biochemical pregnancy losses and failed pregnancies of unknown location. The German, Austrian and Swiss Societies of Gynaecology and Obstetrics offer similar guidance. The American Society for Reproductive Medicine (ASRM) has defined recurrent miscarriage as 'two or more failed clinical pregnancies'. Since the diagnosis of pregnancy in this definition requires ultrasound or histological confirmation, it excludes biochemical pregnancy losses and failed pregnancies of unknown location. The European Society of Human Reproduction and Embryology (ESHRE) have recently redefined recurrent pregnancy loss as two or more pregnancy losses without the stipulation that these need to be consecutive. This definition would therefore apply even if there had been a successful pregnancy 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 with one previous miscarriage is 10.8%, two miscarriages is 1.9% and three or more miscarriages is 0.7% (Figure 7). If two or more pregnancy losses is adopted 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.[36-43]

Table 4. Differences in definition of recurrent miscarriage amongst national guidelines

Guidelines	UK (RCOG)[44]	USA (ASRM)[20]	Europe (ESHRE)[21]	Japan[45]	German, Austrian and Swiss Societies of Gynaecology and Obstetrics[46]
Definition of pregnancy loss	Includes clinical and pre-clinical losses	Includes clinical losses only (identified on ultrasound or histology)	Includes clinical and pre-clinical losses	Includes clinical losses only (identified on ultrasound or histology)	Includes clinical losses only (identified on ultrasound or histology)
Number previous of losses	≥3	≥2	≥2	≥2	≥3
Consecutive losses	Yes	No	No	No	Yes

Table 7. Population prevalence of miscarriage

	Miscarriages / women	Prevalence of miscarriage (%) (95% CI)
1 miscarriage		
Hemminki and Forssas, 1999	193 / 2,189	8·8 (7·7, 10·2)
Oliver-Williams and Steer, 2015	21,658 / 196,040	11·0 (10·9, 11·2)
Woolner et al, 2019	3,513 / 31,565	11·1 (10·8, 11·5)
	Sub-total	10·8 (10·3, 11·4)
2 miscarriages		
Hemminki and Forssas, 1999	57 / 2,189	2·6 (2·0, 3·4)
Oliver-Williams and Steer, 2015	3,624 / 196,040	1·8 (1·8, 1·9)
Woolner et al, 2019	590 / 31,565	1·9 (1·7, 2·0)
	Sub-total	1·9 (1·8, 2·1)
3 miscarriages		
Hemminki and Forssas, 1999	22 / 2,189	1·0 (0·7, 1·5)
Oliver-Williams and Steer, 2015	1,426 / 196,040	0·7 (0·7, 0·8)
Roepke et al, 2017	7,842 / 1,524,130	0·5 (0·5, 0·5)
Woolner et al, 2019	181 / 31,565	0·6 (0·5, 0·7)
	Sub-total	0·7 (0·5, 0·8)

The current definitions of recurrent miscarriage do not go beyond the inclusion or exclusion of pre-clinical losses and the setting of an arbitrary number of prior losses. However, the risk of miscarriage increases independently with maternal age and with the number of previous losses (Table 3). 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[47] but less than 1% of live births, when pre-natal diagnosis is not used.[48] Amongst miscarriages, autosomal trisomy is the most frequent abnormality followed by monosomy X and triploidy.[47] In addition, developmental abnormalities of embryos not seen in live births are found in miscarriages with normal chromosomes.[49,50]

Endometrial defects

Endometrium transforms into decidua during implantation to accommodate the invading placenta.[51] A defect in decidualization can result from changes in immune cells,[52] foremost uterine natural killer cells,[53] or endometrial stem cells,[54,55] which may result in endometrial breakdown and miscarriage. Multiple risk factors of recurrent miscarriage, including metabolic (e.g. obesity) and endocrine (e.g. hypothyroidism) disorders (Table 6), have been shown to impact adversely on the decidual process in the endometrium.[57,58]

Parental risk factors of miscarriage

There are demographic, lifestyle, clinical and environmental risk factors for miscarriage (Table 6). The inferences about the risk factors are based on the strength of association (represented by the size of odds ratios), consistency amongst the studies, biological gradient, and the persistence of association after adjustments for key confounding variables, particularly female age.[59]

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 (Table 6). There is a strong association between female age and miscarriage risk, with a powerful biological gradient, found consistently in several studies (Table 6). This association is attributed to an age-related increase in the frequency of embryonic trisomies, particularly trisomy 13, 14, 15, 16, 18, 20, 21, and 22.[60,61] The risk of trisomy 16, the commonest cause of miscarriage, rises linearly from 20 years to 40 years of age, whilst the risks of other trisomies generally show a sharp upward inflection around the age of 35 years.[47] Our literature searches 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 (Table 6). Black ethnicity is associated with a higher risk (aOR 1·64; 95% CI 1·07-2.49; Table 6), as is male age of ≥40 years, even after adjusting for confounders such as the age of female partner (aOR 1.61; 95% CI 1.27 – 2.03; Table 6).

Table 6. Demographic, lifestyle, clinical and environmental risk factors for miscarriage

	Crude estimates		Adjusted estimates	
	Number of women (studies)	**Odds ratio [95% CI]**	**Number of women (studies)**	**Odds ratio [95% CI]**
Demographic risks				
Female age				
<20 years of age	1,132,164 (6)	1·60 [1·02, 2·53]	273,209 (2)	1·47 [0·94, 2·30]
20-29 years of age	-	Reference	-	Reference
30-39 years of age	1,709,852 (3)	1·43 [1·13, 1·81]	273,209 (2)	1·54 [1·23, 1·93]
≥40 years of age	1,030,387 (3)	6·43 [4·69, 8·82]	273,209 (2)	5·85 [3·67, 9·34]
Male age				
<20 years of age	20,808 (5)	0·87 [0·62, 1·21]	12,794 (3)	1·12 [0·81, 1·55]
20-29 years of age	-	Reference	-	Reference
30-39 years of age	29,795 (6)	1·23 [0·95, 1·60]	539 (1)	1·14 [0·75, 1·74]
≥40 years of age	16,108 (6)	1·69 [1·18, 2·43]	6,875 (2)	1·61 [1·27, 2·03]
BMI				
<18·5	117,936 (11)	1·57 [1·05, 2·34]	74,324 (7)	1·21 [0·96, 1·52]
18·5-24·9	-	Reference	-	Reference
25-29	131,896 (10)	1·33 [1·10, 1·59]	88,286 (6)	1·04 [0·91, 1·18]
≥30	118,102 (10)	1·93 [1·18, 3·18]	74,362 (4)	1·09 [0·99, 1·21]
Ethnicity				
Caucasian	-	Reference	-	Reference
Black	504,224 (19)	1·43 [1·17, 1·75]	88,286 (6)	1·64 [1·07, 2·49]
Asian	415,207 (13)	1·27 [0·99, 1·63]	74,362 (4)	1·25 [0·90, 1·75]
Lifestyle Risks				
Smoking				
Current smoking and in the first trimester	281,689 (29)	1·30 [1·20, 1·41]	265,827 (8)	1·17 [1·05, 1·30]
Caffeine				
High caffeine intake during the first trimester	45,990 (3)	1·26 [1·05, 1·51]	128,900 (3)	1·56 [0·98, 2·50]
Alcohol				
High alcohol intake during the first trimester	170,856 (17)	1·29 [1·16, 1·43]	152,881 (11)	1·67 [1·31, 2·19]
Work pattern				
Overworking (>40 hours per week)	16,315 (4)	1·93 [1·16, 3·21]	14,760 (4)	1·26 [0·94, 1·70]
Night shifts	74,011 (6)	1·31 [1·14, 1·50]	74,011 (6)	1·46 [1·25, 1·71]
Stress				
High stress	23,393 (5)	1·35 [1·18, 1·56]	29,498 (7)	1·43 [1·16, 1·77]

Clinical Risks				
Previous miscarriages				
No previous miscarriage	-	Reference	-	Reference
1 previous miscarriage	347,292 (12)	1·69 [1·49, 1·91]	209,168 (6)	1·54 [1·46, 1·62]
2 previous miscarriages	254,575 (6)	2·24 [1·62, 3·10]	177,596 (4)	2·21 [2·08, 2·34]
3 or more previous miscarriages	249,384 (6)	4·13 [2·62, 6·52]	174,252 (4)	4·46 [3·48, 5·72]
DNA damage				
High DNA damage in sperm	1,252 (16)	2·67 [1·67, 4·28]	-	-
Thyroid disease				
Thyroid antibodies	7,946 (17)	2·29 [1·86, 2·81]	3,202 (2)	2·95 [1·71, 5·11]
Subclinical hypothyroidism (TSH 2·5-5·0mIU/L)	188,736 (7)	1·58 [1·18, 2·12]	181,978 (3)	1·35 [0·97, 1·89]
Subclinical hypothyroidism (TSH 4·0-10·0mIU/L)	159,194 (7)	1·64 [1·46, 1·85]	154,232 (2)	1·93 [1·17, 3·18]
Uterine anomalies				
Septum defects	2,695 (4)	3·93 [2·57, 6·01]	-	-
Mullerian anomalies	970 (3)	3·20 [0·93, 10·98]	-	-
Fibroids	23,864 (32)	1·42 [1·24, 1·63]	6·057 (3)	0·82 [0·64, 1·05]
Polycystic ovary syndrome				
Polycystic ovary syndrome	22,235 (27)	1·33 [1·05, 1·68]	2,418 (2)	0·97 [0·64, 1·45]
Thrombophilia				
Acquired (Antiphospholipid syndrome)	10,781 (13)	2·28 [1·46, 3·57]	-	-
Inherited (Factor V Leiden, Protein S deficiency, Protein C deficiency, Antithrombin III deficiency, Prothrombin deficiency)	36,758 (12)	1·12 [0·93, 1·36]	18,395 (4)	1·29 [0·90, 1·85]
Parental Karyotype				
Abnormal parental karyotype (any)	2,569 (3)	2·20 [1·09, 4·42]	-	-
Environmental risks				
Air pollution				
Industrial pollution	15,177 (4)	1·58 [1·08, 2·29]	20,044 (4)	1·54 [1·03, 2·31]
Household pollution	1,125 (2)	1·11 [0·22, 5·50]	819 (1)	2·10 [0·91, 4·81]
Pesticides				
Exposure to pesticides	20,729 (8)	1·71 [1·24, 2·37]	10,407 (4)	3·40 [1·20, 9·63]

Lifestyle risk factors

Smoking is an important modifiable risk factor for miscarriage (Table 6). The risk is greater when smoking exposure occurs specifically during the pregnancy in which miscarriage risk was measured.[41] Miscarriage risk increases with the amount smoked (1% increase in relative risk per cigarette smoked per day).[41] Our literature review found 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 (aOR 1·67; 95% CI 1·31-2·19; Table 6).[25,39,62-70] Our review indicated that high caffeine intake might be associated with miscarriage (aOR 1·56; 95% CI 0.98-2·50; Table 6), although there was statistical uncertainty in the finding.[25,39,71] Furthermore, any association between caffeine and miscarriage is likely to be confounded by the fact that a healthy pregnancy is associated with nausea and vomiting (due to pregnancy hormones), which in turn may reduce caffeine consumption.[72] Our literature searches found that night shift work is associated with an increased risk of miscarriage (aOR 1·43; 95% CI 1·25-1·71; Table 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 (aOR 1·46; 95% CI 1·16-1·77; Table 6)[66,71,73-77]; however, there is no evidence that the association represents a causal link because, for example, preconception stress, as measured by basal salivary cortisol and alpha-amylase concentrations, did not predict subsequent pregnancy loss.[78]

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.[79-82] Once the pregnancy reaches 8 weeks, the risk of miscarriage decreases significantly; conversely, the likelihood of having a successful live birth approaches 97-98%.[82]

The number of previous miscarriages is a major determinant of miscarriage risk; the relationship is consistent across various studies, and demonstrates a biological gradient according to the number of previous miscarriages.[83] Several maternal conditions, including antiphospholipid antibodies, thyroid autoantibodies and subclinical hypothyroidism, are associated with miscarriage (Table 6). Uterine anomalies, in particular canalization defects such as uterine septae, have been associated with both spontaneous and recurrent miscarriage.[84]

Bacterial (bacterial vaginosis, brucellosis, chlamydia trachomatis, and syphilis), viral (herpes virus: HSV-1 and HSV-2, human CMV, human papillomavirus, parvovirus, adeno-associated viruses, parvovirus B19, bocavirus, HIV, polyomavirus, Dengue fever, hepatitis B, hepatitis C, rubella, coronaviruses [SARS, MERS and H1N1]) and protozoa (malaria and toxoplasmosis) infections have all been linked to miscarriage.[85] In the era of bacterial community assessment using DNA sequencing, there is evolving evidence linking the composition of the vaginal microbiome to miscarriage.[86] Miscarriage is more commonly associated with a lactobacillus deplete microbiota, but whether this is cause or effect, or what the potential mechanisms are remains unclear. These findings are supported by older data using more traditional microbiology techniques which showed an increase in the risks of miscarriage in women with bacterial vaginosis.[87] Sperm DNA fragmentation is associated with miscarriage (Table 6).[88] Association between sperm DNA fragmentation and smoking, recreational drugs, and obesity, as well as treatment with lifestyle changes and anti-oxidants are important research questions.

Environmental risk factors

Air pollution, composed of both primary pollutants, those emitted directly from the source, and secondary air pollutants formed from the interaction of primary pollutants within the atmosphere, has a wide impact on human health. In the context of pregnancy air pollution is linked to stillbirth, preterm delivery and low birthweight.[89,90] A large study assessed the effect of exposure to air pollution on miscarriage rates in Beijing, demonstrating a strong relationship with miscarriage (OR 1·51; 95% CI 1·33-1·69) .[91] Similarly, a case-control study on women attending an emergency department in Utah[92] found that a 10 parts-per-billion rise in nitrogen oxide levels was associated with an increased risk of miscarriage (OR 1.16; 95% CI 1·01-1·33). The Nurses' Health Study II showed a positive association between particulate air pollution and miscarriage.[93] Exposure to air pollution therefore appears to increase miscarriage risk and constitutes a modifiable risk factor (Table 6). Pesticides have been linked to recurrent miscarriage (Table 6). Exposure to sprayed pesticides in rural South Africa in the first three months of pregnancy was associated with an increased risk of miscarriage (OR 2·8; 95% CI 1·1-7·2).[94] This epidemiological study correlates with a clinical study demonstrating higher levels of serum organochlorine pesticides in women with recurrent miscarriage compared with controls.[95]

Risks and complications of miscarriage

Threatened miscarriage and obstetric complications

Threatened miscarriage, defined as vaginal bleeding in early pregnancy, is among the most common reasons for women to seek medical care in early pregnancy .[96] It is increasingly clear that events in early pregnancy have a significant impact on pregnancy outcomes.[97-100] A systematic review of 14 studies (n=64,365) found that women who experienced threatened miscarriage have a higher risk of antepartum haemorrhage due to placenta previa (OR 1·62; 95% CI 1·19-2·22) or antepartum hemorrhage of unknown origin (OR 2·47; 95% CI 1·52-4·02).[97] There is also an association with preterm prelabour rupture of membranes (OR 1·78; 95% CI 1·28-2·48), preterm delivery (OR 2·05; 95% CI 1·76-2·40), and fetal growth restriction (OR 1·54; 95% CI 1·18-2·00).[97] Significantly higher rates of perinatal mortality (OR 2·15; 95% CI 1·41-3·27) and low-birthweight neonates (OR 1·83; 95% CI 1·48-2·28) have been reported.[97] Ultrasound diagnosis of intrauterine haematoma (IUH) is also associated with an increased risk of antenatal complications such as preeclampsia (Relative Risk [RR] 4·0; 95% CI 2·4-6·7), placental abruption (RR 5·6; 95% CI 2·8-11·1) and preterm delivery (RR 2·3; 95% CI 1·6-3·2).[99]

Miscarriage and obstetric complications

Our literature review demonstrated striking associations between a history of miscarriage and several adverse obstetric outcomes in subsequent pregnancies (Table 7). The risk of preterm birth increases stepwise with each previous miscarriage, demonstrating a biological gradient; this association persists even with adjustment for confounding variables (Table 7). It is possible that adverse outcomes after miscarriage may be at least partly attributable to the management of miscarriage. Repeated uterine curettage after cervical dilatation may cause injury to the uterine cervix and endometrial cavity or change the uterine microbiome, increasing the risk of preterm birth due to cervical insufficiency or chronic endometritis. Injury to the uterine wall or endometrium may also cause abnormal placentation in subsequent pregnancies, resulting in increased risk of placental abruption and placenta praevia (Table 7). 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.[101] Abnormal placentation may also contribute to low birthweight (Table 7). However, it is plausible that the increased frequency of low birthweight and perinatal complications is an inherent part of the recurrent miscarriage syndrome. Women who experience recurrent miscarriage are themselves born with a significantly reduced birthweight,[102] and a history of perinatal complications has been found in women in their pregnancies before they acquire a recurrent miscarriage diagnosis.[103] An inadequate decidual response, if it does not lead to miscarriage, may 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.[104-106] Therefore, the likelihood is that the association between miscarriage and adverse obstetric outcomes may partly be driven by a common aetiology, perhaps originating in suboptimal endometrial repair and decidualisation. The increasing incidence of perinatal complications with increasing number of previous pregnancy losses[107] suggests a need for heightened antenatal surveillance in patients with a history of multiple miscarriages. In addition, miscarriage is an opportunity to consider prophylactic interventions, such as lifestyle improvements before another pregnancy.

Table 7. Risks and complications associated with past history of miscarriage

	Crude estimates		Adjusted estimates	
	Number of participants (trials)	**Odds ratio [95% CI]**	**Number of participants (trials)**	**Odds ratio [95% CI]**
Maternal risks				
Pre-eclampsia or pregnancy induced hypertension				
1 miscarriage	719,644 (4)	1·02 [0·98, 1·06]	697,122 (3)	0.99 [0.95, 1.03]
2 miscarriages	622,504 (2)	1·03 [0·95, 1·12]	622,504 (2)	0.94 [0.85, 1.04]
3 or more miscarriages	671,060 (5)	1·04 [0·72, 1·51]	616,146 (3)	1.22 [0.86, 1.73]
Placental abruption				
1 miscarriage	719,644 (4)	1·09 [0·98, 1·21]	697,122 (3)	1.07 [0.95, 1.20]
2 miscarriages	74,925 (2)	1·33 [1·07, 1·66]	622,504 (2)	1.26 [1.00, 1.59]
3 or more miscarriages	646,199 (4)	1·70 [1·31, 2·19]	616,146 (3)	1.67 [1.21, 2.30]
Placenta praevia				
1 miscarriage	115,290 (3)	1·41 [1·17, 1·69]	92,768 (2)	1.40 [1.15, 1.70]
2 miscarriages	74,925 (2)	1·86 [1·34, 2·57]	74,925 (1)	1·86 [1·34, 2·58]
3 or more miscarriages	106,207 (3)	2·71 [1·54, 4·76]	76,154 (2)	2.81 [0.87, 9.04]
Neonatal risks				
Preterm birth				
1 miscarriage	875,911 (7)	1·24 [1·09, 1·41]	733,199* (7)	1.17 [1.05, 1.31]
2 miscarriages	767,888 (4)	1·40 [1·10, 1·80]	675,655** (5)	1.36 [1.13, 1.63]
3 or more miscarriages	1,451,303 (9)	2·23 [1·68, 2·97]	668,615** (6)	1.76 [1.39, 2.22]
Low birthweight ◊				
1 miscarriage	115,182 (3)	1·11 [0·88, 1·40]	115,182* (3)	1.09 [0.91, 1.30]
2 miscarriages	74,829 (1)	1·08 [0·96, 1·21]	74,829* (1)	1.37 [0.81, 2.32]
3 or more miscarriages	76,614 (3)	1·87 [1·07, 3·27]	76,061* (3)	1.98 [1.09, 3.58]
Stillbirth				
1 miscarriage	715,168 (3)	1·13 [0·96, 1·33]	715,168 (3)	1.00 [0.88, 1.13]
2 miscarriages	623,133 (2)	1·08 [0·83, 1·41]	623,133 (2)	1.04 [0.79, 1.38]
3 or more miscarriages	613,013 (2)	2·01 [1·43, 2·82]	613,013 (2)	1.69 [1.17, 2.45]
Health risks				
Cardiovascular complications				
1 miscarriage	2,431,899 (6)	1·18 [0·83, 1·68]	2,450,098 (6)	1.06 [0.98, 1.15]
2 miscarriages	50,605 (2)	1·58 [0·64, 3·89]	162,259 (5)	1.22 [1.10, 1.35]
3 or more miscarriages	176,081 (4)	5·04 [1·68, 15·14]	290,188 (7)	1.42 [1.16, 1.74]
Stroke				
1 miscarriage	2,430,267 (4)	1·05 [0·65, 1·72]	2,448,174 (5)	0.98 [0.91, 1.06]
2 miscarriages	2,250,752 (4)	1·00 [0·38, 2·61]	86,319 (3)	1.10 [0.99, 1.21]
3 or more miscarriages	59,735 (3)	1·52 [0·70, 3·30]	17,645 (1)	1.15 [0.98, 1.36]
Venous thromboembolism				
1 miscarriage	94,595 (1)	1·30 [0·73, 2·32]	94,595 (1)	1.11 [0.59, 2.06]

2 miscarriages	80,792 (1)	1·57 [0·57, 4·36]	-	-
3 or more miscarriages	78,020 (3)	10·91 [5·16, 23·06]	78,020 (3)	6.13 [2.48, 15.16]
Mental health risks				
Anxiety				
1 miscarriage	3,028 (3)	1·74 [1·11, 2·73]	3,889 (4)	1.62 [1.25, 2.11]
2 or more miscarriages	146 (1)	4·34 [2·08, 9·03]	-	-
Depression				
1 miscarriage	4,179 (6)	2·79 [1·56, 5·01]	4,095 (5)	2.38 [1.65, 3.42]
2 or more miscarriages	146 (1)	3·88 [1·87, 8·03]	-	-
Post traumatic stress disorder				
1 miscarriage	1,513 (2)	4.39 [0.18, 105.50]	-	-
2 or more miscarriages	146 (1)	4.89 [1.57, 15.27]	-	-
Suicide				
1 miscarriage	3,655 (1)	5·27 [4·12, 6·74]	3,655 (1)	3.80 [2.80, 5.20]

The reference group for all comparisons is women without previous miscarriages. * Number of women missing for one study; ** Number of women missing for two studies; ◊ Excluding growth restriction.

Miscarriage and long-term health risks

Recurrent miscarriage is associated with long term health problems beyond pregnancy. Our literature review found that recurrent miscarriage is associated with cardiovascular disease and venous thromboembolism (Table 7). No association was identified between miscarriage and stroke (Table 7). These findings are important because they add to the concept of a recurrent miscarriage syndrome, and may 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.[108] The psychological consequences of miscarriage may have little or no outward physical manifestation and so can go unrecognised by healthcare professionals, family and friends. This is the case particularly in a society which views miscarriage as unimportant or shameful, thus leading to concealment of a pregnancy loss and its consequences.

Our literature review identified that anxiety (aOR 1·62; 95% CI 1·25-2·11), depression (aOR 2·38; 95% CI 1·65-3·42) and suicide (aOR 3·80; 95% CI 2·8-5·2) are strongly associated with miscarriage (Table 7). A multicentre prospective cohort study of 537 women following a miscarriage found that nine 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.[109] Identifying women at risk of psychological distress following miscarriage and the development of optimal treatment strategies have been identified as research priorities.[110]

Economic burden

We conducted 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 using economic methods. A total of 30 articles were included; 15 articles reported costing studies, 12 articles reported economic evaluations, and 3 articles reported preference elicitation studies. Due to heterogeneity in study design, outcomes and intervention types, and variations in healthcare practices and relative prices for resource inputs, a narrative synthesis of economic evidence is presented. All economic costs are presented in Pounds Sterling (2018 prices) for comparative purposes.

Published evidence on the economic consequences of miscarriage has focussed largely on direct health service costs associated with miscarriage treatment procedures. Cost estimates vary by the nature of the intervention (e.g. expectant, medical or surgical management), location of care (inpatient or outpatient), cost accounting methodology and jurisdiction. Most published studies have aimed to provide information about options that are less costly than current practice,[111-118] or to probe the value of adjuncts to current practice.[119] 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,[111,118] mainly as a means of tracking cumulative costs over different treatment pathways particularly where additional treatment may be required following failure of initial therapy. Unit costs estimates have been derived from a number of sources, including primary research methods[113,115,116] and administrative tariffs.[120,121]

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 United States[120] through to £1067 in a study from Hong Kong.[118] Direct health service costs for medical management ranged from £298 in a study from the United States[120] through to £1421 in a UK study.[113] Direct health service costs for surgical management, usually curettage, ranged from £455 in a study from Finland[122] through to £2242 in a study from Spain.[111] In a comparison of outpatient versus inpatient treatment in the United States, the cost of manual vacuum aspiration as an outpatient (£852) was much lower than that for inpatient treatment (£1729).[121] Direct health service costs associated with evacuation procedures are generally lower in low income countries. For example, in Pakistan manual vacuum aspiration was estimated to cost on average £56,[123] curettage £146[123] and electrical vacuum aspiration £193,[115,116]; in Swaziland manual vacuum aspiration was estimated to cost on average £131 and dilation and curettage £201 for incomplete first trimester miscarriages.[124] 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)[117] to £973 in the UK (progesterone as a preventive therapy).[119]

A few studies have estimated the non-health care costs associated with miscarriage or its management. Where these have been estimated, the focus has largely been on the economic value of lost productivity for women experiencing miscarriage. As part of the economic evaluation conducted 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.[113] 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, 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 time off work.[125] A broadly similar estimate of £428-£521 (depending on the treatment strategy) emerges in another economic evaluation from the Netherlands[126] that compared misoprostol treatment and curettage in women who had been managed expectantly for at least one week. Amongst women allocated to the misoprostol arm, the mean value of lost productivity exceeded mean direct costs to the health care system.

The economic studies emerging from our literature review typically adopt a short-term time horizon, 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 consequences 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,[113] costs to patients[127] and broader societal costs associated with lost productivity[113] generates an annual national estimate of economic burden of £471 million. Economic estimates such as these can contribute to clinical and budgetary service planning.

Discussion

Miscarriage is common, but its scale and impact are not fully appreciated by women, family, care providers, policy makers and healthcare funders. There are multiple risk factors for miscarriage, most prominently female age and the number of previous losses. Certain risk factors are modifiable, for example, BMI, smoking and alcohol. Environmental risk factors are an emerging concern. However, it is important to appreciate that 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 article. The physical consequences of miscarriage are well appreciated, but psychological sequelae less so. Even less well appreciated 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.

Whilst there are data on the short-term costs of miscarriage, the long-term costs might be considerable and may outweigh short-term concerns, although the data are limited. Newly emerging cohort studies with long term follow-up, such as the Tommy's Net Cohort Study,[128] 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, receipt of social welfare benefits and reproductive health, which might in turn have economic sequelae. Future research should use evidence from economic evaluations encompassing information on incremental costs and incremental 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 miscarriages rates amongst countries, to accelerate research, and to improve patient care and policy development. Key epidemiological research priorities include determining how can we monitor miscarriage rates on a population basis; ascertaining if miscarriage risk and prevalence differs across nations and ethnic groups, whether miscarriage rate are increasing, and if so why; what are the key outcomes from women's point of view; and which risk factors for miscarriage are potentially causative, modifiable, and the impact 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 detect women suffering from 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 impact 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 pre-term birth. Therefore, these women should be treated as high risk patients 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 a review of all sections and agreed to submit the manuscript. The manuscript represents the view of named authors only.

Declaration of interests

The authors have no conflicts of interest to declare.

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