

Review

# A Narrative Review: Maternal Comorbidities and Amniocentesis-Related Complications

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## Abstract

**Objective:** To evaluate whether common maternal conditions—such as vaginitis, infection, gestational diabetes mellitus (GDM), hypertensive disorders, hepatitis B virus (HBV) infection, Rh-negative pregnancy, and the use of low-molecular-weight heparin (LMWH)—influence the safety or outcomes of amniocentesis, and to provide practical recommendations to optimize maternal and fetal safety.

**Mechanism:** Amniocentesis is the most widely used invasive prenatal diagnostic procedure worldwide. It involves inserting via a trans-abdominal approach to obtain fetal samples, including cells, metabolites, urine, or secretions, from the amniotic fluid. Complications include premature rupture of membranes (PROM), infection, spontaneous miscarriage, and pregnancy loss, although their overall incidence is <1%. Although most studies have focused on procedure-related risks for pregnancy outcomes, the impact of maternal conditions on these outcomes has been less systematically evaluated. **Findings in Brief:** This review found no solid evidence that maternal vaginitis, infection, GDM, hypertensive disorders, or HBV infection increase the risk of adverse outcomes following amniocentesis. Similarly, available data suggest that the use of LMWH does not significantly increase the risk of bleeding when appropriately. **Conclusions:** Amniocentesis can generally be performed safely when maternal disorders are in a relatively stable phase. For Rh-negative women, anti-D immunoglobulin should be administered prior to invasive testing to reduce the risk of alloimmunization. For pregnant women receiving prophylactic LMWH, discontinuation 24 hours before the procedure is recommended; while routine anti-Xa monitoring is not required except in cases of severe renal insufficiency. Although based on limited evidence, these recommendations aim to minimize procedure-related complications and optimize maternal and fetal safety.

**Keywords:** amniocentesis; prenatal diagnosis; maternal disorders; pregnancy complications

## 1. Introduction

Amniocentesis was first used to treat polyhydramnios in the 1880s, and later to introduce drugs into the amniotic sac for pregnancy termination [1]. Since the 1960s, amniocentesis has been a commonly used invasive procedure to obtain amniotic fluid for the analysis of fetal genetic abnormalities or metabolic disorders [2]. It is normally performed during the second trimester, during which there is sufficient amniotic fluid and a maximal ratio of viable cells to nonviable cells [3,4]. The primary concern arising from amniocentesis is pregnancy loss, which may be associated with the procedure itself, fetal genetic defects, or maternal health conditions. The risk of procedure-related fetal loss ranges from 0.36% to 1% after correction for the background rate of loss [5–8]. However, the impact of maternal health conditions such as vaginitis, infection, gestational diabetes mellitus (GDM), hypertensive disorders, hepatitis B, Rh-negative blood type, and heparin use on miscarriage following amniocentesis has not been systematically studied. In this paper, we review the risk of amniocentesis-

associated complications related to these maternal health conditions.

## 2. Methods

### Literature Search and Study Selection

We searched PubMed, Embase, and Cochrane Library for all relevant peer-reviewed articles, reviews, case reports, meta-analyses and guidelines, with no language restrictions or time limitations. The search terms used as keywords were: ‘Amniocentesis’, ‘Pregnancy’, ‘Vaginal Microbiota’, ‘Vaginal infection’, ‘Intra-amniotic infection/inflammation’, ‘Gestational Diabetes Mellitus’, ‘Hypertensive Disorders’, ‘Hepatitis B Virus Infection’, ‘Rh-Negative Pregnancy’, ‘Thrombosis’, and ‘low molecular weight heparin’. All of the included studies were read in full-text form to identify the relevant information for our study.



### 3. Literature Review

#### 3.1 Vaginal Microbiota and Infection Risk

##### 3.1.1 Composition and Protective Role

The vaginal microbiota is a complex ecosystem composed predominantly of *Lactobacillus* species, which coexist with various anaerobic bacteria [9,10]. *Lactobacillus* plays a crucial role by modulating local immune responses to infection and suppressing inflammation [11,12].

##### 3.1.2 Vaginal Dysbiosis and Intra-Amniotic Infection

Vaginal dysbiosis refers to an imbalance in the microbial community, characterized by a decline in *Lactobacillus* and an overgrowth of organisms such as *Gardnerella*, *Prevotella*, *Porphyromonas*, *Bacteroides*, *Peptostreptococcus*, *Megasphaera*, and *Sneathia*. This condition often presents as vaginitis and is associated with an increased risk of intra-amniotic infection and postpartum infectious morbidity during pregnancy [13]. Cobo *et al.* [14] demonstrated that lower levels of *Lactobacillus* spp. correlated with higher interleukin-6 concentrations in amniotic fluid, indicating a greater level of intra-amniotic inflammation, which is also associated with earlier gestational age at delivery.

##### 3.1.3 Microbial Ascension

Romero *et al.* [15] analyzed amniotic fluid and vaginal samples from eight women with intra-amniotic infection using 16S rRNA gene sequencing. The results showed that 75% (6/8) of infections were caused by typical vaginal microbiota, and 62.5% (5/8) of women with bacteria in their amniotic fluid had the same bacteria present vaginally. This suggests that microbial ascension from the vagina is a primary route of intra-amniotic infection.

##### 3.1.4 Impact of Amniocentesis on Barrier Function

Chorioamniotic membranes serve as a physical barrier against pathogens and are capable of producing antimicrobial peptides and hosting immune cells [16,17]. Amniocentesis may compromise membrane integrity, leading to amniotic fluid leakage in approximately 1% of cases, typically within one week post-procedure [18].

Bacterial ascension into the amniotic cavity can occur if the membrane ruptures, as seen by the high incidence of intra-amniotic infection in patients with preterm premature rupture of membranes (PROM) [19]. The prevalence of intra-amniotic infection is higher in women with preterm PROM compared to those with intact membranes [20], and earlier occurrence of PROM is associated with a more pronounced inflammatory response [21]. Conversely, intra-amniotic infection/inflammation is itself an independent risk factor for PROM [22]. A 7-year cohort study of 250,566 pregnant women found the incidence of intra-amniotic infection following amniocentesis was as low as 0.05% [23]. However, further large-scale studies are necessary for more robust evidence.

While vaginitis may increase the risk of ascending intra-amniotic infections, amniocentesis itself may also compromise membrane integrity, leading to the risk of infection. At present, the added risk of intra-amniotic infection following amniocentesis in women with vaginitis remains unclear. Examination of vaginal discharge is recommended for pregnant women with suspected vaginitis symptoms, such as itching and abnormal discharge. For those with positive findings, it is recommended that whenever possible, amniocentesis should be delayed until after treatment. If the procedure must be performed immediately, patients should be fully informed of the potential risks of intra-amniotic infection.

#### 3.2 Infection Risk and Amniocentesis Safety

##### 3.2.1 White Blood Cell Count and Infection Diagnosis

Severe infections can pose significant risks to both mother and fetus, potentially complicating the safety of amniocentesis. Many healthcare organizations require a normal blood test within one week prior to the procedure. The normal white blood cell (WBC) count in pregnant women ranges from 5000 to 12,000 per microliter ( $5.0\text{--}12.0 \times 10^9/\text{L}$ ), sometimes reaching 15,000 per microliter. Elevated WBC counts and a left shift are commonly observed in bacterial infections [24]. The key question is whether elevated WBC levels or the presence of systemic infection increase the risk of complications following amniocentesis.

##### 3.2.2 Limitations of Peripheral Blood Tests

Diagnosing intrauterine infection prior to amniocentesis can be challenging because many women who experience preterm labor and are later diagnosed with chorioamnionitis do not exhibit typical symptoms (e.g., fever, abdominal pain, peripheral leukocytosis, fetal tachycardia). Peripheral WBC counts are slightly higher in patients with preterm PROM and intra-amniotic inflammation than in those without infection. However, no significant difference was observed between the two groups, suggesting that WBC count is not a reliable indicator of infection [25]. Tarim *et al.* [26] reported that neither the WBC count nor C-reactive protein levels in the amniotic fluid were associated with preterm delivery following amniocentesis when compared to term deliveries. Therefore, intrauterine infection cannot be excluded based solely on normal blood test results. Nonetheless, significant abnormalities detected during pre-amniocentesis screening should prompt a thorough investigation for potential systemic or localized infections before going ahead with the procedure.

#### 3.3 Gestational Diabetes Mellitus and Amniocentesis

##### 3.3.1 Maternal and Fetal Risks Associated With GDM

GDM is a condition where hormones produced by the placenta impair the body's ability to use insulin effectively. This leads to accumulation of glucose in the blood, rather than being absorbed by cells. Women with GDM have a

greater risk of spontaneous miscarriage, hypertension, and infection, while the fetus is more likely to develop macrosomia and congenital malformation [27,28]. A large cohort study of 6597 women with GDM and 51,981 controls found a significantly higher prevalence of congenital anomalies, particularly chromosomal abnormalities, in GDM-exposed pregnancies (adjusted Odds Ratio = 1.93, 95% CI: 1.25–2.99,  $p = 0.003$ ) [29].

### 3.3.2 Safety of Amniocentesis in Women With GDM

A critical question is whether the risk of amniocentesis is greater in women with GDM. The safety and patient acceptance of amniotic fluid insulin measurements were evaluated in 194 women with GDM who underwent third-trimester amniocentesis, along with 268 control subjects. This found no increase in procedure-related risks such as PROM, preterm birth, infection, or procedure-related pain, suggesting that amniocentesis is safe and acceptable in women with GDM [30]. A case-control study of 167 women who underwent third-trimester amniocentesis, half of whom had GDM, also found no additional risk of adverse pregnancy outcomes due to the procedure [31]. Furthermore, a large retrospective cohort study of singleton pregnancies that underwent invasive prenatal diagnostic procedures (amniocentesis or chorionic villus sampling [CVS]) found that GDM did not increase the risk of miscarriage with either procedure [7]. Based on these studies, we conclude that amniocentesis is relatively safe for pregnant women with GDM.

### 3.3.3 Current Knowledge Gaps

Nevertheless, the studies referenced above have several limitations. They did not specify the blood glucose levels of the participants or whether their diabetes was well controlled. Without this information, it remains unclear whether poorly controlled blood glucose levels have any impact on the safety of amniocentesis. Further research is needed to better understand the potential risks posed by high blood glucose in women with GDM undergoing amniocentesis.

## 3.4 Hypertensive Disorders in Pregnancy and Amniocentesis

### 3.4.1 Maternal Hypertension and Pregnancy Risks

Hypertension in pregnancy affects about 10% of women, including those with chronic hypertension (diagnosed before or early in pregnancy, i.e., <20 weeks of gestation) and those with pregnancy-related hypertension (gestational hypertension and pre-eclampsia) [32]. Hypertension increases the risk of preterm delivery, fetal growth restriction, perinatal death, and long-term maternal cardiovascular disorders [33].

### 3.4.2 Controversy Regarding CVS and Hypertensive Disorders in Pregnancy

Some studies have suggested that CVS performed in early pregnancy (10–13 weeks) may impair placental formation and increase the risk of hypertensive disorders later in pregnancy [34,35]. However, other studies have not found this association, and the evidence remains controversial [36,37].

### 3.4.3 Amniocentesis Safety and Procedure-Related Risks in Hypertension

A large retrospective study involving 3243 women who underwent CVS and 6875 women who underwent amniocentesis found a significantly higher incidence of hypertensive disorders in the CVS group (3.8%) compared with the amniocentesis group (1.7%). However, both rates were within the normal range of <6%, suggesting that both CVS and amniocentesis are unlikely to increase the risk of hypertensive disorders [38]. In a larger cohort comprising 21,748 cases of amniocentesis and 1984 cases of CVS, no increase in any type of gestational hypertension, mild pre-eclampsia, or severe pre-eclampsia was observed compared with 7854 non-exposed women [36]. A case-control study analyzing the risk of preterm delivery found an odds ratio (OR) of 1.59 for amniocentesis compared to 4.26 for hypertension, although it did not investigate whether hypertension increased the preterm delivery risk in amniocentesis cases [39]. Maternal hypertension can affect amniocentesis in several ways. One early study reported that maternal hypertension (prior to conception) increased the incidence of spontaneous fetal loss after amniocentesis, with a loss rate of 11.1% (3/27) in the hypertension group versus 2.6% (50/1888) in the non-hypertension group [40].

## 3.5 Hepatitis B Virus Infection and Vertical Transmission

### 3.5.1 Risk of HBV Transmission During Amniocentesis

For women carrying hepatitis B virus (HBV), one of the principal concerns with amniocentesis is the possibility of vertical transmission (VT) to the fetus. This procedure entails the insertion of a needle through the maternal abdomen into the amniotic sac, potentially exposing the fetus to maternal blood. To mitigate this risk, rigorous infection control measures must be implemented, including the use of antiviral medications for the mother, administration of immunoprophylaxis protocols to the newborn, and standardized amniocentesis techniques. In some communities, perinatal transmission and VT are the predominant modes of HBV infection [41].

### 3.5.2 Maternal Viral Load and Transmission Rates

The VT rate in HBsAg-positive women without immunoprophylaxis is approximately 70–90% [42]. A retrospective matched cohort study found that the VT rate was significantly higher in HBsAg-positive women who underwent amniocentesis compared to those without amniocen-

tesis (2.80% vs. 0.50%; relative risk [RR] = 5.64; 95% CI: 1.28–24.93) [43]. Moreover, a maternal HBV DNA level of  $\geq 7.0 \log_{10}$  IU/mL increased the transmission rate (10.81% vs. 0%,  $p = 0.004$ ). Another case-control study also found a higher HBV VT rate in infants following amniocentesis than in those without, although this did not reach significance (6.35% vs. 2.53%;  $p = 0.226$ ) [44]. These authors also observed that maternal HBV DNA levels of  $\geq 7.0 \log_{10}$  IU/mL were associated with a higher VT rate. Based on clinical findings, the Royal College of Obstetricians and Gynaecologists (RCOG) concluded that amniocentesis conducted on HBsAg+ mothers with HBV DNA  $\geq 7.0 \log_{10}$  IU/mL significantly increases the likelihood of VT [45]. RCOG recommends that HBsAg+ women who are planning to undergo amniocentesis should be evaluated for the risk of VT based on their HBV-DNA level.

### 3.5.3 Role of Immunoprophylaxis

Recent studies indicate that amniocentesis does not increase the risk of mother-to-child transmission of HBV in infants receiving standardized immunoprophylaxis, including those born to HBeAg-positive mothers or those with high viral loads [46]. However, the abnormal appearance of amniotic fluid (bloody or brown) during amniocentesis may indicate an elevated risk of HBV transmission [47]. Collectively, the current evidence indicates that amniocentesis does not increase the risk of VT of HBV when rigorous immunoprophylaxis protocols are followed, even in high-risk subgroups such as HBeAg-positive mothers or those with high viral loads. Nevertheless, careful vigilance is warranted in cases with abnormal amniotic fluid characteristics. Newborns should also receive standardized immunoprophylaxis regimens post-delivery.

## 3.6 Rh-Negative Pregnancy and Alloimmunisation Prevention

### 3.6.1 Guidelines for Anti-D Prophylaxis

Rh-negative women exposed to Rh-positive red blood cells may become sensitized and produce anti-D immunoglobulin antibodies, which can cross the placenta and cause hemolytic disease in the fetus and newborn [48]. According to the SOGC clinical practice guidelines for the prevention of Rh alloimmunization, the initial prenatal evaluation should include Rh typing and antibody screening. Routine anti-D immunoglobulin (300  $\mu\text{g}$ ) should be administered to all Rh-negative, non-sensitized women at 28 weeks of gestation if the fetal blood type is unknown or known to be Rh-positive. Alternatively, two doses of 100–120  $\mu\text{g}$  may be given, with one at 28 weeks and another at 34 weeks. Additionally, anti-D immunoglobulin (300  $\mu\text{g}$ ) must be administered within 72 hours of delivery to a postpartum, non-sensitized Rh-negative woman who has delivered an Rh-positive infant. Alternatively, anti-D immunoglobulin (120  $\mu\text{g}$ ) may be given within 72 hours of delivery, with subsequent testing for fetal-maternal hemor-

rhage (FMH). If FMH exceeds 6 mL of fetal red blood cells (equivalent to 12 mL of whole fetal blood), additional anti-D immunoglobulin is required [49]. The implementation of guidelines for antenatal and postnatal use of anti-D has significantly reduced the prevalence of Rhesus D alloimmunisation in pregnancy [50,51]. This prophylaxis addresses the risk of FMH, which occurs when fetal red blood cells enter the maternal circulation due to placental trophoblast disruption. Anti-D immunoglobulin is also indicated after pregnancy loss, invasive procedures, external cephalic version, abdominal trauma, or late pregnancy bleeding. For amniocentesis or cordocentesis, 300  $\mu\text{g}$  anti-D immunoglobulin should be administered, while for chorionic villus samplings (CVS), 120  $\mu\text{g}$  should be administered before 12 weeks, or 300  $\mu\text{g}$  at or after 12 weeks [52–54].

### 3.6.2 Risk of Alloimmunisation After Amniocentesis

What if no RhD prophylaxis is given after amniocentesis? No significant difference in sensitization rates was reported between patients receiving post-amniocentesis anti-D immunoglobulin prophylaxis and those not receiving prophylaxis [55]. Another study investigated 9353 women who did not undergo invasive procedures, and 189 who underwent amniocentesis. Among RhD-negative women carrying RhD-positive fetuses, the RhD immunization rate before gestational weeks 25–29 was found to be very low, even in those receiving prenatal invasive testing without rhesus prophylaxis [56]. However, other studies found that Rh-negative women undergoing amniocentesis exhibit higher sensitization rates, particularly before 28 weeks of gestation. Additionally, some immunized women show increased anti-D titers post-procedure [57], and elevated maternal anti-D levels are associated with more severe fetal anemia [58]. Amniocentesis might not induce the same risk of alloimmunisation, as the breach in the fetoplacental barrier and the amount of fetal blood entering the maternal circulation are likely to vary according to the length of the procedure, gestational age at the time of sampling, and whether the amniocentesis is transplacental [59]. If the fetal Rh blood type could be screened by noninvasive prenatal diagnosis, unnecessary administration of anti-D could be avoided for RhD-negative babies [60,61].

### 3.6.3 Clinical Implications

Although the evidence is limited, current recommendations advise that non-sensitized women should receive anti-D immunoglobulin before invasive procedures, whereas previously immunized women require careful risk-benefit evaluation before proceeding with such interventions. Furthermore, written informed consent is recommended for Rh Ig administration due to its status as a blood product [62].

### 3.7 Anticoagulation and Amniocentesis

#### 3.7.1 Pregnancy-Associated Thrombosis

Pregnant women are susceptible to thrombotic diseases due to hypercoagulability, elevated estrogen levels, and increased circulating blood volume, all of which slow blood flow [63]. Other genetic or acquired disorders such as genetic thrombophilia, antiphospholipid syndrome, obesity, and preeclampsia may also increase the risk of venous thromboembolism (VTE) during pregnancy [64,65].

#### 3.7.2 LMWH Use and Bleeding Risk

Anticoagulants are recommended for patients who are at high risk of VTE. Heparin, and especially low molecular weight heparin (LMWH), are the most prescribed [66–70]. LMWH inhibits coagulation by activating antithrombin III, which binds to and inhibits factor Xa. Compared to heparin, LMWHs have a longer half-life, which makes dosing more predictable and less frequent (often just once daily). One of the major risks for LMWH is bleeding. Intra-amniotic uterine wall bleeding was reported in 38% of patients with transabdominal amniocentesis, of which 92% stopped bleeding within 30 seconds [71]. It is unknown whether the use of LMWH before amniocentesis increases the bleeding risk. In patients who take anticoagulants such as heparin, the risk of bleeding or hematoma formation at the puncture site may be increased. For patients who have had a prophylactic dosing of LMWH, the total antepartum bleeding rate was 0.5%, which was no different from that of controls without LMWH use [72]. A similar result was obtained in another study that analyzed 1348 pregnancies and reported an antepartum bleeding rate of 0.42% [73]. However, there is no data concerning the bleeding risk after amniocentesis in patients receiving LMWH. One of the adverse outcomes for bleeding during amniocentesis is that maternal cells may be artificially introduced into the amniotic fluid sample, thereby leading to diagnostic errors [74]. Moreover, in cases of penetration during amniocentesis, bleeding in the placenta could gradually extend to form a hematoma and chronic abruption, resulting in fetal loss [75].

#### 3.7.3 Monitoring and Clinical Recommendations

To reduce the risk of bleeding, discontinuation of LMWH and coagulation monitoring should be considered prior to amniocentesis. There is currently insufficient data regarding the optimal time to discontinue LMWH before amniocentesis. Based on the anticoagulant activity of enoxaparin, the elimination half-life after a single subcutaneous dose is approximately 4.5 hours, extending to about 7 hours after repeat dosing [76]. By referencing studies on other types of percutaneous invasive procedures, the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe recommend discontinuing one prophylactic dose of enoxaparin and two therapeutic doses or 24 h before am-

niocentesis [77–79]. Although monitoring of anti-Xa has long been the gold standard for monitoring LMWH, the benefits remain controversial. A systematic review found only a weak correlation between anti-Xa levels and bleeding risk, and monitoring of anti-Xa did not help to reduce bleeding events [80,81]. Patients with severe renal insufficiency had an increased bleeding risk with therapeutic doses of enoxaparin, while their peak anti-Xa levels were significantly higher compared to patients with normal renal function [82]. The European Society of Cardiology (ESC) guidelines for pregnant women on LMWH recommended weekly monitoring of anti-Xa levels, or aPTT monitoring [83]. A systematic review and analysis of data from 33 studies concluded there was no need for anti-Xa monitoring when using LMWH as a thromboprophylaxis or treatment during pregnancy [84]. Overall, the use of LMWH before amniocentesis is relatively safe, but should be withheld for 24 h before the procedure. Anti-Xa monitoring is not necessary for pregnant women on LMWH, but should be considered for those with severe renal insufficiency.

## 4. Conclusions

Vaginitis may pose an increased risk for amniocentesis, as it is associated with ascending intra-amniotic infection that can lead to chorioamnionitis due to leakage or rupture of the amniotic membranes. Although normal blood counts do not rule out intrauterine infection, we still recommend performing appropriate tests before amniocentesis to rule out acute systemic infections or local infections of the lower genital tract. There is no conclusive evidence that GDM or hypertension increase the procedural risk. Moreover, maternal HBV infection does not increase the risk of fetal HBV transmission after amniocentesis. Non-sensitized women should receive anti-D immunoglobulin before amniocentesis, while sensitized women should undergo a careful risk-benefit assessment prior to the procedure. Finally, the use of LMWH before amniocentesis should be withheld for 24 h before the procedure, and routine anti-Xa monitoring is not necessary for pregnant women on LMWH, except for those with severe renal insufficiency.

## Author Contributions

HL searched the literature and drafted the manuscript; PW reviewed the literature and drafted the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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