Vasa previa and placenta associated complications
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CHAPTER 8

Summary and general discussion
SUMMARY

This thesis focused on vasa previa and pregnancy complications associated with abnormalities of the placenta. Vasa previa on ultrasound was first reported in 1987 and has received increasingly attention over the last decades. Since the incidence of vasa previa is relatively low, literature on this complication is mostly limited to case reports, case series and reviews. The majority of the studies emphasize the importance of prenatal diagnosis because of the potential fatal neonatal outcome in pregnancies complicated by vasa previa. In many countries including the Netherlands, clear guidelines regarding prenatal diagnosis for vasa previa were unavailable. Therefore, in the first part of this thesis we focused on vasa previa. We evaluated the diagnostic accuracy of ultrasound in the prenatal detection of vasa previa and we investigated the incidence of and identified potential risk indicators for vasa previa. As a final step we initiated the implementation of a national guideline regarding prenatal screening and management in vasa previa.

As vasa previa, other abnormalities of the placenta such as placenta previa, placental abruption and retained placenta also have been associated with adverse maternal and neonatal outcomes. Placenta previa is a condition commonly seen during pregnancy, but the clinical presentation varies between asymptomatic and substantial vaginal blood loss, impeding the efficacy of an uniform guideline. The second part of this thesis aimed to differentiate between high-risk and low-risk women with placenta previa, providing opportunities for individualized antenatal management. Furthermore, we investigated the consequences of placental abruption and retained placental tissue with or without postpartum hemorrhage on a subsequent pregnancy to increase individualized prenatal care.

In this final chapter we will summarize the main findings of our work and outline them within the context of the current literature. Furthermore we will provide implications for further clinical practice and research.

Prenatal diagnosis and management of vasa previa

In current clinical practice multiple sonographic scans are performed during pregnancy, including the second trimester anomalies scan. The possibility to detect vasa previa prenatally has been described in many studies before, though the diagnostic performance of ultrasound in the prenatal detection of vasa previa was unknown. In chapter two we performed a systematic review on the accuracy of ultrasound. We concluded that the accuracy of ultrasound is high, if performed transvaginally and combined with color Doppler. We found prenatal detection rates between 53% and 100%. The sensitivity was 100% and the specificity...
was between 99 and 100%. The diagnosis of vasa previa was best made between 18 and 26 weeks of gestation. An increase in missed cases was seen when scans were performed only trans abdominal and/or exclusively in the third trimester.

Based on the conclusions of publications regarding vasa previa, it appears to be a significant obstetric complication and several recommendations for the implementation of a screening program are made. Unfortunately, the majority of publications are case reports and case series limited by their level of evidence. To objectively estimate the significance of vasa previa, in chapter three we performed a systematic review and meta-analysis on the incidence of vasa previa. Furthermore we identified risk indicators for vasa previa. We found vasa previa to have a mean incidence of 0.60 per 1000 pregnancies or 1 in 1667 pregnancies. Risk indicators for vasa previa were placenta previa in the second trimester, velamentous cord insertion, conception by assisted reproductive technologies, placental morphological anomalies such as bilobed or succenturiate placenta and lower umbilical cord insertion at first trimester ultrasound.

In chapter four we combined our results on vasa previa found in the previous chapters. In addition, we searched the literature for evidence on the management of vasa previa. The combination of these resulted in a national guideline which will be implicated in clinical practice in the Netherlands and advises to actively search for vasa previa in the presence of risk indicators.

Placenta previa and the risk for emergency Cesarean delivery
The current state of the art in women with diagnosed with placenta previa by ultrasound in the second trimester is to perform a follow-up scan in the third trimester. In case of a persistent placenta previa, an elective Cesarean delivery is scheduled. Several recommendations for timing of delivery are available and mainly concentrate on the late preterm period. Because of prematurity, administration of antenatal corticosteroids is suggested. But some pregnancies with placenta previa remain uncomplicated and are in no need for premature delivery, therefore it is important to distinguish high from low risk women to minimize iatrogenic prematurity. In a national cohort described in chapter five we found a history of Cesarean section, increasing number of episodes of antepartum bleeding and need for blood transfusion as independent predictors for an emergency delivery. In this cohort 43% of the women delivered in an emergent setting at a mean gestational age of 35 weeks and 3 days, the majority of these women had one or more episodes of antenatal bleeding. On the contrary, elective Cesarean deliveries in this Dutch cohort were scheduled from 38 weeks of gestation and 57% of the women reached this date. This supports the potential reduction of iatrogenic preterm delivery in women with placenta previa, stratification thus remains very important.
Consequences for a subsequent pregnancy after placental abruption or retained placental tissue

It is long known that placental abruption is associated with neonatal mortality and morbidity. Several risk factors have been identified including a history of placental abruption although most studies on this subject included relatively small samples and are dated. In a large retrospective national cohort study in chapter six we found an incidence of placental abruption of 0.22% among 1,570,635 singleton pregnancies. The incidence was significantly higher in women with a hypertensive disorder compared to normotensive women. The risk of placental abruption in a subsequent pregnancy was 5.8% vs 0.06% for women with and without a history of placental abruption. We found the risk of recurrence to be associated with the gestational age of first placental abruption. Women with a placental abruption in the term period of their first pregnancy were more at risk of recurrence than women with an early preterm (<32weeks) or late preterm (32-37weeks) placental abruption in their first pregnancy compared to women without a history of placental abruption. Although hypertensive disorders increased the risk of placental abruption, no interaction was found on the recurrence rate.

In chapter seven we investigated the incidences of severe postpartum hemorrhage (>1000mL) and retained placental tissue in a cohort of 359,737 women. Retained placental tissue with and without severe postpartum hemorrhage occurred in 2.1% and 5.4% respectively in the first pregnancy. For women with a history of severe postpartum hemorrhage the risk in a subsequent pregnancy was significantly higher compared to women without a history of severe postpartum hemorrhage (18% vs. 3.9%). A history of retained placental tissue followed by severe postpartum hemorrhage increased the risk of recurrence even more compared to women with a history negative for these complications. We found that gestational age of the first delivery complicated by severe postpartum hemorrhage is associated with the rate of recurrence. Women with a history of severe postpartum hemorrhage after a term or late preterm delivery were at risk of recurrence compared to women without a history of severe postpartum hemorrhage. On the contrary, women with a history of an early preterm delivery before 32weeks did not have a significantly increased risk of recurrence of severe postpartum hemorrhage.
Chapter 8

GENERAL DISCUSSION

Conclusion, clinical implications and suggestions for future research

Since vasa previa complicates one in 1667 pregnancies, can be accurately diagnosed by ultrasound in pregnancy and can result in neonatal mortality we should aim to optimize prenatal management. The diagnosis of vasa previa should be made by experienced clinicians because either false negative and false positive diagnoses imply several neonatal and maternal consequences. A false negative diagnosis may result in rupture of membranes and one or more fetal vessels in a setting outside the hospital where immediate delivery by Cesarean section and sufficient resuscitation of the neonate cannot be realized. On the contrary, a false positive diagnosis creates uncertainty and stress among the future parents and moreover it results in iatrogenic preterm Cesarean delivery with respiratory problems in the neonate and maternal consequences for potential future pregnancies. Because of the potential serious consequences associated with vasa previa any suspicion of this complication during ultrasound legitimizes referral to experienced clinicians.

As the majority of vasa previa is preceded by one or more risk factors, we do not advise a screening strategy as part of routine midgestation scanning in the general population. The publication of Cipriano et al supports this by demonstrating that general screening for vasa previa is not cost-effective. In this thesis we suggest to exclude vasa previa in women with one or more risk indicators. Therefore, one should actively search for velamentous cord insertion, bilobed or succenturiate placenta and placenta previa at the midgestation scan and perform a transvaginal color Doppler in one of these situations as defined in chapter four.

For the Netherlands, implementation of a screening program involves additional demands on the prenatal care provided in and outside hospitals nowadays, including additional training in sonography. Current midgestation scanning should be augmented with color Doppler. Besides the acquirement of practical skills, there is a need to increase knowledge and awareness regarding vasa previa. Previous research found one third of questioned obstetricians not sufficiently expert to name at least one risk factor for vasa previa.

Besides the implementation of a screening program, we must contemplate the perinatal management in case of vasa previa. It is presumed that ruptured vasa previa almost certainly ends in perinatal death but the effectiveness of a Cesarean delivery to prevent hemorrhage of the fetal vessels is never investigated. Randomized clinical trials regarding the method of delivery are not possible due to the low incidence, but the extent of neonatal morbidity and mortality due to vasa previa can potentially be investigated by evaluation of all cases of perinatal death due to exsanguination and all neonates that required blood transfusion over a certain period of time.
Consensus based guidelines advise elective Cesarean delivery from 35 weeks of gestation. It is believed that the mild complications associated with prematurity outweigh the complications that could result from spontaneous rupture of membranes in women with vasa previa.

A decision analysis is available on the effectiveness of different timing strategies for delivery in vasa previa, varying gestational age and administration of corticosteroids. Since Cesarean delivery was performed for all individuals, strategies were based on differences in perinatal but not maternal outcomes. This decision analysis indicates that the preferred timing of delivery is 34 or 35 weeks of gestation under most circumstances. Under no circumstances a benefit was to be expected from delivery beyond 37 weeks of gestation. However, this study does not allow for obstetric history. Women with a previous preterm birth <34 weeks of gestation are at risk for recurrence of preterm birth and should potentially receive more intensive monitoring and earlier delivery in case of vasa previa than nulliparous women or women with a previous term delivery.

In addition to timing of delivery many questions remain unanswered. Should women with a prenatal diagnosis of vasa previa be admitted to the hospital prior to delivery and receive corticosteroids? Does hospital admittance reduce the rates of fetal exsanguination and fetal death in spontaneous rupture of membranes in case of vasa previa? An alternative could be to monitor cervical length (and additional fetal fibronectin test in case of shortening) in women with vasa previa in an outpatient setting. In a retrospective cohort study by Baulies et al women remained at home with instructions to attend to the clinic in case of vaginal bleeding or contractions, all neonates were born in a clinical good condition at a mean gestational age of 36 weeks.

Since prospective clinical trials are likely to be precluded, results from cohort studies and decision analyses might be the only way to answer the question on perinatal management in vasa previa. With the information available from these studies, we should strive to nationalize our guideline and increase awareness on the subject of vasa previa.

Clinical implications that can be made on the second part of this thesis can be summarized as follows. Women with a diagnosis of placenta previa in the second trimester should be followed up in the third trimester, as many cases of placenta previa resolve over time during pregnancy. How many of these placenta previas resolve over time is unknown; at this moment we are conducting a prospective cohort study in the Academic Medical Center to evaluate all placenta localizations from the second trimester of pregnancy. However, in case the placenta is no longer low lying in the third trimester, an additional transvaginal color Doppler should be performed to exclude vasa previa. In case of persistent placenta previa, perinatal management in women diagnosed with placenta previa should become more individualized. Women with asymptomatic placenta previa and absence of a
Cesarean delivery in their obstetric history can be monitored in an outpatient setting and scheduled for elective Cesarean delivery at 37 or 38 weeks of gestation.\textsuperscript{8, 9} Administration of corticosteroids can then be omitted. However, in case of contractions and/or (recurrent) vaginal bleeding women should be admitted to the hospital and scheduled for Cesarean delivery from 35-36 weeks of gestation after administration of corticosteroids, as the chance for emergency Cesarean delivery is significantly increased in these women.\textsuperscript{10}

For women with a history of placental abruption, the decision to conceive again arises several questions.\textsuperscript{5} Especially in the case of perinatal death, parents want to be reassured that this will not happen again. Although there are no interventions to prevent placental abruption, we must try to optimize the factors associated with placental abruption, for example by encouraging patients to quit any smoking and cocaine use. Furthermore we must strictly control hypertension in women trying to conceive or already pregnant. Since >50% of the recurrent placental abruptions occurred after 37 weeks of gestation, we would advise to plan an elective induction at this gestational age, nonetheless the neonatal outcome in the previous pregnancy.

In the Netherlands it is possible for pregnant women to deliver at home in case of a low risk pregnancy. Because women with a history of severe hemorrhage postpartum are at increased risk of recurrence, they have an indication to deliver in the hospital in a subsequent pregnancy. Although we found that women with severe postpartum hemorrhage after an early preterm delivery <32 weeks of gestation are not at increased risk of recurrence in a future pregnancy, this will probably not change antepartum management. Women with a previous preterm delivery <32 weeks of gestation will already be referred for hospital outpatient management because the increased risk of recurrence of premature delivery. The discussion on management in women with a history of postpartum hemorrhage continues and is limited by lack of definition and uniformity in research. Though our research on this subject uses the advised cut-off of 1000mL blood loss, information on shock, blood transfusion, hysterectomy, oliguria and coagulopathy are more informative parameters but often not available in databases and literature. Estimation of amount of blood loss always suffers from inaccuracies.\textsuperscript{11} As suggested by Kerr et al we must be more accurate in patients with (signs) of postpartum hemorrhage and we need different definitions for different purposes; one to decide when to start treatment, one for definition in research and one to use as quality indicator of care.\textsuperscript{12} Since postpartum hemorrhage is still a leading cause of maternal morbidity and mortality, women with suspicion of postpartum hemorrhage should be admitted to specialized centres and receive intensive monitoring and management in the current and subsequent pregnancies.
Although this thesis answers some but not all questions regarding prenatal management in forestalled situations, our implications for clinical practice can be summarized as follows:

- Actively search for (or exclude) vasa previa in women with one or more risk factors (Figure 1).
- Withhold from premature Cesarean delivery in women with asymptomatic placenta previa but schedule these women for elective Cesarean delivery between 37 and 38 weeks of gestation.
- Admission to the hospital and administration of corticosteroids in women with a symptomatic placenta previa and schedule Cesarean delivery at 35 or 36 weeks of gestation
- Schedule induction of labor at 37 weeks of gestation in women with a history of placental abruption and strictly control any form of hypertension.
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