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Signs and Symptoms of Early Pregnancy Loss: A Systematic Review

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Abstract

Approximately one-third of pregnancies end in loss; however, the natural history of early pregnancy loss, including signs and symptoms preceding loss, has yet to be fully described and its underlying mechanisms fully understood. We searched PubMed/MEDLINE and Embase to identify articles with prospective ascertainment of signs and symptoms, including vaginal bleeding, nausea, and vomiting, of pregnancy loss < 20 weeks gestation in spontaneous conceptions to ascertain existing literature on symptomatology of pregnancy loss. Two preconception and 16 pregnancy cohort studies that ascertained information on bleeding and/or nausea/vomiting prior to pregnancy loss ascertainment were included. Data from these studies indicated increased risk of loss with vaginal bleeding and decreased risk of loss with nausea/vomiting, though these studies were mostly comprised of pregnancies surviving into late first trimester. While such associations are biologically plausible, these study designs are subject to bias, given recruitment of women at later gestational ages and reliance on women presenting to care. Reporting symptoms to clinicians and over long periods may introduce reporting error. Data gaps remain regarding (1) relationships between signs and symptoms and losses occurring very early, prior to care entry; (2) empirical testing of whether relationships between signs and symptoms and loss differ across gestational age; (3) whether similar relationships between signs and symptoms and loss are observed in populations using assisted reproductive technologies; (4) the patterning of multiple signs and symptoms in relation to loss; and (5) how hormonal and physiologic adaptions to early pregnancy relate to symptomatology and pregnancy loss.

Keywords

bleeding, miscarriage, nausea, pregnancy loss, vomiting

Introduction

Pregnancy loss is the spontaneous end of a pregnancy resulting in demise at any point from implantation through delivery. Pregnancy loss affects approximately one-third of pregnancies and most often occurs before viability during the first and early second trimesters.[1,2] It is frequently an upsetting event for both women and their partners and can be associated with considerable psychological trauma.[3-8] Despite the frequency and potentially distressing nature of pregnancy loss, the pathophysiology of loss remains poorly understood, and its natural history, including temporal ordering of signs and symptoms, in early pregnancy has yet to be fully described.

The signs and symptoms of pregnancy and loss most often evaluated in clinical studies include nausea, vomiting, and vaginal bleeding. Nausea and vomiting are believed to be protective against pregnancy loss, while bleeding is believed to be more ominous. Given the need to more thoroughly delineate the signs and symptoms of pregnancy loss, the objectives of this qualitative review were (1) to determine the state of existing knowledge on the incidence of signs and symptoms and the risk of early pregnancy loss (<20 weeks gestation) in women with and without signs and symptoms from the general population and (2) to identify any data gaps, particularly with regard to populations studied (care-seeking women vs all women) and signs and symptoms evaluated, to guide future clinical and basic science research.

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Materials and methods

Literature Search

We conducted PubMed/MEDLINE and Embase searches using parameters listed in Table 1. Searches for abortion, spontaneous (MeSH Term), and miscarriage (MeSH Term) yielded the same results. Reference lists of all included papers were crosschecked, and the reference lists of prior review papers on bleeding[9,10] or nausea and/or vomiting of pregnancy (NVP)[11,12] were searched. No restrictions were placed on publication date. Only articles published in English were included. The first author completed all searches and data extraction; the last search was completed on March 21, 2016.

Inclusion/Exclusion Criteria

Studies among women recruited preconception are ideal for evaluating the relationships between signs and symptoms and early pregnancy loss as they can capture all pregnancies detectable by available technology (eg, highly sensitive home pregnancy tests), and they do not depend upon pregnancies surviving until clinical detection. However, due to the dearth of preconception studies on signs and symptoms associated with pregnancy loss, we also included prospective cohort studies recruiting women during pregnancy; the implications of including pregnancy cohort studies are addressed in ''Discussion'' section.

The exclusion criteria were defined prior to review and reflect the fact that we were (1) interested in describing the associations between signs and symptoms and pregnancy among women in the general population (eg, not those with underlying medical or reproductive conditions) and (2) concerned about possible information bias of signs and symptoms in studies in which data were obtained after loss ascertainment or were ascertained using proxies. Therefore, we excluded the following types of studies: (1) couples seeking infertility treatment because these women have underlying fertility concerns and are also likely to receive exogenous hormones that may impact their signs and symptoms and risk of pregnancy loss; (2) women with recurrent pregnancy loss because they have underlying fertility concerns and are at increased risk of loss; (3) ectopic and molar pregnancies because their signs and symptoms may be different from losses of intrauterine pregnancies, which comprise the majority of pregnancies and losses; (4) twin pregnancies because they may have different signs and symptoms and have an increased risk of loss relative to singleton pregnancies; (5) antepartum hemorrhage, subchorionic hematoma (without vaginal bleeding), and hyperemesis gravidarum because these rarer conditions may reflect underlying physiologic processes that may be different from vaginal bleeding or nausea/vomiting in early gestation and may have different relationships with loss; (6) women with preexisting medical conditions because their signs and symptoms and risk of loss may be different from the general population; (7) studies with report of symptoms exclusively after pregnancy loss

Table 1. Literature Search Terms in PubMed/MEDLINE and Embase.

- Applying the "prospective studies," "English," and "Humans" MeSH term restriction in PubMed
  - Abortion, spontaneous (MeSH Term) and nausea (Title/Abstract)
  - Abortion, spontaneous (MeSH Term) and vomiting (Title/Abstract)
  - Abortion, spontaneous (MeSH Term) and cramping (Title/Abstract)
  - Abortion, spontaneous (MeSH Term) and bleeding (Title/Abstract)
  - Abortion, spontaneous (MeSH Term) and (symptoms (Title/Abstract) or signs (Title/Abstract))
  - Fetal death (MeSH Term) and nausea (Title/Abstract)
  - Fetal death (MeSH Term) and vomiting (Title/Abstract)
  - Fetal death (MeSH Term) and cramping (Title/Abstract)
  - Fetal death (MeSH Term) and bleeding (Title/Abstract)
  - Fetal death (MeSH Term) and (symptoms (Title/Abstract) or signs (Title/Abstract))
  - Pregnancy loss (Title/Abstract) and nausea (Title/Abstract)
  - Pregnancy loss (Title/Abstract) and vomiting (Title/Abstract)
  - Pregnancy loss (Title/Abstract) and cramping (Title/Abstract)
  - Pregnancy loss (Title/Abstract) and bleeding (Title/Abstract)
  - Pregnancy loss (Title/Abstract) and (symptoms (Title/Abstract) or signs (Title/Abstract))
- Applying the "Humans" and "English" MeSH term restrictions in PubMed
  - Miscarriage (Title/Abstract) and vaginal bleeding (Title/Abstract)
  - Miscarriage (Title/Abstract) and nausea (Title/Abstract)
  - Miscarriage (Title/Abstract) and symptoms (Title/Abstract)
  - Pregnancy loss (Title/Abstract) and pregnancy symptoms (Title/Abstract)
- Applying only the "English" restriction in PubMed
  - Pregnancy complications [MeSH Major Topic] AND bleeding [Title/Abstract]
  - Pregnancy complications [MeSH Major Topic] AND (vomiting [Title/Abstract] or nausea [Title/Abstract])
  - Pregnancy complications [MeSH Major Topic] AND cramping [Title/Abstract]
- Applying the "English" and "Humans" limitations in Embase
  - Spontaneous abortion and nausea
  - Spontaneous abortion and vomiting
  - Spontaneous abortion and cramping
  - Spontaneous abortion and bleeding
  - Spontaneous abortion and (symptoms or signs)
  - Fetal death and nausea
  - Fetal death and vomiting
  - Fetal death and cramping
  - Fetal death and bleeding
  - Fetal death and (symptoms or signs)
  - Pregnancy loss and nausea
  - Pregnancy loss and vomiting
  - Pregnancy loss and cramping
  - Pregnancy loss and bleeding
  - Pregnancy loss and (symptoms or signs)
  - Miscarriage and vaginal bleeding
  - Miscarriage and nausea
  - Miscarriage and symptoms
  - Pregnancy loss and pregnancy symptoms
  - Pregnancy complications AND bleeding
  - Pregnancy complications AND (vomiting or nausea)
  - Pregnancy complications AND cramping

(including case–control studies), studies where prescription of antiemetic drugs was used as proxy for vomiting, studies on treatments for nausea and vomiting, and studies where indication for ultrasound or chief complaint for emergency department presentation were used as proxies for bleeding due to concerns about information bias of signs and symptoms; (8) studies focused on prediction of viability using ultrasound or biological markers because this review focused on signs and symptoms of pregnancy loss; (9) studies without a comparison group or an inappropriate comparison group (eg, ectopic pregnancies), studies on stillbirth, preterm birth or other adverse pregnancy outcomes and studies without data on pregnancy outcomes because the risks of pregnancy loss by presence or absence of signs and symptoms could not be calculated; (10) studies using matched cohort designs because the incidence of signs and symptoms could not be estimated; and (11) cross-sectional studies because the outcomes for all pregnancies were not known at study's end. Studies on threatened abortion were only included if they compared loss rates in women with and without other signs and symptoms (eg, nausea and/or vomiting). First, titles were screened to rule in studies that may satisfy the inclusion/exclusion criteria. For articles passing the title screen, abstracts were read to ensure articles passed inclusion/exclusion criteria; if ambiguous, the full manuscript was read to ascertain whether it merited inclusion in our review.

Data Synthesis

Given the paucity of data from preconception studies, our synthesis considered both preconception and pregnancy cohort studies together; the potential biases of including pregnancy cohort studies is addressed in the Discussion section. The cumulative incidence of each sign and symptom as well as the cumulative incidence of pregnancy loss among women experiencing and not experiencing specific signs and symptoms were reported. Risk of pregnancy loss in women with signs and symptoms was compared with risk of loss in women without signs and symptoms using data abstracted from the articles to estimate risk ratios (RR) and 95% confidence intervals (CIs). Although we restricted our review to pregnancy losses <20 weeks gestation in keeping with the Centers for Disease Control and Prevention's definition of loss (compared with stillbirths occurring at $\geq$ 20 weeks gestation),[13] in the data synthesis, we did not divide losses into early or late losses because (1) there is no uniformly agreed upon approach by which to categorize losses, and (2) we sought to describe relationships between signs and symptoms of loss among the general population of women, particularly among women who have not entered prenatal care at the time of loss. In presenting results of the review, however, we did distinguish between care-seeking and community-based cohorts (described subsequently), given that gestational age of losses and reporting of signs and symptoms may differ between these 2 populations. We did not stratify results by potential confounding variables, since we were interested in signs and symptoms of loss among the entire population; furthermore, given the limited literature on signs and symptoms of loss, we were not aware of any variables that met consensus criteria for confounding. Given the relatively small number of eligible studies, no meta-analysis was undertaken; thus, quality of studies was not scored, as we did not need to pool and weight estimates by their quality.

Ethical Approval

As this study used data obtained from previously published papers, no Institutional Review Board approval was needed.

Results

Figure 1 shows the number of articles identified, excluded, and ultimately included in the review. The exhaustive literature search yielded 20 775 articles of which 3193 were duplicates leaving 17 582 unique titles. After all exclusions, 18 studies, including 2 preconception and 16 pregnancy cohort studies, were included in the review on the incidence of signs and symptoms and associations with pregnancy loss <20 weeks gestation.

Cumulative Incidence of Vaginal Bleeding and Its Associations With Pregnancy Loss

Care-seeking cohorts. Four prospective studies on vaginal bleeding and its association with pregnancy loss from cohorts of women seeking prenatal care were included (Table 2).[14-17] The studies were conducted from the 1960s into the 2000s in 3 different countries, and sample sizes ranged from 550 in a general practice to >16 000 patients in a multicenter trial for trisomy 21 screening. The cumulative incidence of vaginal bleeding in pregnancy ranged from 7% to 21%. The risks of loss were greater among women with than among women without bleeding in all 4 studies. In one study reporting on severity of bleeding, the risk of loss was greater for women with heavy bleeding than for women with light bleeding relative to women with no bleeding.[17]

Community-based cohorts. Two prospective cohort studies of women recruited from communities in the United States were included (Table 2).[18,19] In a preconception cohort of 151 pregnancies with daily capture of bleeding, the cumulative incidence of bleeding $\leq$8 weeks gestational age among pregnancies surviving $\geq$6 weeks gestational age was 9%.[18] Only 15 pregnancy losses were recorded, with 2 occurring among 14 women with bleeding (14%) and 13 occurring among 137 women without bleeding (9%). In a pregnancy cohort of 4510 pregnancies, the cumulative incidence of retrospectively reported first-trimester bleeding was 27% with 8% reporting heavy bleeding.[19] Any bleeding versus no bleeding was not associated with pregnancy loss; however, heavy bleeding, longer duration of bleeding, and heavy bleeding

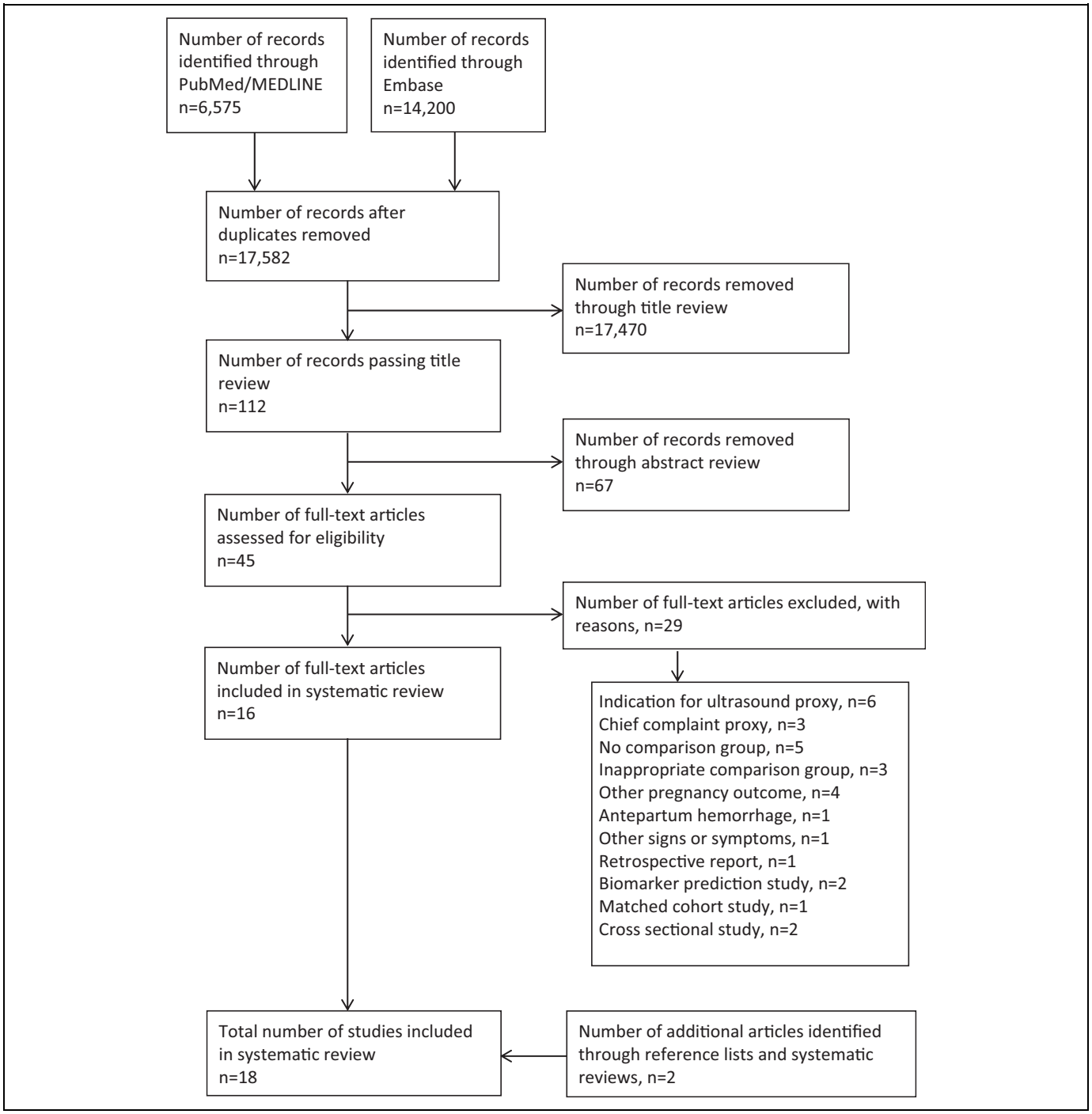

Figure 1. Flowchart for identification, exclusion, and inclusion of studies.

accompanied by pain were associated with increased risk of pregnancy loss.

Cumulative Incidence of Nausea and Vomiting and Its Associations With Pregnancy Loss

Care-seeking cohorts. Nine prospective studies of NVP and its associations with pregnancy loss among cohorts of women seeking prenatal care were included, spanning 4 countries and 50 years, 4 with sample sizes >1000 patients (Table 3).[20-28] These included studies from a large insurance provider,[20,28] the multicenter Collaborative Perinatal Project,[21] and a study of women seeking prenatal care in Malmo, Sweden.[22] Cumulative incidence of NVP prior to 20 weeks gestation ranged from 65% to 89%, with cumulative incidence of loss among women with NVP (range 0%-11%) lower than the cumulative incidence of loss among women without NVP (range 7%-35%). Several studies have reported the cumulative incidence of

Table 2. Cumulative Incidence of Vaginal Bleeding and Associations With Pregnancy Loss.

First Author (Year)	Sampling Frame and Study Size (n)	Assessment of Bleeding and Pain	GA at Assessment	Cumulative Incidence of Bleeding	Cumulative Incidence of Loss in Women With Bleeding	Cumulative Incidence of Loss in Women Without Bleeding	Risk Ratio (95% CI)
Care-seeking cohorts							
Peckham (1970)[16]	Patients with pregnancies who ended (loss or delivery) in the Kaiser Permanente Child Health and Development Studies (n = 6223)	Self-report of vaginal bleeding noted in clinic charts; divided women into those with bleeding ≤6 days and ≥7 days from loss or delivery	First, second, and third trimesters	19% of women had bleeding reported in their clinic charts; 15% of women had onset of bleeding ≥7 days from the end of pregnancy	14% of women with bleeding whose pregnancies ended ≥7 days after onset of bleeding had a loss	2% of women who did not have a record of bleeding experienced a loss	RR: 8.6 (6.6-11.2)
Everett (1997)[15]	Women with a positive pregnancy test at a general practice in England who continued their pregnancies (n = 550)	Self-report of vaginal bleeding recorded in practice notes or hospital discharge note	First, second, and third trimesters	21% of women had record of bleeding <20 weeks GA	56% of women with bleeding < 20 weeks GA had a loss (excludes stillbirth)	0.5% of women without bleeding had a loss (excludes stillbirth)	RR: 120 (30-484)
Makrydimas et al (2003)[14]	Women with a viable fetus on routine ultrasound scan at 6 to -10 at a university hospital in Greece (n = 668)	Self-report of bleeding recorded in hospital notes	First, second, and third trimesters	7% of women had bleeding recorded in hospital notes	17% of women with bleeding had a loss	7% of women without bleeding had a loss	RR: 2.6 (1.3-5.2)
Weiss et al (2004)[17]	Women with a viable pregnancy on ultrasound enrolled at 10 to 14 weeks GA in a trial for trisomy 21 screening in an unselected obstetric population (n = 16 506)	Self-report of no, light (spotting), heavy (similar to menses) bleeding in the 4 weeks prior to enrollment	First trimester	14% of women reported bleeding in 4 weeks prior to enrollment (13% light, 1% heavy)	1% of women with light bleeding and 2% of women with heavy bleeding had a loss <24 weeks GA	0.4% of women with no bleeding in 4 weeks prior to enrollment had loss < 24 weeks GA	Overall RR: 2.8 (1.7-4.4) Light vs no RR: 2.5 (1.5-4.1) Heavy vs no RR: 4.9 (2.0-12.2)
Community-based cohorts							
Harville et al (2003)[18]	Women in North Carolina enrolled in a preconception cohort and whose pregnancies lasted > 6 weeks GA (n = 151)	Self-report of any vaginal bleeding and number of tampons or pads used; excluded bleeding associated with expulsion of fetus (not defined)	First trimester (≤8 weeks GA)	9% of women with pregnancies ≥6 weeks GA reported bleeding ≤8 weeks GA	14% of women with bleeding ≤8 weeks GA had a loss	9% of women without bleeding ≤8 weeks GA had a loss	RR: 1.5 (0.4-6.0)
Hasan et al (2009)[19]	Women recruited in early pregnancy (<12 weeks GA) or prior to pregnancy in 3 Southern cities in the United States; enrolled after positive pregnancy test (n = 4510)	Self-report of all episodes of bleeding in first trimester including number of episodes, date of onset, duration, heaviness, color was reported at end of first trimester; excluded bleeding within 4 days of loss; self-report of pain as mild, moderate, or severe; allowed for reporting after loss	First trimester	27% of women reported first trimester bleeding; 8% of women with bleeding reported heavy (≥heaviest day of menses) episodes	11% of women with any bleeding had a loss. 24% of women with heavy bleeding had a loss. 8% of women with heavy first trimester bleeding had second trimester loss	12% of women without first trimester bleeding had a loss. 1% of women without first trimester bleeding had a second trimester loss	Any vs no RR: 0.9 (0.8-1.1) Heavy vs no RR: 2.0 (1.4-3.0) Heavy/pain vs none RR 3.1 (2.1-4.5)

Abbreviations: GA, gestational age; CI, confidence intervals; RR, risk ratio.

Table 3. Cumulative Incidence of Nausea and Vomiting in Pregnancy (NVP) and Associations With Pregnancy Loss.

First Author (Year)	Sampling Frame (n)	Assessment of NVP	GA at NVP Assessment	Cumulative Incidence of NVP	Cumulative Incidence of Loss in Women With NVP	Cumulative Incidence of Loss in Women Without NVP	Risk Ratio (95% CI)
Care-seeking cohorts							
Speert and Guttmacher (1954)[24]	Private patients in New York City (n = 256)	Self-report of NVP	First trimester	65% of women reported NVP	5% of women with NVP had a first trimester loss	26% of women without NVP had a first trimester loss	NVP RR: 0.2 (0.1-0.4)
Medalie (1957)[23]	Patients in a general practice in rural Israel (n = 100)	Self-report of NVP; moderate NVP was extreme nausea throughout the day or vomiting ≥2/d; severe NVP was vomiting almost every time food was eaten	First trimester	71% of women had NVP; 52% had moderate/severe NVP	0% of women with moderate/severe NVP had a first trimester loss	23% of women with mild/no NVP had a first trimester loss	Cannot calculate
Brandes (1967)[20]	Patients with singleton pregnancies receiving prenatal care in Kaiser Permanente and participating in a study (n = 7027)	Self-report of NVP	First trimester	73% of women had NVP	5% of women with NVP experienced a loss	9% of women without NVP experienced a loss	NVP RR: 0.6 (0.5-0.7)
Kullander and Kallen (1976)[22]	Pregnant women in Malmo, Sweden between 1963 and 1965 with known pregnancy outcome of loss or live birth without congenital anomalies (n = 5377)	Self-report of NVP by questionnaire	First, second, and third trimesters	72% of women with loss or live birth without congenital anomalies reported NVP	5% of women with NVP had a loss	14% of women without NVP had a loss	NVP RR: 0.4 (0.3-0.4)
Klebanoff et al (1985)[21]	Women registered in the National Collaborative Perinatal Project <14 weeks GA with ongoing pregnancy at 14 weeks GA (n = 9098)	Query of vomiting at each obstetric visit	First trimester	52% of women had vomiting by 16 weeks GA	3% of women with vomiting had a loss	5% of women without vomiting had a loss	Vomiting RR: 0.6 (0.5-0.8)
Tierson et al (1986)[25]	Predominately white, upper-class women attending private practice in Albany, New York who had ongoing pregnancy at 12 weeks GA (n = 414).	Self-report of NVP at interview at 12 weeks GA and then every 2 weeks until 20 weeks GA.	First and second trimester (<20 weeks GA)	89% of women reported NVP by 20 weeks GA; 56% reported vomiting.	7% of women with any NVP had a loss; 10% of women with nausea only had loss; 5% of women with vomiting had a loss.	20% of women without NVP had a loss	NVP RR: 0.5 (0.2-0.9) Nausea only RR: 0.5 (0.2-1.1) Vomiting RR: 0.3 (0.1-0.6)

(continued)

Table 3. (continued)

First Author (Year)	Sampling Frame (n)	Assessment of NVP	GA at NVP Assessment	Cumulative Incidence of NVP	Cumulative Incidence of Loss in Women With NVP	Cumulative Incidence of Loss in Women Without NVP	Risk Ratio (95% CI)
Weigel and Weigel (1989)[27]	Women delivering babies at UCLA Medical Center ≥21 weeks GA or miscarriage <21 weeks GA treated at UCLA with >1 prenatal visit <21 weeks GA (n = 903)	Self-report of NVP recorded in the medical chart.	First and second trimesters	69% of women had NVP <21 weeks GA; 23% had nausea only; 46% had vomiting and nausea	2% of women with NVP recorded in medical charts had a loss; 4% of women with nausea only had a loss; 1% of women with vomiting had a loss	7% of women without NVP recorded in medical charts had a loss	NVP RR: 0.3 (0.1-0.5) Nausea only RR: 0.5 (0.2-1.2) Vomiting RR: 0.1 (0.1-0.4)
Weigel et al (2006)[26]	Women in first trimester of pregnancy receiving prenatal care at a public hospital in Quito, Ecuador (n = 849)	Self-report of NVP at interviews in first and second trimester, categorized as nausea only and nausea and vomiting	First and second trimesters	77% of women reported NVP by 20 weeks GA; 21% had nausea only; 56% had nausea and vomiting	3% of women with NVP had a loss; 4% of women with nausea only had loss; 2% of women with vomiting had a loss	7% of women without NVP had a loss.	NVP RR: 0.4 (0.3-0.9) Nausea only RR: 0.7 (0.3-1.6) Vomiting RR: 0.3 (0.2-0.8)
Weng et al (2008)[28]	Women with a positive pregnancy test at Kaiser Permanente in San Francisco (n = 1063)	Self-report of NVP prior to interview; allowed for reporting after loss	Early first trimester (median 10 weeks GA)	78% of women reported NVP and 40% of women reported vomiting prior to interview	11% of women with NVP had a loss	35% of women without NVP had a loss	NVP RR: 0.3 (0.2-0.4)
Community-based cohorts							
Wen et al (2001)[29]	Women in a preconception population-based cohort in Twin Cities, Minnesota with data on nausea (n = 585)	Monthly self-report of nausea including duration in days; allowed for reporting after loss	First trimester	88% of women reported nausea in first trimester	7% of women with nausea in the first trimester had a loss	30% of women without nausea in the first trimester had a loss	NVP RR: 0.2 (0.2-0.4)
Chan et al (2010)[30]	Women recruited in early pregnancy (<12 weeks GA) or prior to pregnancy in 3 Southern cities in the United States; enrolled after positive pregnancy test (n = 2407)	Self-report of onset and cessation of NVP reported at enrollment (<16 weeks GA) and at follow-up at 20 to 25 weeks GA; allowed for reporting after loss	First and second trimesters	89% of women reported NVP in first or second trimesters; 53% reported vomiting	Not reported	Not reported	No NVP vs vomiting RR: 5.7 (4.0-8.0) Nausea only vs vomiting RR: 2.4 (1.8-3.3)

Abbreviations: GA, gestational age; CI, confidence intervals; RR, risk ratio.

vomiting separately, ranging from 46% to 56%.[21,25-27] The cumulative incidence of loss is consistently lower among women with vomiting (range 1%-5%) than among women with nausea alone (range 4%-10%). The RRs for vomiting compared with no NVP ranged from 0.1 to 0.6, whereas the RRs for nausea alone compared with no NVP ranged from 0.5 to 0.7.

Community-based cohorts. Two prospective studies on NVP and its associations with pregnancy loss among cohorts of women recruited from communities in the United States were included (Table 3). In a preconception study of 585 pregnancies using monthly reporting of nausea and allowing for reporting after a loss, 88% of women reported first-trimester nausea.[29] Seven percentof women with nausea had a loss compared with 30% in women without first-trimester nausea. In a pregnancy cohort of 2407 pregnancies with first-trimester recruitment, 89% reported NVP in first or second trimesters and 53% reported vomiting. Odds of loss were greater in women without NVP compared to any NVP and in women with nausea only compared to vomiting.[30]

Nausea and/or Vomiting of Pregnancy in Setting of Vaginal Bleeding and Associations With Pregnancy Loss

Early evidence from clinical reports in the 1950s suggested some combinations of signs and symptoms may portend pregnancy loss. Speert and Guttmacher[24] noted that among 31 private patients with a first-trimester loss, three-quarters had no NVP whereas among 225 women who did not experience loss, including 49 who reported bleeding, 70% reported some NVP. They concluded that heavier, darker bleeding accompanied by lower abdominal cramping in the absence of nausea likely signaled impending loss. Medalie[23] also noted the protective association of NVP against loss in the setting of bleeding among patients in his private practice (Table 4). More recently, among a series of women presenting for threatened abortion between 5 and 10 weeks gestation who were followed through 16 weeks gestational age, women who reported nausea during pregnancy were less likely to experience loss than women without nausea.[31]

Discussion

Main Findings

Data from prospective studies, mostly conducted among care-seeking populations recruited during pregnancy, suggest that vaginal bleeding is associated with increased risk of pregnancy loss, while nausea and vomiting are inversely associated with pregnancy loss. However, there are several potential biases inherent in care-seeking pregnancy cohort studies. Namely, length-biased sampling (selective inclusion of pregnancy losses occurring later in gestation by enrolling women into studies at later gestational ages, see ''Limitations of existing literature on signs and symptoms of pregnancy loss'' section), recall bias (reporting of signs and symptoms after a loss), and underascertainment of signs and symptoms (signs and symptoms not completely captured in medical charts) may affect the validity of these results. Furthermore, the detail of reporting across studies varied greatly, with only 1 study collecting daily data on bleeding.[19] Unstructured reporting (eg, unprompted reporting to clinicians) or reporting over long periods (eg, monthly) may also introduce reporting error, which decreases the precision of the estimates. Caution is particularly warranted in generalizing findings to losses occurring prior to care entry, which constitute the majority of losses.[2,32] Despite the biases inherent in these studies, the observed associations are biologically plausible.

Physiology of Bleeding in Relation to Pregnancy Loss

Bleeding may be a cause and/or consequence of pregnancy loss. Women who experience either a complete or an incomplete abortion must also experience vaginal bleeding by clinical definition.[33] In these cases, bleeding is a consequence of a loss, as this bleeding occurs concurrently with the expulsion of the products of conception from the uterus. Not all women, however, experience bleeding prior to recognition of the pregnancy loss. This is the case in women experiencing a missed abortion. Mechanisms have been proposed to explain bleeding as a cause of pregnancy. Johns and colleagues[34] have suggested that bleeding early in pregnancy causes increased oxygenation of the embryonic environment, which interferes with embryonic and placental development resulting in pregnancy loss. Subchorionic bleeding, which is bleeding between the uterine wall and the chorion detected by ultrasonography,[35] is believed to be one pathway by which the oxygen-rich maternal blood supply prematurely perfuses the intervillous space.[34] Chronic inflammatory processes associated with subchorionic bleeding/hematoma may also lead to myometrial contractions and expulsion of the gestational sac.[34]

Physiology of Nausea and Vomiting in Relation to Pregnancy Loss

Two hypotheses promote NVP as the cause of healthy pregnancies: the ''maternal–embryo protection hypothesis''[36-38] and the ''growth-generating hypothesis.''[39] Under the maternal–embryo protection hypothesis, NVP functions to reduce the consumption of potentially harmful foods (eg, plants with phytotoxins or meats contaminated with parasites or pathogens) during the period of organogenesis to prevent congenital malformations or pregnancy loss.[40] Indeed, women report aversions to meat, alcohol, and caffeine during early pregnancy with an increased preference for carbohydrate-rich foods.[40] Under the growth-generating hypothesis, caloric energy restriction secondary to NVP in the first trimester stimulates placental growth, which is necessary to successfully maintain pregnancy.[39]

An alternative hypothesis suggests that NVP can be a consequence of an already well-developing pregnancy.[41,42] Higher human chorionic gonadotropin (hCG) levels, which are

Table 4. Cumulative Incidence of Nausea and Vomiting in Setting of Vaginal Bleeding and Associations With Pregnancy Loss.

First Author (Year)	Sampling Frame, Assessment of Bleeding, and Study Size (n)	Assessment of Bleeding and NVP	GA at Assessment	Cumulative Incidence of NVP Among Women With Bleeding	Cumulative Incidence of Loss in Women With Bleeding and NVP	Cumulative Incidence of Loss in Women With Bleeding and Without NVP	Risk Ratio (95% CI)
Care-seeking cohorts							
Medalie (1957)[23]	Patients in a general practice in rural Israel with threatened abortion (n = 23).	Self-report of NVP; moderate NVP was extreme nausea throughout the day or vomiting ≥2/d; severe NVP was vomiting almost every time food was eaten.	First trimester	4% of women with bleeding reported moderate/severe NVP.	0%; only 1 woman reported severe/moderate NVP in setting of bleeding; she did not have a loss.	50% of women with bleeding and with no/mild NVP had a loss.	Cannot calculate.
Kouk et al (2013)[31]	Patients with bleeding in 5 to 10 weeks gestation presenting to university hospital in Singapore were followed until 16 weeks gestation for loss (n = 139).	Self-report of nausea prior to presentation for evaluation.	First trimester	41% of women with bleeding reported history of nausea.	~12% of women with both bleeding and nausea had a loss.	~38% of women with bleeding but without nausea had a loss.	RR: 0.3 (0.1-0.6)

Abbreviations: GA, gestational age; CI, confidence intervals; RR, risk ratio.

associated with ongoing pregnancy, are also associated with NVP.[43-45] Nausea and/or vomiting of pregnancy may also serve as a proxy for higher progesterone levels,[46] which are necessary to maintain a successful pregnancy,[47] or it may serve as a marker for length of gestation, which is itself associated with viability of the pregnancy. The NVP peaks late in the first trimester when most pregnancy losses have already occurred. Thus, pregnancies ending in early losses have less time at risk of NVP and their time at risk occurs when NVP is less prevalent. This differential time at risk of NVP may explain the association between absence of NVP and loss.

Limitations of Existing Literature on Signs and Symptoms of Pregnancy Loss

Although data from these studies were collected prior to delivery, many of the pregnancy losses occurring early in gestation were either not captured at all or data on signs and symptoms were ascertained after the loss was recognized. Therefore, data from these pregnancy cohorts must be interpreted with caution, as the incidence of signs and symptoms likely does not include early losses in either the numerator (number of losses) or the denominator (number of pregnancies). Of note, while we only included studies that attempted prospective ascertainment of signs and symptoms to limit recall bias, prospective refers to timing of data collection relative to the *ascertainment* of the pregnancy loss. The day of loss is often unknown, and thus, data on signs and symptoms may be collected after the loss of the pregnancy but prior to loss recognition.

As healthier pregnancies tend toward longer gestations than unhealthy pregnancies, pregnancy cohorts capture more healthy pregnancies and fewer unhealthy pregnancies than the underlying source population of all pregnancies, resulting in length-biased sampling. The pregnancies observed in typical pregnancy cohorts are less likely to end in a loss and possibly more likely to have signs and symptoms of pregnancy such as nausea and vomiting simply because of the gestational age at which signs and symptoms are ascertained. Results from these studies may not be relevant for earlier losses as the relationship between signs and symptoms and loss may change across gestation. Additionally, data from care-seeking cohorts should be interpreted with caution as the extent to which bleeding and/or NVP were captured depends upon (1) gestational age at care seeking, (2) women reporting signs and symptoms to clinicians, and (3) clinicians recording the reports in medical charts.

While over 17 000 records were screened, only 18 studies were included in this review, highlighting the dearth of information on this topic. Given the laborious nature of this screening process, it was undertaken by a single investigator rather than in duplicate, which is a limitation of the review itself. However, the data gaps identified within this review and the directions for future investigations described subsequently have been thoughtfully considered by all investigators on this article and should prove useful for other investigators across disciplines.

Future Directions for Research

To determine whether the associations between signs and symptoms and pregnancy loss observed in pregnancy cohort studies included in this review are replicated among preconception cohorts, which capture the earliest losses prior to clinical care entry, more preconception studies are needed. However, given the expense of conducting preconception cohort studies, existing data, such as that collected at the daily level by mobile applications designed to track signs and symptoms associated with the menstrual cycle and pregnancy, may be leveraged. These data sources also offer an opportunity to examine more signs and symptoms than those reported in this review, for example, lower abdominal cramping, breast tenderness, smell and taste aversions, fatigue, and the opportunity to examine patterning of multiple signs and symptoms in relation to loss.

Future studies should also evaluate whether the associations between signs and symptoms and loss observed in these populations of spontaneous achieved pregnancies are similar in pregnancies achieved through assisted reproductive technologies. For women receiving fertility treatment, signs and symptoms and/or risk of loss may be influenced by underlying fertility problems and/or by receipt of exogenous hormones for infertility treatment. Pregnancies achieved through assisted reproductive technologies also offer unique opportunities to examine biomarkers and possible biological mechanisms that underlie the signs and symptoms of pregnancy loss. For example, the quality of embryos can be assessed in relation to the appearance of signs and symptoms and their relationships with pregnancy loss.

Other comparison groups may also provide fruitful directions for future research. While identifying the causes of pregnancy loss is often difficult, particularly for the earliest pregnancy losses occurring before clinical confirmation, evaluating signs and symptoms by cause (eg, uterine anomalies, chromosomal abnormalities, and hormonal imbalances) may facilitate greater understanding of the biological basis underlying signs and symptoms of loss. Comparing signs and symptoms among women with recurrent pregnancy loss to women with intermittent loss could also help to identify similarities or differences in signs and symptoms by loss etiology, if it can be determined. Finally, examining signs and symptoms across multiple pregnancies within a woman (ie, case–crossover study design) could be used to determine whether signs and symptoms repeat or not across pregnancies and pregnancy outcomes and whether signs and symptoms correspond with a woman's underlying hormonal profile or physiology.

Future work is also needed by clinical and basic scientists to increase our understanding of the physiologic processes underlying (mal)adaption to pregnancy. Using ultrasound, uterine contractility can be observed and correlated with hormonal profiles and other uterine features (eg, presence of subchorionic hematoma, uterine fibroids) to better understand the relationships among bleeding, lower abdominal cramping, and pregnancy loss. Future studies may also assess quantitative values of serum and urinary hCG, as well as serum and urinary levels

of progesterone, estrogen, and their metabolites, over the course of early pregnancy in relation to the appearance of signs and symptoms and their relationships with pregnancy loss. These studies could support or refute the theories that high progesterone and hCG levels are associated with vomiting, providing new insights into the hormonal basis of the symptomatology of early pregnancy and pregnancy loss.

Conclusion

Existing data provide some insights into the relationship between individual signs and symptoms and pregnancy loss among care-seeking populations with gestations that are well into the first trimester. These findings include increased risk of pregnancy loss with vaginal bleeding and decreased risk of pregnancy loss with nausea/vomiting. However, notable data gaps exist. First, data are needed on early first-trimester pregnancy losses, particularly those that would not normally reach clinical care but which comprise a large proportion of pregnancy losses. These losses may be of particular interest to reproductive endocrinologists, and couples undergoing infertility treatment as well as to the general population of couples attempting pregnancy. Second, data on multiple signs and symptoms captured simultaneously are needed to establish temporal patterns of signs and symptoms (eg, bleeding followed by vomiting vs vomiting followed by bleeding) that may be concerning or reassuring for subsequent pregnancy loss; these data will also allow for empirical testing to determine whether signs and symptoms of loss vary across gestation. To address these gaps, preconception cohorts or big data sources with detailed, prospectively collected data on multiple signs and symptoms and accurate measures of gestational age are needed. Third, studies conducted among pregnancies conceived via assisted reproductive technologies, which comprise an increasingly larger proportion of pregnancies, are needed as their underlying infertility or infertility treatments may have different symptom and loss profiles. Finally, more basic science research is needed to illuminate the hormonal and physiologic adaptions to early pregnancy and their relationships with symptomatology and pregnancy loss.

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