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MISCARRIAGE AND ASSOCIATED RISK FACTORS

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Background

Miscarriage or spontaneous abortion (the term miscarriage and abortion are used interchangeably). [1] the term abortion refers to a termination of a pregnancy either natural or induced) is defined as the loss of pregnancy less than 20 weeks gestation. The American College of Obstetricians and Gynecologists (ACOG) estimates it is the most common form of pregnancy loss. It is estimated that as many as 26% of all pregnancies end in miscarriage and up to 10% of clinically recognized pregnancies. [2] Furthermore, 80% of early pregnancy loss occurs in the first trimester. The risk of miscarriage decreases after 12 weeks gestation.

There are several terms that describe different states of pregnancy loss. These terms include threatened, inevitable, complete and missed abortion. Threatened abortion is the presence of vaginal bleeding in early pregnancy but on pelvic exam, the cervical os is closed and the transvaginal ultrasound shows a viable fetus. An inevitable abortion is when there is vaginal bleeding but on the pelvic exam, the cervical os is open meaning that the fetus or products of conception are expected to pass through the cervix in the near future. [3] On transvaginal ultrasound, there can be either being a viable fetus or not. A complete abortion is when there is initially vaginal bleeding and passing of products of conception through the cervix. On transvaginal ultrasound, there would be no remaining products of conception in the uterus. A missed abortion refers to when there was vaginal bleeding and perhaps some passage of tissue or products of conception. On pelvic exam, the cervical os would be closed. On transvaginal ultrasound, there would be retained products of conception and there would not be a viable fetus. [4-5]

The most common cause of spontaneous pregnancy loss in the first trimester is chromosomal abnormalities. When a miscarriage happens in the first 12 weeks, more than half the time it's because of a problem with the chromosomes of the fetus. In most cases, it is too early to determine the exact cause of the abnormality. Risk of early pregnancy loss decreases with increasing gestational age and is relatively low after 15-weeks' gestation in a genetically normal fetus. [6]

INCIDENCE

The most common complication in early pregnancy is early pregnancy loss (EPL). The incidence of EPL can reach 31%, but when only losses in clinically recognized pregnancies are considered, the incidence drops to around 10% [7]. Up to 20 weeks of gestation, the frequency of second-trimester failure is less than 1% [8]. Women with EPL are also more likely to have subsequent normal pregnancies; in one survey of over 53,000 parous women, 43 percent had one or more previous first-trimester pregnancy losses [9]. The rate of pregnancy loss tends to be affected further by maternal age and previous pregnancy loss history.

However, determining the true incidence of EPL is difficult since many casualties go unreported. We consider EPL to occur at two distinct times: after implantation but before clinical recognition, and after clinical recognition (defined as being diagnosed by a clinician or by standard pregnancy testing) [10].

Introduction

Miscarriage is considered being one of the most common complications in pregnancy which end up with fetal loss .It is proved that one out of four clinically recognized pregnancies will complicated with miscarriage during the first-trimester, and around 1% of pregnant women will experience a second-trimester miscarriage. In spite of the prevalence of miscarriage, 50% are attributed to chromosomal abnormalities, and considerable percentages are classified as unexplained causes. [1] For that reason, identifying risk factors and effective interventions to prevent miscarriage has become a priority in the medical and scientific communities. Well-known risk factors include advanced maternal and paternal age, heavy smoking, alcohol consumption, infertility and previous miscarriage.

Medical health care authorities' aims to identify and increase the awareness between the populations in order to reduce the risk associated factors before conception that might affect the future maternal, child and family health. An effort has been made to develop effective estimation of the population-level prevalence of miscarriages and to assess the contributions of clinical, social, and health care use factors as predictors of the first detected occurrence of these losses. One of the main recommendations is to promote effective preconception health care interventions to develop curricula of preconception risk factors. [2] Enhance the awareness of miscarriage might help to assess the effectiveness of pregnancy care education, but also to highlight the gaps of knowledge among this targeted population. Therefore, a cohort study was done among the population of Canadian hospital in Manitoba from 2003 to 2014.

The data are based on information contained in the Health Services Insurance Plan Registry and from health insurance claims routinely filed by physicians and health care facilities with Health centers. The Repository data include the provincial health insurance registry; fee-for-service physician billings, hospital discharge abstracts, and emergency department visits, pharmaceutical prescriptions, individual sociodemographics, and vital statistics, all linked using an encrypted Personal Health Identification Number. Area-level sociodemographics come from the Canadian census. Therefore, a rate of 20% of miscarriage was selected as the cut-off rate in this study. The study compared between two groups across a number of clinical, social, and health care use factors measured before the loss/birth. Some are established risk factors for loss early in pregnancy, while others are potential risk factors that the doctors was uniquely able to investigate given the connections with population databases [3] .they had compared the means and distributions of each of these variables separately to understand their association with experiencing a loss. Given their large sample size, they also calculated standardized differences to assess meaningful differences in characteristics between each group. Standardized differences compare the difference in means in units of the pooled standard deviation and are independent of sample size (a value > 10% indicates a meaningful difference.

A variety of terms are used to describe nonviable pregnancies, which can lead to confusion for clinicians and patients. We take the following approach:

- **Early pregnancy loss –** Although there is no consensus regarding terminology, we prefer the term "early pregnancy loss" (EPL), which is described by several national organizations as a nonviable, intrauterine pregnancy within the first trimester (up to 12+6 weeks from the last menstrual period) [1,2]. However, at least one organization uses 10 weeks of gestational age as the cutoff, which can make study comparisons challenging

[3]. EPL includes pregnancies with an empty gestational sac (sometimes referred to as an anembryonic gestation) and pregnancies with an embryo or fetus without cardiac activity. Past terminology has included "miscarriage," "blighted ovum," "spontaneous abortion," and "missed abortion." These terms are not clearly standardized, do not always convey the information required for clinical decision making, and have sometimes been used interchangeably, all of which has contributed to confusion for patients. In a study of 145 United States English-speaking women being treated for first-trimester EPL, women preferred the terms "miscarriage" and "early pregnancy loss" rather than "early pregnancy failure" or "spontaneous abortion," which they believed to be less clear [4]. It is unclear how language and culture impact women's choice of terminology.

"Threatened miscarriage" or "threatened abortion" has been used in reference to a patient experiencing bleeding in early pregnancy but without a clear diagnosis of pregnancy loss. We find this definition imprecise and more accurately conveyed as bleeding in early pregnancy. "Incomplete miscarriage" and "incomplete abortion" are also terms used historically, typically to indicate that there is persistent pregnancy tissue in the uterus after a diagnosis of pregnancy loss. The authors prefer to avoid this term, as it is imprecise and does not affect the management options for pregnancy loss.

- **Early second-trimester pregnancy loss –** Early second-trimester pregnancy loss is one that occurs after 13+0 and prior to 20+0 weeks of gestation [5]. The 20 week cutoff is arbitrary and not related to any physiologic differences between pregnancies less than 20 weeks versus greater than 20 weeks. By convention, pregnancies lost after 20 weeks are typically referred to as stillbirth or fetal death. Ways in which early second-trimester loss differs from first-trimester loss are discussed below.

- **Stillbirth or fetal death –** Pregnancy loss that occurs at 20 weeks gestation or later, or at a weight of 350 grams or greater, is generally referred to as a stillbirth or fetal death, although differing criteria exist globally [6].

RISK FACTORS

Common risk factors for pregnancy loss include increasing maternal age, medical conditions, medication and/or substance use, and environmental exposures.

1. **Increasing age**

Age extremes raise the risk of pregnancy loss, with age >35 years being the most important risk factor due to the close correlation with fetal chromosomal abnormalities. In a national prospective cohort study of over 421,000 births, the risk of miscarriage (after excluding induced abortions) was lowest (10%) in women aged 25 to 29 years and highest (57%) in women aged 45 years [7]. Early pregnancy loss (EPL) rates by other subgroups were 17 percent for women aged 20 to 24, 11 percent for women aged 20 to 24, 11 percent for women aged 30 to 34, 17 percent for women aged 35 to 39, and 33 percent for women aged 40 to 44.

2. **Medical conditions in parents**

A. **Maternal**

EPL is linked to a number of causes of maternal morbidity, including endocrinopathies and metabolic disorders, including obesity. There are also modifiable risk factors, as well-controlled maternal conditions are far less likely to result in EPL. [8]

While any medical condition that has a negative effect on maternal health may have reproductive implications, some of the more common conditions that increase the risk of EPL are discussed below. [9]

- **Infection:** Overall, approximately 15 percent of EPL is associated with an infectious etiology [14]. Parvovirus B19 infection in pregnancy has a nearly 8 percent cumulative incidence of loss, and the risk of loss is 5.6 times higher with infection in the first trimester as compared with the second trimester [15]. Untreated syphilis leads to a 21 percent increased risk of fetal loss and stillbirth [16] . Maternal cytomegalovirus (CMV) infection has 2.5 increased odds of EPL as compared with non-infection [17]. However, maternal infection with HIV or toxoplasmosis does not appear to be associated with an increased risk of EPL [18,19].
- **Diabetes:** Type 1 and type 2, may have severe consequences in early pregnancy, even resulting in lethal fetal defects or pregnancy loss. Euglycemia during the preconception and periconception phases returns this risk to baseline.
- **Obesity:** is more significantly and reliably linked to miscarriage than either type 1 or type 2 diabetes. A meta-analysis of 16 studies published in 2008 found that having a BMI greater than 25 was associated with a nearly 70% increased risk of EPL after spontaneous or aided conception. [20]
- **Thyroid disease:** Both hyperthyroidism and hypothyroidism have been linked to an increased risk of miscarriage, with some reports showing a doubling of the risk [21]. To meet the increased metabolic needs during a normal pregnancy, there are changes in thyroid physiology that are reflected in altered thyroid function tests. These changes include the following: Thyroid hormone-binding globulin (TBG) excess results in high serum total T4 and total T3 concentrations but not high serum free T4 or free T3 concentrations. High serum human chorionic gonadotropin (hCG) concentrations during early pregnancy and even higher concentrations in women with hyperemesis gravidarum or multiple pregnancies may result in transient subclinical or rarely overt hyperthyroidism.

- **Stress:** Acute and chronic stress can also raise the risk of miscarriage [22,23]. Stress is multifaceted and can be difficult to distinguish from other threats. Chronic stress can raise cortisol levels, lower immunity, and increase susceptibility to infection and other maternal conditions, all of which increase the risk of miscarriage [14,24-27]. If a person's life is otherwise healthy, a brief period of stress, such as a busy period at work or an acute illness in a loved one, is unlikely to have a significant effect. However, racial/ethnic, socioeconomic, or other inequalities, violence risk, significant periods of housing or food insecurity in the past or present, or other long-term life stressors can all have a negative effect on health, including raising the risk of EPL [14].

- **Inherited thrombophilias:** The impact of inheritable thrombophilias on EPL risk is uncertain because the evidence is contradictory.

- **Pregnancy with intrauterine device (IUD) in place:** While IUDs are among the most powerful contraceptive methods, they are not without flaws. Though pregnancy with an IUD in place is uncommon, the risk of EPL tends to be higher for women who chose to have the IUD in place rather than have it removed [28].

B. Paternal

After controlling for maternal age and medical comorbidities, preconception paternal medical conditions may modestly increase the risk of pregnancy loss. In a retrospective cohort study of an insurance database covering 958,804 pregnancies in the United States, compared with men with no components of metabolic syndrome (MetS), the risk of pregnancy loss increased for men with one (relative risk [RR] 1.10, 95% CI 1.09-1.12), two (RR 1.15, 95% CI 1.13-1.17), or three or more (RR 1.19, 95% CI 1.14-1.24) MetS components after stratifying for maternal and paternal age [29].

3. Medication and substance use

The role of medication and substance use on EPL risk is challenging to assess as the impact varies by agent, dose, and timing of exposure. Numerous therapeutic medications are considered teratogenic in pregnancy, and some teratogenic effects can also result in an increased risk of EPL. [30]Alternately, medications may be associated with EPL even in the absence of teratogenicity. As an example of the complicated nature of medication and EPL risk, the nonsteroidal anti-inflammatory drugs (NSAIDs) aspirin and indomethacin are used for specific obstetric indications (preeclampsia prevention and treatment of acute preterm labor) while other NSAIDs, including ibuprofen and diclofenac, [31] may increase EPL risk. Substance use during pregnancy is almost always confounded with other factors that lead to poor health status and increased risk of EPL, and thus it is difficult to assess the independent impact of the drug(s) in epidemiologic studies. In general, smoking, caffeine, and alcohol consumption appear to increase the risk of pregnancy loss in a dose-related fashion [32-38]. Some studies have reported increased risks with exposure to cocaine or methamphetamines [35]. Marijuana use in pregnancy does not appear to increase the risk of pregnancy loss, although it does negatively impact neonatal development [39].

4. Environmental factors and exposures

Toxins, contaminants, and other environmental influences can increase the risk of EPL by causing cell damage, altering normal tissue development, interfering with normal cellular differentiation, or interfering with other processes. Ionizing radiation exposure is linked to EPL [40], while excessive lead, arsenic, and air pollution exposure appear to increase the risk. [40]

Some of these can be avoided, but many exposures occur where one lives or works and may not be avoidable. Lower socioeconomic status is correlated with higher environmental exposures because it can result in less control about where one lives and works.

5. **Race and ethnicity**

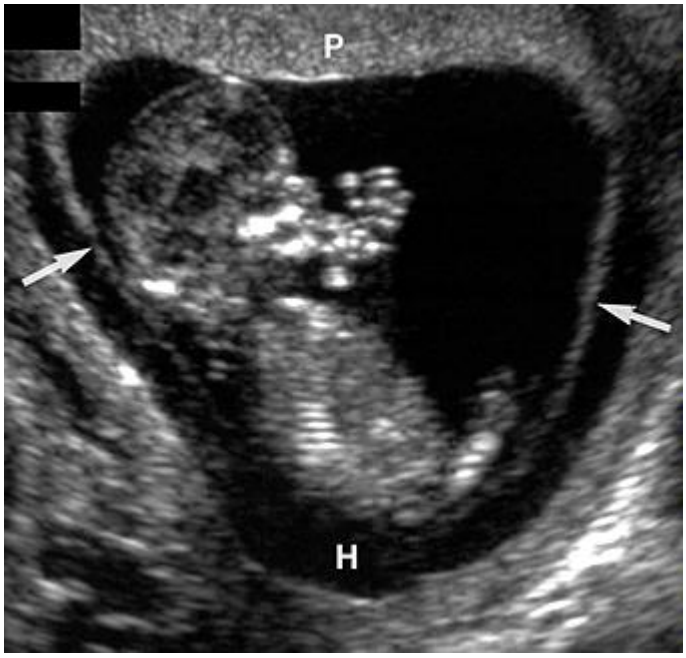
Studies have repeatedly found that Black, Indigenous, and other people of color have a higher risk of EPL than White women [41,42]. This distinction, however, is more likely to reflect the effects of institutional bias, social determinants of health, and inevitable occupational and/or environmental exposure to potential pollutants than a true biologic difference. [43]

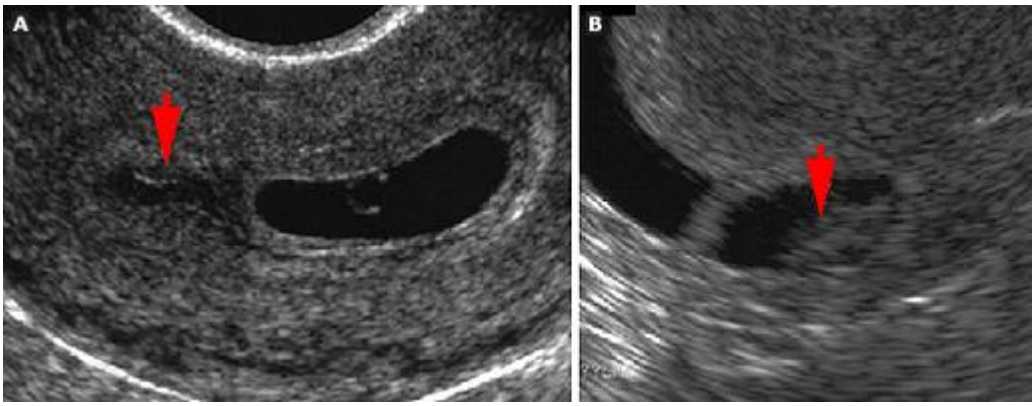
6. **Subchorionic hematoma**

Subchorionic hemorrhage or hematoma is associated with increased risk of EPL, particularly when it amounts to 25 percent or more of the volume of the gestational. A meta-analysis of seven comparative studies found that women with subchorionic hematoma had twice the chances of EPL as women without (18 versus 9%, OR 2.18, 95 percent CI 1.29-3.68) [44]. The location of the hematoma tends to have an impact on outcome, with retroplacental hematomas doing worse than marginal hematomas. Data on the relationship between hematoma size and outcome are inconclusive [45].

Distinction between subchorionic hematoma and unfused amnion in patient with vaginal bleeding at 13 weeks' gestational age

Transabdominal sagittal sonogram of uterus reveals subchorionic hematoma (H) extending posteriorly around chorion (arrows) and lifting edge of anterior placenta (P). Appearance should not be confused with that of unfused amnion. Amnion is the thin membrane continuous along anterior placental edge, but limited by umbilical cord insertion; subchorionic bleeding leads to edge of placenta.





Subchorionic bleeding in fetus at 5.5 weeks' gestational age

(A)Transverse transvaginal sonogram reveals intrauterine gestational sac with yolk sac. Note small amount of blood (arrow) adjacent to gestational sac.
(B) Transvaginal sagittal sonogram obtained 2 weeks after (A) because of vaginal bleeding shows subchorionic hematoma (arrow) with debris. Collection could be mistake for second gestational sac with embryonic demise.

RISK REDUCTION

A meta-analysis of over 40 studies concluded that use of prenatal vitamins in the preconception, periconception, and early pregnancy time frames does not prevent early pregnancy loss [46]. It is unclear if folic acid specifically can reduce the risk of miscarriage, though supplementation does appear to reduce the risk compared with no supplementation [47,48], and multivitamins plus iron and folic acid have been associated with a reduced risk for stillbirth [46]. Progesterone supplementation for patients with first trimester vaginal bleeding has not been associated with increased live birth rates and is not advised for routine use [49-51].

Early pregnancy loss

ETIOLOGY

Common etiologies of early pregnancy loss (EPL) include chromosomal abnormalities, maternal anatomic abnormalities, and trauma.

Chromosomal abnormalities: Chromosomal abnormalities are present in up to 70 percent of pregnancy losses before 20 weeks, though the prevalence varies by gestational age [52-56]. In a study that evaluated 80 women with pregnancy loss at <20 weeks gestation with chromosomal microarray analysis, genetic abnormalities were reported in 9 percent of pre-embryonic losses (from implantation to less than 6 weeks), 69 percent of embryos between 6+0 weeks and 9+6 weeks, and 33 percent of fetuses between 10+0 weeks and 19+6 weeks [54]. The use of chromosomal microarray likely increased the ability to identify earlier preclinical losses that previously were undetected by karyotype. This study challenged historic teaching that earlier gestational age was associated with increased risk of chromosomal abnormality. While embryonic losses are still more likely to result from chromosomal abnormalities compared with

later fetal losses, this relationship does not appear to be valid for pre-embryonic losses (defined as no visible embryo on ultrasound evaluation)

Maternal anatomic anomalies: Anatomic anomalies, such as uterine leiomyomas (fibroids), polyps, adhesions, or septa, may be associated with EPL based on their size and position in relation to the developing pregnancy. These may not be identified prior to experiencing EPL but, once diagnosed, can often be surgically or medically addressed before another pregnancy is attempted. In a study of 104 women with recurrent pregnancy loss of multiple types, the most common structural diagnoses that likely contributed to the loss were intrauterine adhesions (Asherman syndrome, 15 percent), fibroids (14 percent), uterine septum (3 percent), and endometrial polyps (2 percent) [57]. No diagnosis was identified in 18 percent of patients. By contrast, a meta-analysis of five studies including over 21,000 routine obstetric patients reported no association between uterine leiomyomas and pregnancy loss [58]. Thus, the impact of fibroids on pregnancy loss likely varies by other factors, such as distortion of the uterine cavity and/or blood supply

Trauma: significant trauma can cause EPL. The developing embryo is relatively protected within the uterus in early pregnancy, but trauma that results in direct impact to the uterus can result in EPL. This can be due to violent trauma (gunshot wounds, penetrating injuries) or iatrogenic trauma, as with chorionic villus sampling and amniocentesis. A history of intimate partner violence (IPV) is consistently associated with higher incidence of EPL. [59-60]

EARLY SECOND-TRIMESTER PREGNANCY LOSS

Early second-trimester pregnancy loss, or fetal death, occurs in approximately 2 to 3 percent of pregnancies. Conventionally, this is defined as fetal death between 13 and 20 weeks, and losses after 20 weeks gestation are defined as stillbirth, but this cutoff does not have a biological basis [70-77]. Women experiencing second-trimester pregnancy loss are a heterogeneous group, and the underlying pathology overlaps with obstetric complications such as preterm delivery and preterm premature rupture of membranes. Frequently, second-trimester pregnancy loss has more than one cause, and often no etiology is identified [78].

Known and suspected etiologies of second-trimester pregnancy loss include:

- Infection, including chorioamnionitis and maternal viral infection
- Chronic stressors, including contributions from racial/ethnic, financial or other disparities, chronic food or housing insecurity, and other long-term life stressors [14]
- Uterine malformation
- Cervical insufficiency
- Fetal malformation or syndromes such as anencephaly, trisomies, renal genesis, or hydrops
- Thrombophilias
- Abruption
- Premature preterm rupture of membranes
- Preterm labor

Infection appears to often be either a primary or secondary factor. In one study, 77 percent of losses had histologic evidence of chorioamnionitis, compared with a control group undergoing induction pregnancy termination [79]. This is much higher than the 15 percent incidence of infection with early pregnancy loss at less than 12 weeks gestation [14, 69]. Racial disparities in loss are also more pronounced between 10 and 20 weeks, with self-reported black race conferring nearly double the adjusted hazard ratio as compared with white race [41].

Discussion

A team of researchers, led by Maria Magnus at the Norwegian Institute of Public Health, set out to estimate the risk of miscarriage among Norwegian women and to evaluate the association with age and pregnancy history. There were 421,201 pregnancies during the study period. After accounting for induced abortions, the overall miscarriage rate was 12.8%. The risk of miscarriage was lowest among women aged 25-29 (10%), and rose rapidly after age 30, reaching 53% among women age 45 years and over. There was also a strong recurrence risk of miscarriage. After one miscarriage, the risk of another was increased by half, after two, the risk doubled, and after three consecutive miscarriages, the risk was four times greater.

Another study was done by Anne-Marie Nybo Andersen, a total of 634 272 women had 1 221 546 pregnancies, of which 126 673 ended in fetal loss, 285 022 in an induced abortion, and 809 762 in a live birth. The overall risk of fetal loss was 13.5%. The risk of fetal loss according to maternal age at conception followed a J-shaped curve, with a steep increase after 35 years of age. More than one fifth of all pregnancies in 35 year old women resulted in fetal loss, and at 42 years of age more than half of the intended pregnancies (54.5%) resulted in fetal loss. After adjustment for induced abortions, the increased risk of fetal loss disappeared in women aged less than 20 years and the increased risk in women aged more than 35 years was at a slightly lower level.

La Rochebrochard and P Thonneauthe had studied about the possibility of a paternal age weather could effect has rarely been considered. They carried out review of the literature to investigate the effect of paternal age on the risks of infecundity and miscarriage. The risks of infecundity and miscarriage increase with paternal age. Two main hypotheses can be considered. First, these risks increase after the age of 35-40 years. However, a later paternal age effect (after 45-50 years) cannot be excluded. Second, due to the interaction of the ages of the two partners, the risks of infecundity and miscarriage may be higher when both partners are older (woman aged 35 years or over and man 40 years or over).

Conclusion

Misunderstanding of causes and risk factors for miscarriage is a public health issue. The findings of this study highlight an opportunity for public health interventions to improve reproductive health education. Past health care follow up and social factors may contribute important knowledge about women who experience a miscarriage, above and beyond the known clinical estimation. While giving the attention to modifiable risk factors may help to prevent fetal loss,

the current context of advanced maternal age, increased prevalence of comorbidities, and increased use of IVF suggests these events are likely to have more impaction. Awareness and carful follow up should be given to those females who are at a high risk of miscarriage by health care providers and administrators. A better understanding of risk factors which women are more likely to experience a loss, may also contribute to better planning of health care system resources. Further research is needed for better understanding the association of miscarriage with the anticipated risk factors such as advance of maternal age, traumatic events, drugs abuse, short interval between the last pregnancy and the most recent one, and uterine or chromosomal abnormalities.

REFERENCES

1. National Institute for Health and Clinical Excellence. Ectopic pregnancy and miscarriage: diagnosis and i nitial management. NICE Clinical Guideline 154. Manchester (UK): NICE; 2012. www.nice.org.uk/guida nce/cg154 (Accessed on March 12, 2019).
2. ACOG Practice Bulletin No. 200 Summary: Early Pregnancy Loss. Obstet Gynecol 2018; 132:1311.
3. Kolte AM, Bernardi LA, Christiansen OB, et al. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. Hum Reprod 2015; 30:495.
4. Clement EG, Horvath S, McAllister A, et al. The Language of First-Trimester Nonviable Pregnancy: Patient-Reported Preferences and Clarity. Obstet Gynecol 2019; 133:149.
5. ACOG Practice Bulletin No. 135: Second-trimester abortion. Obstet Gynecol 2013; 121:1394. Reaffirmed 2019.
6. ACOG Practice Bulletin No. 102: management of stillbirth. Obstet Gynecol 2009; 113:748. Reaffirmed 2019.
7. Magnus MC, Wilcox AJ, Morken NH, et al. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ 2019; 364:l869.
8. Wyatt PR, Owolabi T, Meier C, Huang T. Age-specific risk of fetal loss observed in a second trimester serum screening population. Am J Obstet Gynecol 2005; 192:240.
9. Cohain JS, Buxbaum RE, Mankuta D. Spontaneous first trimester miscarriage rates per woman among parous women with 1 or more pregnancies of 24 weeks or more. BMC Pregnancy Childbirth 2017; 17:437.
10. Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy. N Engl J Med 1988; 319:189.
11. Nybo Andersen AM, Wohlfahrt J, Christens P, et al. Maternal age and fetal loss: population based register linkage study. BMJ 2000; 320:1708.
12. Slama R, Bouyer J, Windham G, et al. Influence of paternal age on the risk of spontaneous abortion. Am J Epidemiol 2005; 161:816.
13. Woolner AMF, Raja EA, Bhattacharya S, et al. Inherited susceptibility to miscarriage: a nested case-control study of 31,565 women from an intergenerational cohort. Am J Obstet Gynecol 2020; 222:168.e1.
14. Frazier T, Hogue CJR, Bonney EA, et al. Weathering the storm; a review of pre-pregnancy stress and risk of spontaneous abortion. Psychoneuroendocrinology 2018; 92:142.
15. Xiong YQ, Tan J, Liu YM, et al. The risk of maternal parvovirus B19 infection during pregnancy on fetal loss and fetal hydrops: A systematic review and meta-analysis. J Clin Virol 2019; 114:12.
16. Gomez GB, Kamb ML, Newman LM, et al. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. Bull World Health Organ 2013; 91:217.

17. Rasti S, Ghasemi FS, Abdoli A, et al. ToRCH "co-infections" are associated with increased risk of abortion in pregnant women. Congenit Anom (Kyoto) 2016; 56:73.
18. Ghasemi FS, Rasti S, Piroozmand A, et al. Toxoplasmosis-associated abortion and stillbirth in Tehran, Iran. J Matern Fetal Neonatal Med 2016; 29:248.
19. Wedi CO, Kirtley S, Hopewell S, et al. Perinatal outcomes associated with maternal HIV infection: a systematic review and meta-analysis. Lancet HIV 2016; 3:e33.
20. Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertil Steril 2008; 90:714.
21. Maraka S, Ospina NM, O'Keeffe DT, et al. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid 2016; 26:580.
22. Li Y, Margerison-Zilko C, Strutz KL, Holzman C. Life Course Adversity and Prior Miscarriage in a Pregnancy Cohort. Womens Health Issues 2018; 28:232.
23. Qu F, Wu Y, Zhu YH, et al. The association between psychological stress and miscarriage: A systematic review and meta-analysis. Sci Rep 2017; 7:1731.
24. Nepomnaschy PA, Welch KB, McConnell DS, et al. Cortisol levels and very early pregnancy loss in humans. Proc Natl Acad Sci U S A 2006; 103:3938.
25. Wainstock T, Lerner-Geva L, Glasser S, et al. Prenatal stress and risk of spontaneous abortion. Psychosom Med 2013; 75:228.
26. Bruckner TA, Mortensen LH, Catalano RA. Spontaneous Pregnancy Loss in Denmark Following Economic Downturns. Am J Epidemiol 2016; 183:701.
27. Sastra C. Higher Cortisol Level Would Increase the Risk of Spontaneous Abortion. In J Obstet Gynecol 2013; 31.
28. Ozgu-Erdinc AS, Tasdemir UG, Uygur D, et al. Outcome of intrauterine pregnancies with intrauterine device in place and effects of device location on prognosis. Contraception 2014; 89:426.
29. Kasman AM, Zhang CA, Li S, et al. Association between preconception paternal health and pregnancy loss in the USA: an analysis of US claims data. Hum Reprod 2021; 36:785.
30. Nakhai-Pour HR, Broy P, Sheehy O, Bérard A. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. CMAJ 2011; 183:1713.
31. Li DK, Ferber JR, Odouli R, Quesenberry C. Use of nonsteroidal antiinflammatory drugs during pregnancy and the risk of miscarriage. Am J Obstet Gynecol 2018; 219:275.e1.
32. Avalos LA, Roberts SC, Kaskutas LA, et al. Volume and type of alcohol during early pregnancy and the risk of miscarriage. Subst Use Misuse 2014; 49:1437.
33. Henriksen TB, Hjollund NH, Jensen TK, et al. Alcohol consumption at the time of conception and spontaneous abortion. Am J Epidemiol 2004; 160:661.
34. Pineles BL, Park E, Samet JM. Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. Am J Epidemiol 2014; 179:807.
35. Ness RB, Grisso JA, Hirschinger N, et al. Cocaine and tobacco use and the risk of spontaneous abortion. N Engl J Med 1999; 340:333.
36. Chen LW, Wu Y, Neelakantan N, et al. Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose-response meta-analysis of prospective studies. Public Health Nutr 2016; 19:1233.
37. Lee SW, Han YJ, Cho DH, et al. Smoking Exposure in Early Pregnancy and Adverse Pregnancy Outcomes: Usefulness of Urinary Tobacco-Specific Nitrosamine Metabolite 4-(Methylnitrosamino)-1-(3-Pyridyl)-1-Butanol Levels. Gynecol Obstet Invest 2018; 83:365.
38. Sundermann AC, Zhao S, Young CL, et al. Alcohol Use in Pregnancy and Miscarriage: A Systematic Review and Meta-Analysis. Alcohol Clin Exp Res 2019; 43:1606.
39. Conner SN, Bedell V, Lipsey K, et al. Maternal Marijuana Use and Adverse Neonatal Outcomes: A Systematic Review and Meta-analysis. Obstet Gynecol 2016; 128:713.
40. Radiation and pregnancy: a fact sheet for clinicians. Centers for Disease Control and Prevention, 2014 https://emergency.cdc.gov/radiation/prenatalphysician.asp (Accessed on January 28, 2019).

41. Mukherjee S, Velez Edwards DR, Baird DD, et al. Risk of miscarriage among black women and white women in a U.S. Prospective Cohort Study. Am J Epidemiol 2013; 177:1271.
42. Oliver-Williams CT, Steer PJ. Racial variation in the number of spontaneous abortions before a first successful pregnancy, and effects on subsequent pregnancies. Int J Gynaecol Obstet 2015; 129:207.
43. Pearlstone M, Baxi L. Subchorionic hematoma: a review. Obstet Gynecol Surv 1993; 48:65.
44. Tuuli MG, Norman SM, Odibo AO, et al. Perinatal outcomes in women with subchorionic hematoma: a systematic review and meta-analysis. Obstet Gynecol 2011; 117:1205.
45. Bennett GL, Bromley B, Lieberman E, Benacerraf BR. Subchorionic hemorrhage in first-trimester pregnancies: prediction of pregnancy outcome with sonography. Radiology 1996; 200:803.
46. Balogun OO, da Silva Lopes K, Ota E, et al. Vitamin supplementation for preventing miscarriage. Cochrane Database Syst Rev 2016; :CD004073.
47. Gindler J, Li Z, Berry RJ, et al. Folic acid supplements during pregnancy and risk of miscarriage. Lancet 2001; 358:796.
48. Gaskins AJ, Rich-Edwards JW, Hauser R, et al. Maternal prepregnancy folate intake and risk of spontaneous abortion and stillbirth. Obstet Gynecol 2014; 124:23.
49. Coomarasamy A, Devall AJ, Cheed V, et al. A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy. N Engl J Med 2019; 380:1815.
50. Cook R, Thomas V, Taft R, NIHR Dissemination Centre. Routine use of progesterone does not prevent miscarriage. BMJ 2019; 367:l5721.
51. Coomarasamy A, Harb HM, Devall AJ, et al. Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT. Health Technol Assess 2020; 24:1.
52. Hsu LYF. Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In: Genetic Disorders of the Fetus, 4th ed, Milunsky A (Ed), The Johns Hopkins University Press, Baltimore 1998. p.179.
53. Levy B, Sigurjonsson S, Pettersen B, et al. Genomic imbalance in products of conception: single-nucleotide polymorphism chromosomal microarray analysis. Obstet Gynecol 2014; 124:202.
54. Romero ST, Geiersbach KB, Paxton CN, et al. Differentiation of genetic abnormalities in early pregnancy loss. Ultrasound Obstet Gynecol 2015; 45:89.
55. Soler A, Morales C, Mademont-Soler I, et al. Overview of Chromosome Abnormalities in First Trimester Miscarriages: A Series of 1,011 Consecutive Chorionic Villi Sample Karyotypes. Cytogenet Genome Res 2017; 152:81.
56. Smits MAJ, van Maarle M, Hamer G, et al. Cytogenetic testing of pregnancy loss tissue: a meta-analysis. Reprod Biomed Online 2020; 40:867.
57. Young BK. A multidisciplinary approach to pregnancy loss: the pregnancy loss prevention center. J Perinat Med 2018; 47:41.
58. Sundermann AC, Velez Edwards DR, Bray MJ, et al. Leiomyomas in Pregnancy and Spontaneous Abortion: A Systematic Review and Meta-analysis. Obstet Gynecol 2017; 130:1065.
59. Fanslow J, Silva M, Whitehead A, Robinson E. Pregnancy outcomes and intimate partner violence in New Zealand. Aust N Z J Obstet Gynaecol 2008; 48:391.
60. Silverman JG, Gupta J, Decker MR, et al. Intimate partner violence and unwanted pregnancy, miscarriage, induced abortion, and stillbirth among a national sample of Bangladeshi women. BJOG 2007; 114:1246.
61. Nur N. Association between domestic violence and miscarriage: a population-based cross-sectional study among women of childbearing ages, Sivas, Turkey. Women Health 2014; 54:425.
62. Nelson DB, Grisso JA, Joffe MM, et al. Violence does not influence early pregnancy loss. Fertil Steril 2003; 80:1205.
63. Strobino B, Pantel-Silverman J. Gestational vaginal bleeding and pregnancy outcome. Am J Epidemiol 1989; 129:806.
64. Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. BMJ 1997; 315:32.
65. Hasan R, Baird DD, Herring AH, et al. Patterns and predictors of vaginal bleeding in the first trimester of pregnancy. Ann Epidemiol 2010; 20:524.

66. Sapra KJ, Joseph KS, Galea S, et al. Signs and Symptoms of Early Pregnancy Loss. Reprod Sci 2017; 24:502.
67. DeVilbiss EA, Naimi AI, Mumford SL, et al. Vaginal bleeding and nausea in early pregnancy as predictors of clinical pregnancy loss. Am J Obstet Gynecol 2020; 223:570.e1.
68. Zhang J, Gilles JM, Barnhart K, et al. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. N Engl J Med 2005; 353:761.
69. Giakoumelou S, Wheelhouse N, Cuschieri K, et al. The role of infection in miscarriage. Hum Reprod Update 2016; 22:116.
70. Dalton VK, Harris LH, Clark SJ, et al. Treatment patterns for early pregnancy failure in Michigan. J Womens Health (Larchmt) 2009; 18:787.
71. Batzer FR. Hormonal evaluation of early pregnancy. Fertil Steril 1980; 34:1.
72. Connolly A, Ryan DH, Stuebe AM, Wolfe HM. Reevaluation of discriminatory and threshold levels for serum β-hCG in early pregnancy. Obstet Gynecol 2013; 121:65.
73. al-Sebai MA, Kingsland CR, Diver M, et al. The role of a single progesterone measurement in the diagnosis of early pregnancy failure and the prognosis of fetal viability. Br J Obstet Gynaecol 1995; 102:364.
74. Lek SM, Ku CW, Allen JC Jr, et al. Validation of serum progesterone <35nmol/L as a predictor of miscarriage among women with threatened miscarriage. BMC Pregnancy Childbirth 2017; 17:78.
75. Doubilet PM, Benson CB, Bourne T, et al. Diagnostic criteria for nonviable pregnancy early in the first trimester. N Engl J Med 2013; 369:1443.
76. Abdallah Y, Daemen A, Kirk E, et al. Limitations of current definitions of miscarriage using mean gestational sac diameter and crown-rump length measurements: a multicenter observational study. Ultrasound Obstet Gynecol 2011; 38:497.
77. McPherson E. Recurrence of stillbirth and second trimester pregnancy loss. Am J Med Genet A 2016; 170A:1174.
78. McNamee KM, Dawood F, Farquharson RG. Mid-trimester pregnancy loss. Obstet Gynecol Clin North Am 2014; 41:87.
79. Allanson B, Jennings B, Jacques A, et al. Infection and fetal loss in the mid-second trimester of pregnancy. Aust N Z J Obstet Gynaecol 2010; 50:221.