From DEPARTMENT OF CLINICAL SCIENCE,
INTERVENTION AND TECHNOLOGY
DIVISION OF OBSTETRICS AND GYNECOLOGY
Karolinska Institutet, Stockholm, Sweden

# MASSIVE TRANSFUSION IN RELATION TO OBSTETRIC HEMORRHAGE

## WITH SPECIAL ATTENTION TO PLACENTA ACCRETA

Lars Thurn


Karolinska Institutet

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# Massive transfusion in relation to obstetric hemorrhage, with special attention to placenta accreta

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By


## Lars Thurn

*Principal Supervisor:*
Pelle G Lindqvist M.D. Associate Professor
Karolinska Institutet, Södersjukhuset
Department of Clinical Science and Education
Division of Obstetrics and Gynecology

*Co-supervisors:*
Agneta Wikman M.D. Associate Professor
Karolinska Institutet
Department of Laboratory Medicine
Division of Clinical Immunology and Transfusion Medicine

Prof. Magnus Westgren
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Obstetrics and Gynecology

*Opponent:*
Prof. Bo Jacobsson
Göteborg University
Institute of Clinical Science
Department of Obstetrics and Gynecology

*Examination Board:*
Ylva Vladic Stjernholm, M.D. Associate Professor
Karolinska Institutet
Department of Women's and Children's Health
Division of Obstetrics and Gynecology

Prof. Gösta Berlin
Linköping University
Department of Clinical Immunology and Transfusion medicine

Prof. Marie Blomberg
Linköping University
Department of Clinical and Experimental Medicine
Division of Children's and Women's Health

*In loving memory of my mother Gerd.*

# ABSTRACT

The overall purpose of this thesis was to assess risk factors, incidences, and complications of massive blood transfusions in relation to obstetric hemorrhage postpartum. Obstetric hemorrhage requiring blood transfusion postpartum has recently shown an increasing trend in many high resource countries. Massive transfusion, defined as more than 10 units of RBC within 24 hours is well described in surgery and trauma care, however little is known about its occurrence and risk factors in obstetric patients. Most blood transfusions are safe and necessary, but there are potential complications, including transfusion reactions, transfusion transmitted infections, and post transfusion thrombosis, which have to be taken into consideration when choosing between blood transfusion and other alternatives. The increasing rate of cesarean deliveries since the 1970's, has contributed to complications in sequential pregnancies. One of the more severe complications is abnormally invasive placenta, a condition with a high risk of requiring massive blood transfusion and peripartum hysterectomy.

In Study 1, the incidence, risk factors, and rate of antenatal detection of abnormally invasive placenta in the Nordic countries were investigated. The study was conducted as a Nordic collaboration from 2009 to 2012, and included 605,000 deliveries. Cases of abnormally invasive placenta were reported on a monthly basis directly from maternity wards, and were complemented with data from the National Health Registries to confirm or to identify missing cases. In total, 205 cases of invasive placentas associated with a laparotomy were identified, corresponding to a prevalence of 3.4 per 10,000 deliveries. Major risk factors were placenta previa (OR = 290) and prior cesarean section (OR = 7). Only one third of the cases identified as invasive placentas were detected antenatally, and among those cases not detected, more than one third had had a prior cesarean section.

Study 2 was a retrospective population-based cohort study investigating risk factors, incidence, and trends over time for massive blood transfusion in women who gave birth in the County of Stockholm between 1990 and 2011. Data from the Medical Birth Registry was cross-linked to the Stockholm Transfusion Database. Massive transfusion was defined as transfusion of $\geq$10 units of red blood cells from time of partus through the next day. Altogether 517,874 pregnancies were included. The study found the incidence of massive transfusion to be 5.3 per 10,000 deliveries and showed an increasing trend over time. Major antenatal risk factors were abnormal placentation (OR = 41) and prior cesarean section (OR = 4).

Study 3 was a retrospective cohort study investigating whether postpartum hemorrhage and red blood transfusion are significant and independent major risk factors for venous thromboembolism postpartum. Women who gave birth between 1999 and 2002 in the Stockholm region were included in the study. A time period before the implementation of national thromboprophylaxis guidelines was chosen. Data from the Medical Birth Registry

was linked to the transfusion database and to the National Discharge Registry. Among 82,376 deliveries 56 cases of venous thromboembolism were identified. The study found transfusion of red blood cells postpartum (OR = 5) - but not postpartum hemorrhage without blood transfusion - to be a significant major risk factor for venous thromboembolism postpartum.

In Study 4 the aim was to assess the risk of transfusion reactions in women receiving postpartum blood transfusion. This populations based cohort study is based on the same cohort as Study 2. Data on pregnancies from the Medical Birth Registry was linked to the Stockholm Transfusion Database. Women with postpartum blood transfusion and a transfusion reaction within seven days from partus were identified. The study found a two-fold increased risk (OR = 2.0) of a transfusion reaction in women postpartum compared to non-pregnant women receiving a blood transfusion. Among all women who had a blood transfusion postpartum, women with preeclampsia were twice as likely to have a transfusion reaction.

In summary, abnormally invasive placenta occurs in 3.4 out of 10,000 deliveries and is the major risk factor for massive blood transfusion postpartum. A reduction in the rate of cesarean deliveries might be the best way to lower the incidence of both invasive placenta and massive blood transfusion postpartum. A focused ultrasound in pregnant women with a placenta previa or a low-lying placenta covering the scar of a previous cesarean section might improve antenatal detection of abnormally invasive placentas and allow better planning for delivery, thereby reducing maternal morbidity in those complicated pregnancies.

Postpartum blood transfusion and especially massive blood transfusion are independent major risk factors for postpartum thromboembolism. As such, they should be implemented in the Swedish thromboprophylactic guidelines during pregnancy. The risk of transfusion reactions in women during pregnancy seems to be increased, especially in pregnancies complicated by preeclampsia. Therefore, a heightened attention is recommended to women with preeclampsia when a blood transfusion is to be administrated.

# LIST OF SCIENTIFIC PAPERS

This doctoral thesis is based on the four original papers listed below. The papers are referred to in the text by their Roman numerals.

I. **Thurn L**, Lindqvist PG, Jakobsson M, Colmorn, LB, Klungsoyr K, Bjarnadóttir RI, Tapper AM, Børdahl PE, Gottvall K, Petersen KB , Krebs L, Gissler M, Langhoff-Roos J, Källen K. Abnormally invasive placenta – prevalence, risk factors and antenatal suspicion: results from a large populationbased pregnancy cohort study in the Nordic countries.
*BJOG, an International Journal of Obstetrics & Gynecology, 2016, volume 123; p 1348-1357.*

II. **Thurn L**, Wikman A, Westgren M, Lindqvist PG. Massive blood transfusion in relation to delivery: incidence, trends and risk factors.
*Manuscript submitted.*

III. **Thurn L**, Wikman A, Lindqvist PG. Postpartum blood transfusion and hemorrhage as independent risk factors for venous thrombosis.
*Thrombosis Research, 2018, volume 165; p 54-60.*

IV. **Thurn L**, Wikman A, Westgren M, Lindqvist PG. Incidence and risk factors of transfusion reactions in postpartum blood transfusion.
*Blood Advances 2019 3:2298-2306.*

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AFE | Amniotic Fluid Embolism |
| AIP | Abnormally Invasive Placenta |
| PAS | Placenta Accreta Spectrum |
| AOR | Adjusted Odds Ratio |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CS | Cesarean Section |
| FFP | Fresh Frozen Plasma |
| FIGO | The International Federation of Gynecology and Obstetrics |
| ICD | International Classification of Disease |
| IPR | Swedish National Inpatient Register |
| L | Liters |
| MBR | Medical Birth Register |
| MRI | Magnetic Resonance Imaging |
| MT | Massive Transfusion |
| NOSS | Nordic Obstetric Sureveilance System |
| OR | Odds Ratio |
| PAR | Swedish Patient Register |
| PPH | Postpartum Hemorrhage |
| RBC | Red Blood Cells |
| SD | Standard Deviation |
| SOFT | Svensk Förening För Obstetrik och Gynekologi |
| TACO | Transfusion Associated Circulatory Overload |
| TR | Transfusion Reaction |
| TRALI | Transfusion Related Lung Injury |
| UKOSS | United Kingdom Obstetric Surveillance System |
| WHO | World Health Organization |
| VTE | Venous Thromboembolic Event |

# 1 HISTORICAL INTRODUCTION

Historical introduction to blood transfusion and invasive placenta

Blood has been considered a mysterious but vital fluid since the beginning of mankind. It is the very basis for life and as such has also played an important role in many religions, cultures and magic rituals. In Mayan and Aztec cultures bloodletting and human sacrifices were carried out in order to honor their gods. Drinking human blood as a mean to survive is described in Scottish folklore where a female blood sucking fairy (Baobahn Sith) lures wayfarers in the highlands. In fiction and movies we have vampires, such as Bram Stoker's Dracula, dependent on blood from another individual to survive.

Although bloodletting was a popular treatment for a number of conditions from time of the Egyptians some 4000 years ago up to the middle of the nineteenth century, there was an early understanding that great blood loss was associated with death.[1]

The idea of transfusing blood as a treatment for illnesses (and madness) is old, but the knowledge of how to perform safe transfusions in humans took centuries to develop and many early attempts were unsuccessful and often fatal.

The first step toward safer blood transfusions was taken in 1628 when the British physician William Harvey described the circulatory system and showed that blood was being pumped, by the heart, through a single system of arteries and veins to the whole body.[2] Prior to Harvey it was believed that the body contained two completely separate blood systems and that blood did not circulate at all, but was consumed at the same rate it was produced.

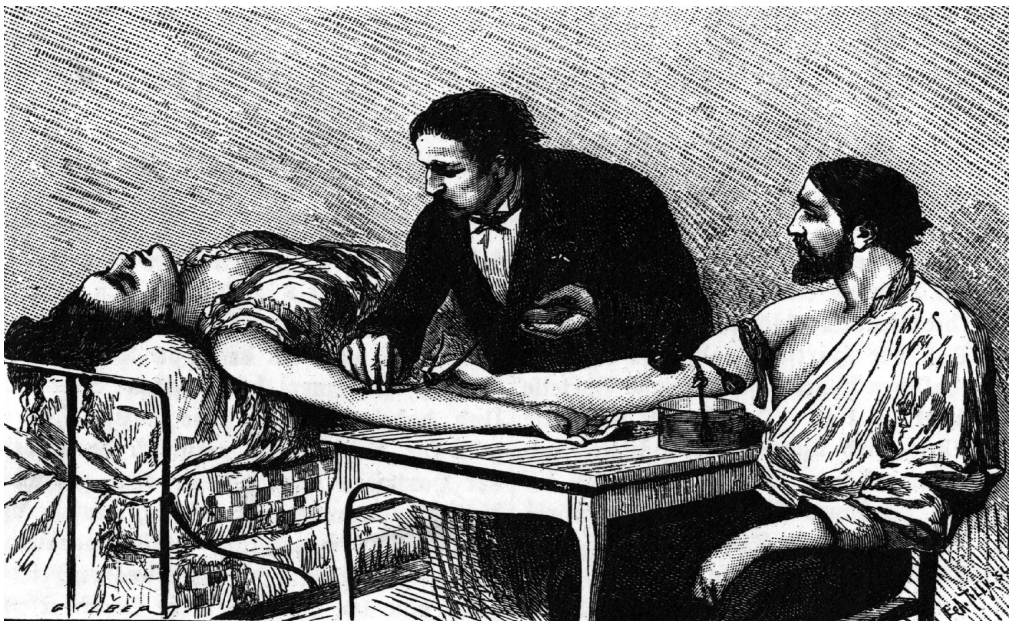
In 1825, almost two centuries later, came the first report of a successful human-to-human transfusion. It was performed by British obstetrician James Blundell and his friend Charles Waller on a woman with a life-threatening postpartum hemorrhage, with her husband as the blood donor Figure 1.[3] While the procedure was successful, blood transfusions at that time were hazardous and associated with more than 50% mortality.[4]

The next significant step in the evolution of safer blood transfusions was the understanding of the ABO system described by the Austrian physician Karl Landsteiner in 1901.[5] This discovery made it possible to avoid most acute hemolytic transfusion reactions, which probably was a common fatal complication.

Today postpartum hemorrhage (PPH) is still a major cause of maternal mortality worldwide. In low-resource countries 26% of all deaths in relation to delivery are due to bleeding and lack of blood transfusions, as was the case in London almost 200 years ago, when James Blundell and colleges pioneered in blood transfusions after massive postpartum hemorrhage.[6]

In high-resource countries death due to hemorrhage at delivery is rare (1:100,000 deliveries).[7] Blood transfusions occur in approximately 3 in 100 deliveries, and there seems to be a progressively increasing trend.[8-11]

Figure 1. Illustration of a woman with a postpartum hemorrhage
and the first human to human blood transfusion. © Photos/Alamy, printed with permission.



One important reason for major PPH and massive blood transfusion is abnormally invasive placenta (AIP), also referred to as the placenta accreta spectrum (PAS), a condition where there is abnormal adherence of the placenta to the myometrium. It requires complicated surgery and involves the risk of heavy bleeding at the time of delivery.[12] The first cases of AIP were reported by Irving and Hertig in 1937.[13] Since then we have seen a dramatic increase in of this condition, parallel with the rising rate of cesarean deliveries in many high resource countries.[14] Improvements in prenatal diagnosis of AIP by ultrasound and in recent years by MRI, has allowed clinicians to make necessary preparations before delivery in an attempt to prevent massive hemorrhage. Since Tabsh et al. in 1982 reported the first case of a pregnancy with AIP that was diagnosed before delivery using ultrasound, great effort has been made to standardize ultrasound protocols and improve its efficacy as a screening method for AIP.[15,16]

# 2 PREVIOUS CESAREAN DELIVERIES AND ITS CONSEQUENCES

Cesarean section (CS) has been described as far back in history as ancient Hindu, Greek and Roman times. It has been suggested that Julius Caesar himself was born by cesarean section, and for this reason the procedure was named cesarean. However, the story is doubtful since Ceasar's mother, Auriel, is said to have lived to hear of the Roman invasion of Britain many years later, whereas cesarean procedures at that time would only have been performed on women who were already dead or dying. The word cesaerean is more likely to come from the Latin verb *caedare* meaning to cut out.

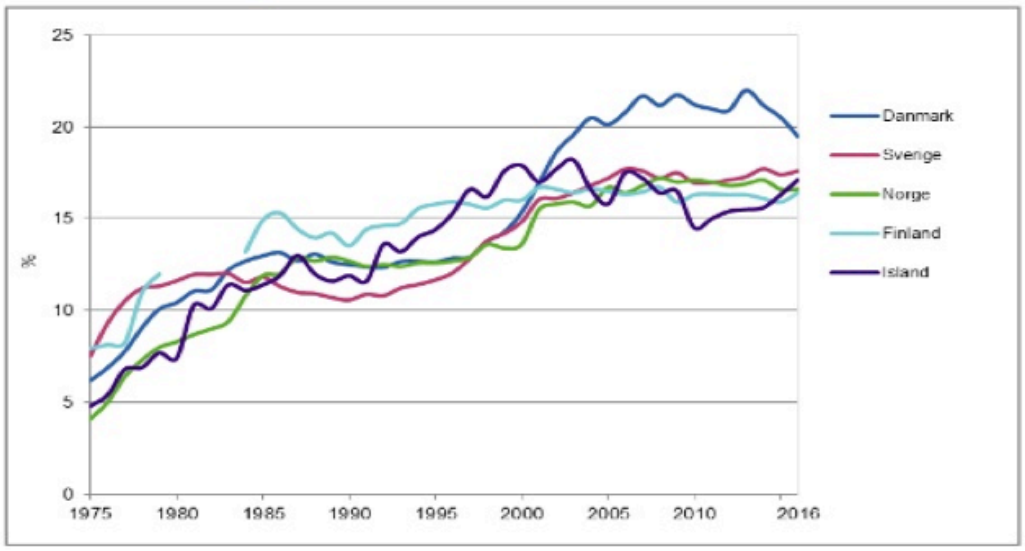
According to Agneta Pleijel's novel *The Queen's Surgeon*, the first CS in Sweden was performed by the obstetrician Herman Schützer in 1758.[17] At this time short-term complications after surgery and complicated deliveries were extremely high and many women died from hemorrhage or postoperative infections.[18]

In 1985 the World Health Organization (WHO) stated in its guidelines on appropriate technologies for birth that there is no justification or health benefits in having a CS rate below 10% or higher than 15%.[19] However, there is no consensus on an optimal fixed rate of CSs, and WHO amended the statement in 2015 by adding that the goal is not a specific rate, but rather the provision of CS to pregnant women in need. During the past 50 years there has been a drastic rise in rate of cesarean deliveries worldwide. Between the years 2000 and 2015 the number of births by CS almost doubled from 16 million to 30 million, equivalent to an increase in the overall CS rate worldwide from 12% to 21% in 2015.[20] Globally there are significant disparities between countries and regions with rates of CS varying from 0.6% to 60%, primarily due to differences in economy, resources, and health care systems.[20] In Sweden and in the Nordic countries the rate of CSs in the early 1970s was approximately 5%; it has increased to about 18% in 2016 (Figure 2).[21,22]

Most deliveries by CS in Sweden and in other high resource countries are safe, but there are both short and long-term complications that have to be considered. As always there should be a balance between benefits and risk of doing harm.

Dominant short-term complications after CS, that have been previously described, are hemorrhage, infection, hysterectomy and thrombosis.[23-25] A cesarean delivery is reported to increase the risk of severe postpartum hemorrhage by 2 to 4 times and a venous thromboembolic event (VTE) by 3 to 5 times, compared to a spontaneous vaginal delivery.[23,25-28]

Figure 2. Rate (%) of cesarean deliveries in the Nordic Countries 1975 to 2016. Used with permission from THL, The National Institute for Health and Welfare, Finland 2018.




However, interpretations of these risk estimations are difficult as the complications registered could be a result of the underlying indication for the CS instead of the surgical procedure itself. For example, preeclampsia with impaired hemostasis might be the indication behind a CS that in turn leads to a postpartum hemorrhage and a transfusion of blood products. All of the above mentioned risk factors are associated with each other and with the risk of an eventual VTE in the postpartum period. In the analysis of risk factors based on data from long-term studies one has to consider that both the rate of CS as well as characteristics and risk-profiles of pregnant women change over time. Thus, compared to the last decades, pregnant women today are older, have higher BMI, and are more often conceived through IVF, which has to be considered when evaluating prior CS as an independent risk factor in seeking to improve prophylactic guidelines for postpartum hemorrhage or thrombotic events. Since we lack controlled prospective studies, observational studies can give important information on rare pregnancy complications. Still, the effect of confounders has to be considered. This can be achieved by the use of stratifications and adequate adjustments in regression analysis.

Long-term maternal complications after CS mainly occur in regard to subsequent pregnancies. Severe complications refer to uterine rupture, placental abnormalities such as placenta previa and abnormally invasive placenta (AIP), with its possible consequences of an acute hysterectomy and risk of massive blood transfusion. In a Nordic population-based study from 2017, incidence of severe complications in a second delivery occurred in 1.1% of women who had a first cesarean delivery as compared to 0.2% in the general pregnant population.[24] The risk of complications seems to be lower in women with a first emergency cesarean compared to women with a first elective cesarean.[24,29] Surgical techniques using a one or two layer closure of the hysterotomy at CS has not been associated with a difference in risk of either uterine rupture or the risk of AIP in a subsequent pregnancy.[30,31] The number of prior cesarean deliveries progressively increases the risk of complications (especially

abnormal placentation). For women who plan to have more than one child it would be beneficial in most cases to avoid CS in the first delivery.[24,32,33] A study by Williams et al. in 2018 found that a previous cesarean delivery was associated with a small but significant increased risk of preterm birth in a subsequent pregnancy, which further emphasizes the advisability of reducing the rate of CSs, especially in the first pregnancy.[34]

This thesis focuses on incidences, trends, and risk factors (including prior CS) for AIP and massive blood transfusion postpartum. VTEs and transfusions reactions are potential consequences of massive blood transfusions and will be assessed in detail below.

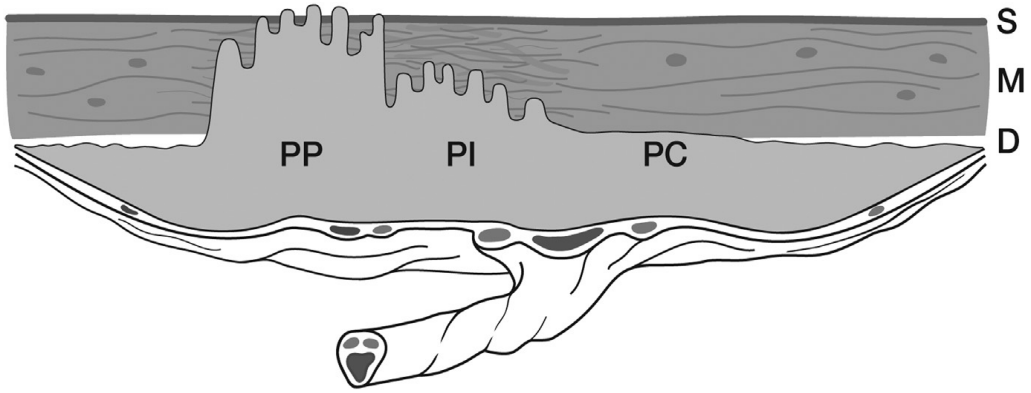
# 3 INVASIVE PLACENTA/PLACENTA ACCRETA

Abnormal adherence and invasiveness of the placenta is a severe obstetric complication associated with catastrophic hemorrhage and a high risk of maternal morbidity and mortality. It is a condition that has only been reported in human pregnancies.[35] When the normal detachment of the placenta fails, it causes uncontrolled bleeding that often requires complex surgery. Today, invasive placenta is a major cause of peripartum hysterectomy.[36,37] As already mentioned the first series of cases were described by Irving et al. in1937 in a review of 18 clinical cases with "abnormal adherence of the afterbirth to the underlying uterine wall most likely caused by a partial or complete absence of the decidua basalis".[13] They concluded that attempting to manually extract the adherent placenta was extremely dangerous, and when this procedure was attempted two-thirds of the mothers died. Maternal mortality in cases of invasive placentas is much lower today, but still is reported to be as high as 7% in high resource countries.[38] Abnormal placentation has not been studied to the same extent in low-income countries.

*Terminology*

The term "placenta accreta" refers to all variations of adherent placenta. The spectrum includes three different subtypes, depending on how deeply the trophoblasts penetrate into the myometrium: a) placenta accreta/creta represents the mildest form, where the villi reach the inner surface of the myometrium but do not invade; b) placenta increta represents cases where the villi invade deep into the myometrium but without engaging the serosa; and c) placenta percreta represents the most severe cases where the villi penetrate through the uterine serosa, as illustrated in Figure 3.[16] Abnormally invasive placenta (AIP) is another commonly used, broader term for the condition, but often refers to the more invasive cases that include placenta increta and percreta.[39,40] In recent guidelines the term Placenta Accreta Spectrum (PAS) has been suggested; it includes all histopathological subtypes of abnormal placentation.[40]

Figure 3. Spectrum of invasive placenta.[16]




S = serosa; M = myometrium; D = decidua; PC = placenta creta; PI = placenta increta; PP=placenta percreta. Copyright © American Journal of Obstetrics and Gynecology, printed with permission.

The lack of an international consensus on definition and the heterogeneity in the terminology over the past decades has made it difficult to directly compare studies, incidences, and other results. Definitions have been based on antenatal ultrasound, clinical findings, histopathological findings or a combination of the above.[41] The diagnosis of PAS is originally made by histopathological findings, including an absent decidua and presence of myometrial fibers alongside chorionic villi in the basal plate.[12] Using histopathology as the only means of diagnosing PAS can be questioned. For instance, myometrial fibers in the basal plate have been reported even in normal placentas.[12] Today, conservative and uterine saving strategies in managing cases of PAS have become more frequent. In these cases hysterectomies are not performed, making histopathologic examinations unfeasible. The same is true of scar pregnancies, where there is a no decidua or myometrial tissue to eaxamine.[42] Therefore, the clinical description of the invasiveness of the placenta has become more important in diagnosing PAS/AIP. A clinical grading system has been suggested in the International Federation of Gynecology and Obstetrics (FIGO) consensus guidelines on placenta accreta spectrum disorders (Figure 4).[42]

Placenta accreta is the most common subtype of PAS and represents approximately two-thirds of all cases. The most severe cases, placenta percreta, are rare and constitute about 5% of all PAS cases. Milder forms may include retained placentas.[12,42] In some cases, retained placentas is due to a constricted cervix, not abnormal attachment, and should hence not be included among PAS cases. This might have occurred in some previous studies, resulting in an overestimation of the reported prevalence of PAS. In this thesis the term abnormally invasive placenta (AIP) will be used.

Figure 4. Clinical grading system of AIP, printed with permission, Int J Gynecol Obstet.[42]

| Grade | Definition |
|---|---|
| 1 | *At cesarean or vaginal delivery:* Complete placental separation at third stage. Normal adherence of placenta |
| 2 | *(A) Cesarean/laparotomy*: No placental tissue seen invading through the surface of the uterus. Incomplete separation with uterotonics and gentle cord traction, and manual removal of placenta required for remaining tissue and parts of placenta thought to be abnormally adherent*(B) Vaginal delivery*: Manual removal of placenta required and parts of placenta thought to be abnormally adherent |
| 3 | *(A) Cesarean/laparotomy*: No placental tissue seen invading through the surface of the uterus. No separation with uterotonics and gentle cord traction with manual removal of placenta required and the whole placental bed thought to be abnormally adherent*(B) Vaginal delivery*: Manual removal of placenta required and the whole placental bed thought to be abnormally adherent |
| 4 | *Cesarean/laparotomy:* Placental tissue seen to have invaded through the serosa of the uterus but a clear surgical plane can be identified between the bladder and uterus to allow nontraumatic reflection of the urinary bladder at surgery |
| 5 | *Cesarean/laparotomy*: Placental tissue seen to have invaded through the serosa of the uterus and a clear surgical plane cannot be identified between the bladder and uterus to allow nontraumatic reflection of the urinary bladder at surgery |
| 6 | *Cesarean/laparotomy*: Placental tissue seen to have invaded through the serosa of the uterus and infiltrating the parametrium or any organ other than the urinary bladder |

*Incidence*

The worldwide incidence of AIP has increased dramatically over the past 50 years and is now reported to be between 2 and 90 per 10,000 births.[43-48] To a great extent the wide range in incidence can be explained by differences in study design, the definition of AIP used, and to some extent differences in the population studied. The incidence has risen ten-fold from the 1970s. The increased rate of AIP is parallel to the rise in rate of cesarean deliveries.

In a study from the US in the 1980s, Read et al. found the incidence of AIP to be 1 in 4,000. It was a small study, including only 14 confirmed cases, but with a solid definition of placenta accreta based on histopathological findings after hysterectomy.[49]

Twenty years later, in another US population, Wu et al. found a much higher incidence of 1 in 533.[45] However, the authors included both histopathological and clinical findings, which might partially explain the higher incidence. Their study retrospectively included cases from 1982 to 2002, and compared the last 10 years with the first. They found an increase in the CS rate from 12.5% to 23.5% and, parallel to this, an almost five-fold increase in AIP from 0.4 per 1000 births to 1.9 per 1,000 births. This strongly supports the association between AIP and the increase in CS rate.

In a 2017 Australian case-control study using the Australasian Maternity Outcomes Surveillance System (AMOSS), Farquhar et al. found an incidence of 0.5 per 1,000 deliveries using a wide definition of AIP including assessment by antenatal imaging, at surgery or by pathological examination.[48]

Using a similar obstetric surveillance system a study from the UK found a much lower incidence of AIP: 1.7 per 10,000 deliveries.[47] A combination of strict clinical and pathological criteria was used to define AIP cases and designed to capture severe cases. Data was collected prospectively using a monthly reporting system (UKOSS). The lower incidence found might be because the majority of cases were placenta increta and percreta, excluding milder forms of the placenta accreta spectrum and cases with retention placentas. The higher incidence in the AMOSS study might also be due to reporting of cases based on only antenatal imaging. Cases detected antenatally may not necessarily have been AIP at time of delivery, which might result in an overestimation of the true rate of AIP.

In a more recent US study from 2016 they found a high prevalence of 37 per 10,000 deliveries.[50] However, it relied exclusively on the International Classification of Disease codes (ICD) and had no strict clinical definition and no histopathological data, which might have resulted in a lack of specificity. In addition, the study included some cases with retention of placenta and membranes, which will result in a registration bias and an expected higher rate compared studies with more strict inclusion criteria. In the UK study the authors concluded that the rates of AIP during the study period did not parallel the increasing rate of prior CSs.[47] This might be because of the time lag. The rate of AIP is estimated to lag the rate of CS by six years.[51] The association between prior CS and AIP is well established and has been reported in several studies.[32,46]

The highest reported incidence of 90 per 10.000 deliveries is reported from Israel in 2002. However, they included several women diagnosed with placenta accreta in a previous pregnancy and had a low rate of hysterectomy (3.5%) among identified cases, indicating they had a very broad definition of AIP and most likely included cases with retention placenta.[44]

The challenge in optimal management at delivery lies mainly within the placenta increta and percretas. True incidence of these subtypes of AIP is still uncertain.

Most studies on AIP are from countries with a less homogeneous population and a much higher rate of CS than in Sweden and the Nordic Countries. Therefore, previously reported incidence rates, risk profiles and complications are not necessarily the same in the Nordic Countries, which was a main reason for conducting the research in Paper I.

*Consequences*

The degree of invasiveness of the villi into the myometrium and the engagement of the bladder or parametrical tissues corresponds to the risk of massive bleeding and surgical

complications. The mean estimated blood loss at delivery in women with AIP is reported to be approximately 3 L, and blood transfusion is required in up to 90% of those cases.[52] Surgical complications include damage to the urethras, cystotomies and, need for a reoperation.[53] AIP has also become the main cause of peripartum hysterectomy on vital indication.[54,55] In a prospective Nordic obstetric surveillance study (NOSS) from 2015 (including 211 cases of hysterectomy), and in a retrospective Australian study from 2018 (including 72 cases of hysterectomy), AIP accounted for 43% and 67%, respectively, of all emergency peripartum hysterectomies.[37,56] Data from the 2018 World Maternal Antifibrinolytic (WOMAN) trail, included reports from Africa, Asia, Europe and the Americas, found that hemorrhage from abnormal placentation had the highest risk of hysterectomy (17%) compared to obstetric trauma (5%) and uterine atony (3%).[57] The psychological trauma and long-term consequences of AIP may be severe but is scarcely studied. The reported mortality rate due to AIP varies widely. From 7 % in the early 1990's to 0.7% in more recent reports.[38,48] A summary of the most common complications from AIP is presented in Figure 5.

Figure 5. Complications associated with abnormally invasive placenta (AIP)[42]

| | |
|---|---|
| Median estimation of blood loss | 2-3 L |
| Median units of packed red blood cells transfused | 3.5-5.4 L |
| Large-volume blood transfusions (>10 L) | 5%-40% |
| Injury to bladder | 7%-48% |
| Injury to ureter | 0-18% |
| Admission to intensive care unit | 15%-66% |
| Bowel injury/obstruction | 2%-4% |
| Venous thromboembolism | 4% |
| Surgical site infection | 18%-32% |
| Reoperation | 4%-18% |
| Maternal mortality | 1%-7% |

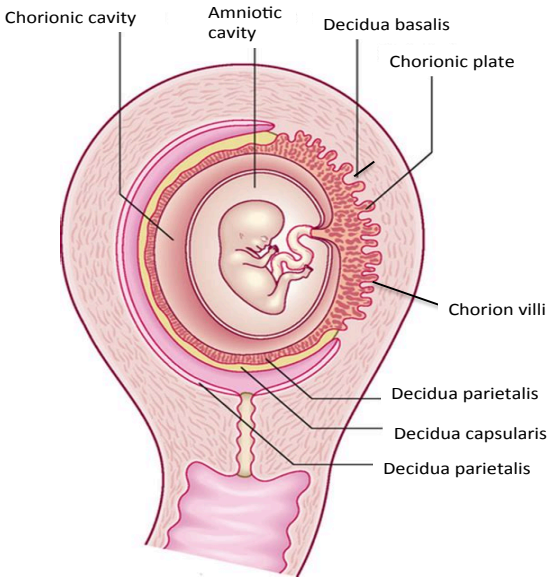
*Pathophysiology*

The leading hypothesis as to why AIP occurs is that damage to the interface between the endometrium and myometrium causes an abnormal decidualisation, with a resulting deep infiltration of the trophoblasts. The most common histopathological findings of AIP are a) absence of decidua, b) chorionic villi directly adjacent to myometrial fibers, and/or c) presence of myometrial fibers in the basal plate on the placental side.

*Placentation*

To prepare implantation of the embryo, the endometrium undergoes decidualisation. This complex process begins in the mid-secretory phase of the menstrual cycle, when high levels of estrogen and progesterone transform the endothelium and the stroma cells into larger decidual cells to create an optimal environment for the attachment of the blastocyst.[58] After implantation the decidua divides into three regions. Directly beneath the implantation site lies the decidua basalis or basal plate that forms the maternal part of the placenta. The rim around the embryo is the decidua capsularis, and the decidua parietalis covers the rest of the uterine cavity (Figure 6).[59]

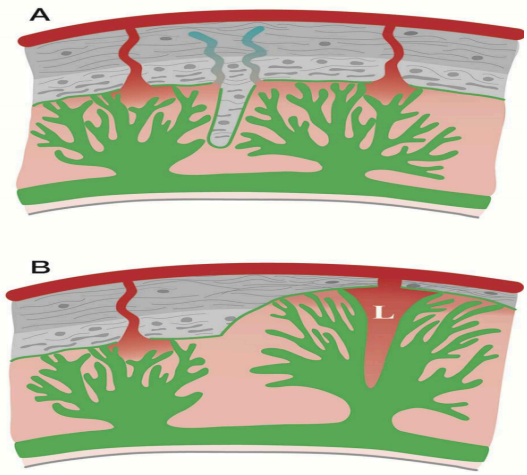
Figure 6 Decidua- basalis, capsularis and parietalis. 




From the embryo, cytotrophoblast cells on top of the anchoring villi proliferate and transform themselves into extravillous trophoblast cells (EVT) that invade the decidual stroma. In a normal pregnancy these EVT cells penetrate no further than the first third of the myometrium layer. Here they fuse and are formed the multinucleated trophoblast giant cells. It has been suggested that this fusion contributes to the EVT cells losing their invasive capability.[60]

Figure 7 illustrates how a stem chorionic villus with its branches (placental cotyledon) penetrate deeper into the myometrium in an increta placentation (B) than in a normal placentation (A).

Figure 7 A = Normal placentation, B = Placenta Increta placentation, L = Lacuna (placental lake). 

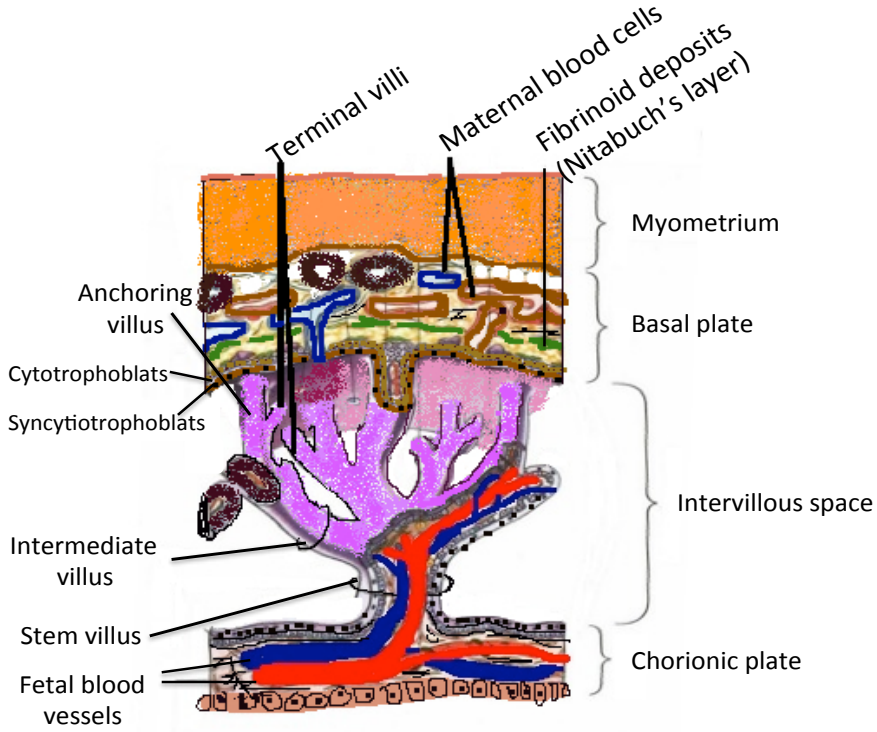



The small spiral and radial arteries in the myometrium of non-pregnant women are rich in smooth muscle cells and sensitive to vasoactive substances. During pregnancy these arteries are remodulated by specific proteases from the EVT cells, causing them to lose their elasticity and their responsiveness to vasoactive substances, and hence become the high flow vascular system that is vital for the exchange of oxygen and nutritional substances between mother and fetus.[61] In pregnancies with preeclampsia and fetal growth restriction this remodeling of spiral arteries fails. However, in women with AIP there seems to be no increased risk of placental insufficiency and fetal growth restriction.[16] That may be because the placental defect in AIP is focal, as compared to growth restricted fetuses in preeclamptic patients where AIP involves the entire placenta.

*Abnormal placentation*

In a normal pregnancy, the basal part of the decidual plate, also called Nitabuch's layer, is where the placenta separates from the myometrium Figure 8. The Nitabuch's fibrinoid consists of an eosinophilic matrix and a deposit of maternal fibrin that prevents the trophoblasts from penetrating further into the myometrium.[62] The placental separation is caused by the tearing action between the contracting movements of the myometrium and the non-contracting placenta. In the absence of the decidua or the Nitabuch's layer, this natural separation of the placenta might not happen, resulting in damage to the large blood vessels that have supported the pregnancy and massive hemorrhage.

Figure 8. Decidua basalis with Nitabuch's layer.




There have been several theories as to why AIP occurs. The primary hypotheses have been excessive extravillous trophoblasts, a primary defect in or absence of the decidua, abnormal vascular remodeling, or a combination of all these.[60] It is no longer believed that AIP is caused by excessively invasive trophoblasts invading the myometrium. Instead, the main hypothesis is that AIP is primarily caused by a defect in the interface between the endometrium and the myometrium.[63] This defect, often the result of a scar from a previous CS or other uterine surgery, prohibits normal decasualization and enables the chorion villi and trophoblasts to invade directly deep into the myometrium.[63] Chorionic villi in the vascular space of the myometrium have been detected in patients with AIP, supporting this theory.[64] A further explanation for the defective decidua might be that the blood circulation in the myometrium around a uterine scar is impaired by poorer vascularization, thereby leading to myometrial degeneration. This is supported by a 2013 study from Norway that found that women with a prior CS had a higher uterine resistance and reduced uteroplacental blood flow compared to women with a previous vaginal birth.[65]

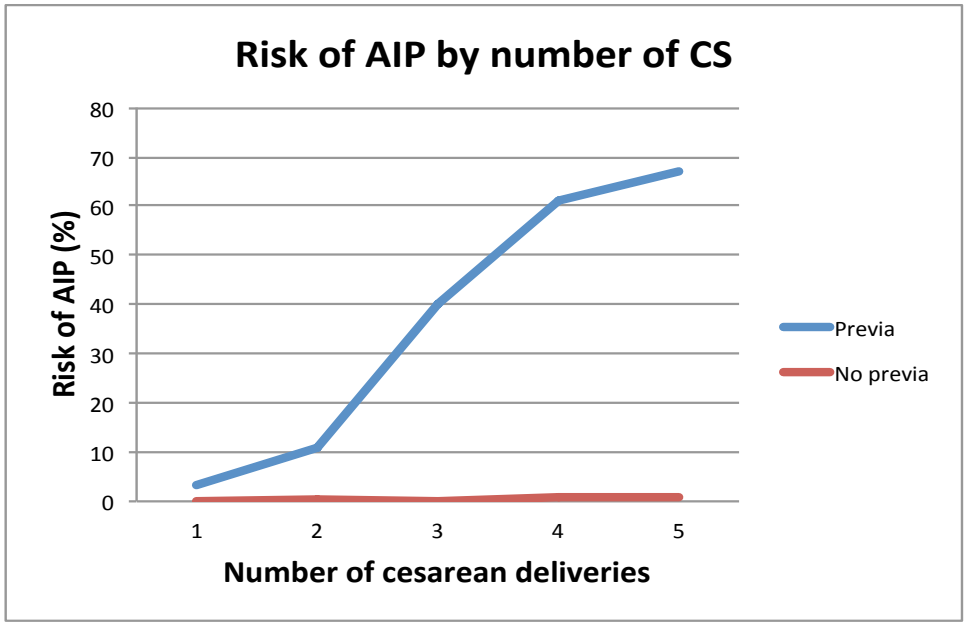
The aggressive invasiveness of trophoblasts in interstitial or ectopic pregnancies, where there exists no endometrium, is a further indication that it is in fact the decidua that modulates placentation and the invasiveness of trophoblasts. The etiology and management of AIP cases differs from molar pregnancies, where the trophoblasts are more invasive.[66]

Although rare, AIP even exists among primiparous women. This might be caused by a superficial defect in the endometrium after such minor gynecological surgery as hysteroscopy or curettage, and probably represent less invasive cases in the spectrum of AIPs.[67]

*Risk factors*

The single most important risk factor for AIP is placenta previa. In approximately 80% of all AIP pregnacies placenta previa is present.[68-70] In a meta-analysis from 2013 the overall incidence of placenta previa was 5.2 per 1,000 deliveries worldwide, and 3.6 per 1,000 deliveries in Europe.[71] Previa is strongly dependent on maternal age, IVF, and prior SC.[72] Silver et al. found the risk of AIP in women with placenta previa and no previous SC to be 3%, but it rose dramatically for every prior cesarean delivery (Figure 9).[32] The risk of AIP in women with placenta previa and one prior CS was 11% but after three prior CSs it reached 60%. The progressively increased risk of AIP by number of prior SC is supported by several authors.[46,73] The risk would presumably be even greater in cases with a higher number of CSs; however, in most cases the treatment for AIP is hysterectomy, which eliminates the possibility of further pregnancies.

Figure 8 Increasing risk of AIP by number of prior CS. Modified from Silver et al.




There are indications that prior elective CSs are associated with a higher risk of AIP than emergency CSs.[73] Whether this might be dependent on surgical technique or the placement of the incision is not completely known. The effect of suturing techniques, closing the uterus with a single or double layer or the impact of suture materials have all been debated but none seem to have a significant effect on the risk of AIP in a subsequent pregnancy.[73,74]

The presence of myometrial fibers in the delivered placenta is associated with AIP in the subsequent pregnancy. Deliveries complicated by placental retention or postpartum hemorrhage leading to manual removal of the placenta might be considered a risk factor for the future.[75] The risk of AIP is also reported to increase after other uterine surgery such as

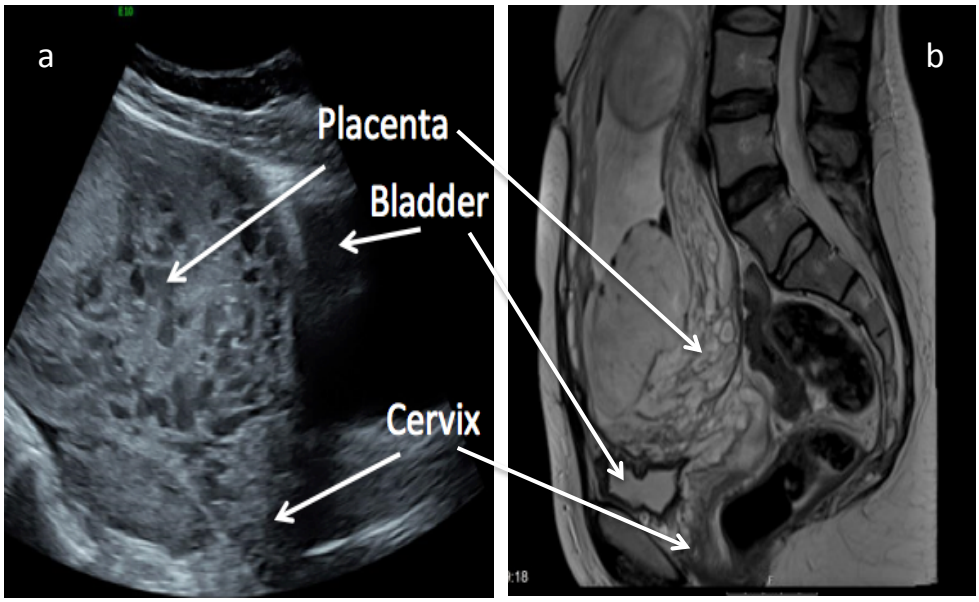
myomectomies, hysteroscopic procedures, Asherman's syndrome, increasing maternal age (> 35), increasing parity, smoking, and IVF.[32,43-45,47,76]

*Diagnostics*

Antenatal awareness of AIP has been shown to reduce complications.[77] It is advantageous to identify women at high risk for AIP in order to prepare a detailed delivery plan involving a multidisciplinary surgical team at a center with appropriate medical resources.[68,69]

Clinical evaluation, ultrasound assessment, magnetic resonance imaging (MRI), and biomarkers all play a role in the antenatal diagnosis of AIP. Both ultrasound and MRI are technologies that may be used to identify AIP disorders (Figure 10 a and b).[70,78] Ultrasound is today the primary diagnostic modality. Identification of AIP by ultrasound in the first trimester is possible, especially in cases with scar pregnancies, but most cases are diagnosed in the second and third trimester.[78,79] Both gray-scale and color doppler signs are used in diagnosing AIP. Apart from presence of a placenta previa the typical signs are multiple lacunae and uterovesical hypervascularity. However, in difficult cases with high BMI or a posterior low laying placenta where deep penetration into parametrium is suspected, MRI may be beneficial.[80] On the other hand, as a screening method, MRI is less practical since it has limited accessibility, is time-consuming and more costly. Therefore ultrasound is still the preferred diagnostic modality.

Figure 10 a,b. Images of abnormally invasive placenta in a twin pregnancy using (a) ultrasound and (b) MRI. One normal and one abnormal placenta (arrows).




The two different imaging modalities have been shown to be highly effective in diagnosing AIP. In a recent study from France, the sensitivity and the specificity were reported to be 0.92 and 0.67 for ultrasound, and 0.84 and 0.78 for MRI, respectively.[81] Meng et al. described

similar results in another meta-analysis. The average sensitivity and specificity for ultrasound was 83% and 82%, respectively. The figures for MRI were 95% and 88%, respectively, with no significant difference in diagnostic value.[82] In a third systematic review from 2013 that included 23 studies, D'Antonio et al. found an average sensitivity of 91% and a specificity of 97% in using ultrasound for diagnosing AIP.[83]

Even though the above diagnostic results above are promising the performance of the methods might be overestimated. This is suggested by recent large observational studies where almost half of the AIP cases were undiagnosed at delivery.[84,85] A majority of the studies were performed in highly specialized centers on a high-risk population. Results are likely to be operator dependant. The skill of interpreting ultrasound signs varies and interobserver discrepancies are substantial.[86]

In order to improve overall performance in diagnosing AIP, there continues to be a great need for standardization in interpreting antenatal ultrasound signs. Recently standardized ultrasound descriptors for AIP have been suggested by The European Working Group on Abnormally invasive placenta.[87] The major signs and definition are summarized in Table 1.[16,78,87] An extensive description of the pathophysiology behind the different signs has been published by Jauniaux et al.[16,88]

*Biomarkers*

Several biomarkers associated with AIP have been proposed. Those biomarkers studied include alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and pregnancy associated plasma protein-A (PAPP-A).[12] More recently, higher levels of cell-free beta-HCG mRNA, cell-free placental mRNA, and cell-free fetal DNA seen in pregnancies have been reported as being associated with AIP.[89,90] However, all of the biomarkers tested remain too nonspecific, and therefore more prospective data is needed. Perhaps combining ultrasound findings and biomarkers might be of clinical value in the future.

Table 1. Ultrasound signs of AIP. Modified from Collins et al.

| Ultrasound sign | Definition | Presence in AIP (%) |
|---|---|---|
| Presence of placenta previa | Placenta previa | 80 |
| Loss of "clear zone" | Loss of hypo-echogenic zone between the placenta and myometrium (abnormal extension of placental villi into myometrium) | 70 |
| Placental lacunae | Presence of numerous large irregular lacunae | 80 |
| Myometrial thinning | Decreased retroplacental myometrial thickness (< 1 mm) | 50 |
| Interruption of bladder wall | Interruption of bright bladder wall between uterine serosa and bladder lumen | no data |
| Placental bulge | Abnormal bulge of placental tissue into neighboring organ, usually the bladder | no data |
| Focal exophytic mass | Placental tissue seen breaking through uterine serosa, often seen inside filled urinary bladder | 33 |
| Bridging vessels | Vessels from placenta, across myometrium and beyond serosa into bladder or other organs; often running perpendicular to myometrium | 66 |
| Placental lacunae feeding vessel /turbulent lacunar blood flow | Vessels with high-velocity blood flow from myometrium into placental lacunae, causing turbulence | no data |
| Subplacental/uterovesical hypervascularity | Complex of numerous irregular vessels with multidirectional flow | 75-81 |

*Management*

The main risk associated with AIP is catastrophic hemorrhage and need for complex surgery. Optimal management in surgical or expectant approaches are still under debate. Hysterectomy is performed today in the majority of AIP cases (up to 90%), but several uterine saving techniques have also been described.[91]

After the antenatal detection of an invasive placenta, recent guidelines suggest management according to the following main categories:[53,92,93]

- Multidisciplinary team care (MDT)
- Counseling and providing information to the pregnant women about her condition and the different options available
- Pre-delivery optimizing of hemoglobin
- Optimal timing of delivery
- Level of care
- Preoperative preparations
- Intraoperative considerations and management
- Choice of expectant or conservative management
- Follow-up, future pregnancies

*Multidisciplinary team care (MDT)*

The medical care of patients with AIP disorders is complex and the positive impact of an MDT approach has been clearly demonstrated.[68,69,94] Shamshirsaz found that even though the group with MDT care had more cases of placenta percreta, they tended to require fewer blood transfusions and less emergency deliveries.[95] In 2017 Smulian reported significantly less blood loss and administration of blood products, and Eller cited fewer cases that needed reoperation in the group receiving MDT care compared to standard care.[68,94] In agreement with these results, a 2019 US study found less blood loss and lower rates of blood transfusion in the group where AIP was suspected antenatally as compared to a group where it was not expected and they attributed the better outcome to the MDT approach seen in the first group.[96] As these were all retrospective cohort studies and the selection of patients and degree of invasiveness might be different in the various groups, which could potentially have had an effect on the results. The exact composition of a multidisciplinary team may vary, but recent

guidelines recommend that they include the following key personnel; experienced obstetricians, a pelvic surgeon (gynecologic oncologist), an interventional radiologist, a urologist, an obstetric anesthesiologist, a neonatologist, specialized nursing staff, and access to a blood bank with resources to handle massive transfusion protocols.

*Timing of delivery*

Data from several authors has indicated that a planned cesarean delivery, before the onset of labor decreases the risk of maternal morbidity as compared to an emergent delivery.[70,97] Among women with suspected AIP the risk of an unscheduled delivery, and hence minimal preoperative planning, is significantly increased. Such women may have pre-partum bleeding episodes, increased uterine activity, and preterm premature rupture of membranes.[46,53] The optimal gestational week for delivery of women with suspected AIP is not known and no randomized controlled studies regarding timing of delivery exist. However most authors recommend delivery between 34+0 and 36+6 weeks of gestation in high-risk cases (placenta previa with episodes of bleeding or placenta percreta) and 36+0 to 37+0 weeks in more uncomplicated pregnancies (no episodes of bleeding, placenta accreta/increta).[53,93]

*Intraoperative considerations*

A detailed description of the different surgical techniques used in handling AIP disorders have been presented in recent guidelines.[36,53,93] After delivery of the fetus and with the placenta in utero, hysterectomy it is still the preferred primary surgical approach and is recommended by most authors[37,98,99] Total hysterectomy is often required because of cervical engagement and bleeding from the lower uterine segment.[92]

Monitoring of blood loss, urine output, hemostasis, and ongoing communication between the surgical and anesthesia teams is essential. Preoperative preparation for the transfusion of large numbers of erythrocyte concentrates, plasma, and platelets should be made. A high plasma/erythrocyte ratio ($\geq 1$) is recommended in trauma and surgical care but optimal ratios have not been extensively studied in obstetric patients.[100]

The most common surgical complication in AIP patients is urinary tract injuries, reported to be as high as 29%.[101] The general use of ureteral stents or catheters to minimize the risk of injuring the ureter is recommended by some but not all authorities.[97] The procedure enables

evaluation of the invasiveness of the placenta through the bladder wall, and the stents provide fast identification of the ureters during difficult surgery in cases involving massive hemorrhage. In cases with a high suspicion of bladder invasion, ureteral stents are recommended.[69,102]

Most authors and guidelines recommend a midline skin incision in cases where a hysterectomy is planned or there is an anterior placenta that goes above the level of the umbilicus.[36,69,93,103]

It is preferable that intra/preoperative ultrasound be used to identify the upper placental margin in order to avoid the placenta when performing the uterine incision.[93,104] If not spontaneously delivered, the placenta should not be manually removed.[94,97] The use of prophylactic oxytocin is not clear, but is recommended in cases in cases of ongoing hemorrhage. After suture of the fundal hysterotomy and confirmation of the AIP diagnosis, is confirmed, options remaining are to a) perform a hysterectomy b) do a focal resection of the wall with invasive placenta, c) or chose expectant/conservative management leaving the placenta in situ.

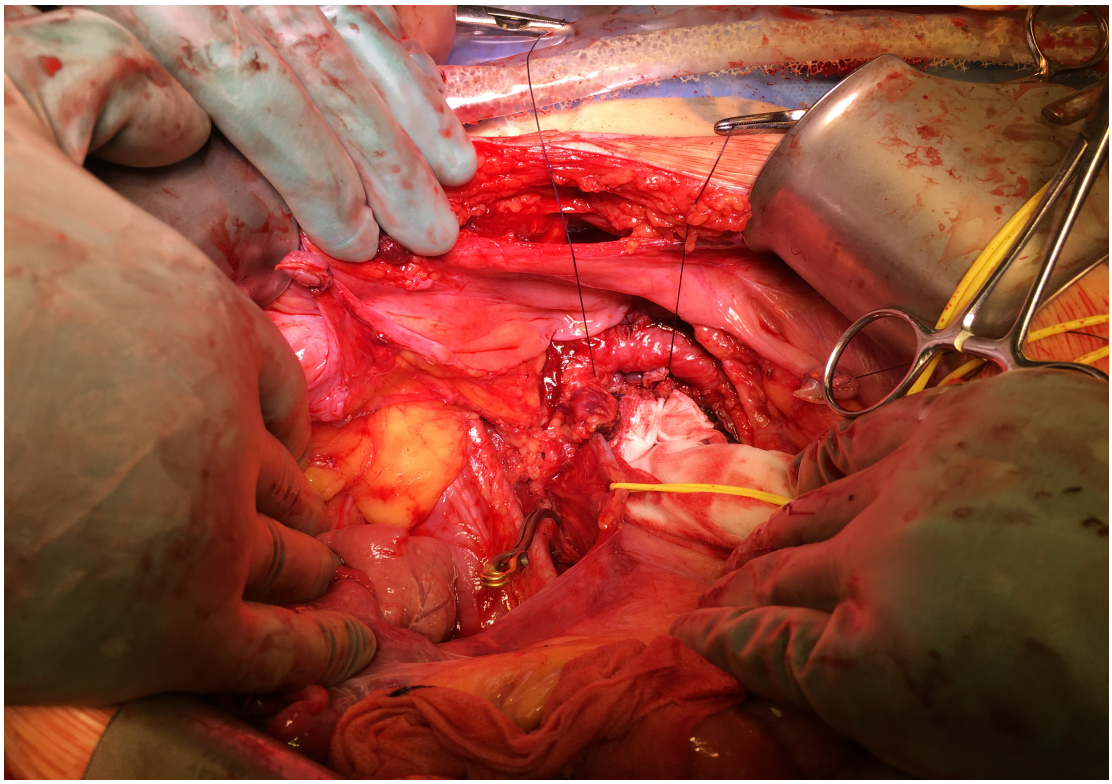
The choice of surgical method depends on several factors. These include the desire for future fertility, the invasiveness of the placenta, and the preferences of the surgical team. A detailed comparison and description of the different surgical methods are beyond the scope of this thesis except for certain aspects of hemostasis, which will be discussed below.

*Devascularization*

If hysterectomy or a focal resection is to be performed, prophylactic devascularization may be performed in order to minimize blood loss. Available techniques are intravascular techniques such as embolization, or temporary balloon occlusion. Extravascular techniques are ligation or temporary clamping (vascular ("bulldog") clamps) of blood vessels to the uterus (uterine artery or the internal iliac artery).[105-108] Temporary clamping of the internal iliac artery by "bulldog" vessel clamps is shown in Figure 11. The major vessels involved are the aorta, common iliac, internal iliac or the uterine arteries. The results are controversial as are the use of these methods. Reduction of blood loss after endovascular balloon occlusion of the aorta and iliac arteries has been demonstrated in several studies.[106,109,110] A study in 2012 comparing occlusion of the abdominal aorta to occlusion of the internal iliac artery showed less blood loss, reduced need for blood transfusion, and shorter insertion time in the aorta

occlusion group.[111] Other authors could not find a positive effect of endovascular occlusion. There are also reports of thromboembolic complications and rupture of the iliac artery.[112,113,114] Data on ligation or clamping of the internal iliac arteries is scant and inconclusive.[108,115] It may be that these procedures are useful only in more severe cases with a percret placenta. However, to demonstrate this would require large multicenter controlled trials.

Figure 11. Clamping of the internal iliac artery in surgery of invasive placenta.



*Cell saver technology*

Cell salvage is a technique in which blood from a bleeding patient is filtered and re-transfused into the patient. It may reduce the need for allogeneic blood transfusion and is used today in many medical facilities that handle AIP cases.[116] If care is taken to avoid suction of amniotic fluid or fetal blood, and in combination with the use of leucocyte filtering techniques, the procedure is considered safe.[117]

*Tranexamic acid*

Tranexamic acid is a fibrinolytic inhibitor that affects the breakdown of fibrin by plasmin. It is recommended as a treatment in cases where there is ongoing hemorrhage and as prophylaxis before CS in high risk-cases.

Two large placebo controlled studies have demonstrated that it reduces mortality in cases with hemorrhage without increasing thromboembolic complications.

The CRASH-2 trial compared 1 g tranexamic acid administered intravenously within one hour of admittance to placebo in trauma patients with ongoing hemorrhage and they found a reduced mortality risk in the treatment group (relative risk (RR) 0.85).[118]

The WOMEN trial compared 1 g intravenous tranexamic acid given within 3 hours postpartum to placebo in women with a postpartum hemorrhage (PPH) greater than 500 ml. It demonstrated that the treatment significantly reduced mortality (RR = 0.69).[119]

However, as prophylaxis for PPH, tranexamic acid has yielded somewhat contradictory results. A 2018 study by Sentilhes found no difference in the rate of PPH (blood loss > 500 ml) between 1 g of tranexamic acid or placebo given intravenously before planned vaginal delivery.[120] However, a meta-analysis of nine trials by Simonazzi concluded that tranexamic acid given before elective cesarean delivery significantly reduced blood loss and the need for blood transfusion.[121] These findings were later supported by two placebo-controlled trials in 2016 and 2017 [121,122]

*Conservative management*

For women who wish to retain their uterus for future pregnancies hysterectomy is not a decision of choice. Conservative management has also been proposed as an option to decrease the risk of maternal morbidity by reducing hemorrhage and the need for blood transfusion in severe cases.

The main strategies in these instances are a) conservative surgery with removal of the focal area of invasive placenta and repair of the uterine wall, b) and leaving the placenta in situ without hysterectomy or resection.

The different techniques for conservative surgery of AIP have similar main principles. They include:[123]

1. Delivery of the fetus from an upper or fundal hysterotomy and not manually removing the placenta
2. Devascularization around the uterus and the uterine−bladder interface either by intra-abdominal ligation of blood vessels or intravascular occlusion
3. Resection of the invasive placenta, including the invaded myometrial tissue
4. Myometrial reconstruction

In a systematic review conducted in 2015 that included 177 cases of AIP, a uterus-preserving surgical intervention was attempted in 76 cases. The success rate, defined as a subsequent menstruation or pregnancy, was 63% (48/76), and the need for secondary hysterectomy was 30% (23/76).[124] Shabana et al. demonstrated an even higher success rate of 91% in preserving the uterus after focal resection by use of extensive pelvic devascularisation.[125] However, this promising result requires advanced pelvic and vascular surgical skills, that will probably limit the widespread adoption of the method.

The Triple- P method (periopertive placental localization, pelvic devascularization, placental non separation) described by Chandraharan in 2012 is a variation of the above procedure. Intravascular balloons are used for pelvic devascularization before performing myometrial excision and uterine wall repair. In this procedure the entire placenta is not removed and some placental tissue is left in situ.[126,127] The method has shown a lower rate of PPH and peripartum hysterectomy but only in small series. Larger studies are needed to evaluate its efficacy and risks.[127]

In addition, there are reports of a hemostatic technique where the cervix is inverted into the uterus as a natural tamponade, and another using special multiple 8-compression suturing.[128,129] Both studies are showing positive results, but again, too few instances have been recorded to draw any conclusions. All of the methods described share a common dilemma in being greatly operator dependent, which makes reproducibility, comparison, and generalization difficult.

*Leaving the placenta after cesarean delivery without hysterectomy or focal resection.*

The largest study to date using this approach is a 2010 French trial that retrospectively included 167 AIP cases. It resulted in an overall success rate of 78% (131/167) with

preservation of the uterus.[130] However, 18 women in the study had a primary hysterectomy and 18 had a delayed hysterectomy. The rate of severe maternal complications was 6% and included sepsis, thromboembolism, uterine necrosis, and secondary postpartum hemorrhage. Spontaneous placental desorption occurred in 75% of the women over a median time of 13.5 weeks. One case of maternal mortality was also reported in connection with methotrexate. Such an approach might be an option in selected cases, but informing women about the risks of complications and the long follow-up time is essential.

*Future fertility*

Data on future pregnancies following successful conservative treatment is limited. While pregnancy may be possible it will have a higher risk of complications, including postpartum hemorrhage uterine rupture and recurrent AIP disorders. The overall risk of a recurrent AIP disorder is reported to be as high as 30%.[131]

*Methotrexate in treatment of AIP disorders*

Methotrexat is a folate antagonist. In contrast to the situation in early pregnancy trophoblast cell turnover is much lower later in pregnancy. Treatment-related complications such as neutropenia and medullar aplasia have been reported even after a single dose of methotrexate.[132]

Data on the efficacy and safety of methotrexate as a treatment for AIP disorders is inconclusive. It is currently not recommended as adjuvant treatment in patients with AIP.[88]

# 4 POSTPARTUM HEMORRHAGE (PPH)

Postpartum hemorrhage (PPH) remains as one of the leading causes of maternal mortality worldwide, causing an estimated 125,000 deaths annually.[6] In Sweden and other high resource countries maternal mortality due to bleeding has fallen dramatically over the past 100 years, and is now as low as 0.9 per 100,000 deliveries in some countries. [7] However, recent studies have indicated an increasing trend toward higher rates of PPH with the accompanying need for blood transfusions.[10,133-135] The explanation for this is unclear but it may be related to an increase in IVF pregnancies, multiple pregnancies, obesity, higher

maternal age, and the increasing frequencies of placental abnormalities such as placenta previa and AIP. The rise in placental complications may be a consequence of the growing rate of cesarean deliveries.[10,136,137] This association has been described in countries with high rates of CS, but has not been studied systematically in the Nordic countries, where there is a comparatively low rate of CS. PPH in high resource countries is reported to occur in 1 to 15% of all deliveries. In 2018 the overall rate of PPH in Sweden was 8%, according to data from the Swedish Maternal Health Care Register (MHCR).[138]

The World Health Organization (WHO) defines primary PPH as a loss of blood greater than 500ml within 24 hours of delivery.[139] In Sweden primary PPH is defined as a blood loss of $\geq$ 1000ml within the above time period. This difference in definition is confusing but understandable since a blood loss of 500 ml in a woman in poor health due to malnutrition or chronic infection (e.g., malaria) might be fatal, whereas most women in high resource countries the same blood loss would be of little consequence due to their better health status. Different definitions of PPH make it difficult to compare results between studies. Another cause of uncertainty is that blood loss is a subjective estimation. It is often overestimated after cesarean and underestimated after vaginal deliveries.[140] Weighing and measuring blood and blood soaked materials have improved the estimation of blood loss. A superior method of estimating the severity of blood loss is to record the number of transfused units of red blood cells (RBC), plasma, and platelets. In Sweden, all transfused blood components have been registered in a computerized system since the early 1980s. Coombs has suggested a clinical definition of PPH as the "need for blood transfusion". However this definition may also be subjective due to variations in transfusion protocols and general attitudes towards blood transfusion.[141]

Risk factors for PPH have been described by several authors and formalized in recent guidelines.[142,143] Atonic uterus is the major cause of PPH and is responsible for approximately 65% of all cases.[143,144] To prevent massive hemorrhage, early identification of risk factors is essential. It has been reported that the majority of all maternal deaths due to hemorrhage, were associated with suboptimal care and could have been avoided.[145]

Risk factors linked to massive blood transfusion postpartum may differ from those described for ordinary PPH, as will be analysed in more detail below and in Paper II.

# 5 MASSIVE BLOOD TRANSFUSION (MT)

In order to maintain adequate circulation, tissue oxygenation, and hemostasis, massive hemorrhage needs to be treated with massive transfusion. While no universally accepted definition of MT exists, it often involves a volume or number of units of RBCs transfused during a specific time frame. The most common definition is the transfusion of $\geq$ 10 units of RBC within 24 hours.[146-148] However, this definition does not necessarily reflect acute clinical cases. Studies using this definition might be "diluted" by including less acute patients, and in the most severe cases patients may die before 10 units are transfused, and will therefore be excluded.

Other proposed definitions are: [136,149,150]

- blood loss of more than 50% of the total blood volume within 3 hours
- $\geq$ 8 units of RBC within 24 hours
- $\geq$ 5 units of RBC within 4 hours
- > 4 units within one hour

The three definitions above have the potential to better represent cases with true acute and life-threatening hemorrhages. In order to better compare studies and results, there is need for an international consensus on the best definition of massive transfusion that reflects the most severe cases.

Patients who require MT have often been reported associated to trauma or military care. In the US, up to 5% of clinical trauma and 10 % of military trauma patients require MT.[151] However, a recent study from Sweden and Denmark found that MT (defined as > 10 units RBC within 2 or 7 days) were most commonly used in cases involving major surgery (61%), as compared to trauma or obstetric hemorrhage (15% and 2%, respectively). [152] Reports from military and trauma care have indicated that protocols for MT and a high plasma/RBC ratio (1:1) have improved outcomes and survival in patients with massive bleeding.[100,153] Holcomb found that 30 day survival significantly increased in patients with a ratio of > 1:2 compared to <1:2.[154] Whether these trauma-oriented protocols are fully applicable to obstetric situations is not clear.

### 5.1 BLOOD TRANSFUSION AND MT IN OBSTETRIC PATIENTS

The successful decrease in the rate of blood transfusions reported in some medical disciplines is not seen in obstetric care.[133,155] Today, the overall frequency of blood transfusions due to obstetric hemorrhage is reported to be 0.2 to 3.2%.[8,9,156,157] Few publications have addressed MT in obstetric care.[8,136,158] The reported incidence of MT in obstetrics is between 2 and 9 per 10,000 births. Of the three published studies addressing MT postpartum, two have used the definition: $\geq$ 8 units of RBC within 24 hours of birth and one the definition of $\geq$10 units of RBC within 24 hours.[136,158] This heterogeneous use of definitions for MT is a dilemma that is further discussed in Paper II.

To prevent unnecessary bleeding and coagulopathy it is important to take early hemostatic action. Compared to other causes of hemorrhage, major obstetric bleeding more often leads to early disseminated intravascular coagulopathy (DIC).[159]

Therefore, transfusion protocols involving early administration of FFP/plasma and platelets in massive obstetric hemorrhage has been suggested. How these new transfusion strategies are implemented and whether they improve severe maternal morbidity, is unclear. Green et al. have suggested the need for targeted transfusions strategies, depending on the different causes of massive obstetric hemorrhage.[160] Their findings suggest that the hemostatic changes in massive obstetric hemorrhage due to placental abnormalities result in lower levels of platelets and fibrinogen, compared to the changes seen in trauma situations. On the other hand, Gutierrez et al. found that a standardized MT protocol in obstetric care was associated with favorable hematologic post-resuscitation.[161] Finally, Tanaka et al., in a recent systematic review of MT protocols in obstetrics, suggested that a FFP/RBC ratio $\geq$ 1 was necessary for optimal hemostatic treatment, concluding that a ratio $\geq$ 1 was associated with higher survival in women with severe obstetric hemorrhage.[162] However, once again conclusive information on the best obstetric transfusion protocol would require large, randomized, controlled, multicenter trials.

# 6 HEMOSTASIS

Hemostasis is a complex, tightly regulated physiological system. Any imbalance can lead to severe hemorrhage or thromboembolism. Knowledge of hemostasis is vital for the

understanding and effective treatment of many pregnancy complications that may affect the coagulation system.

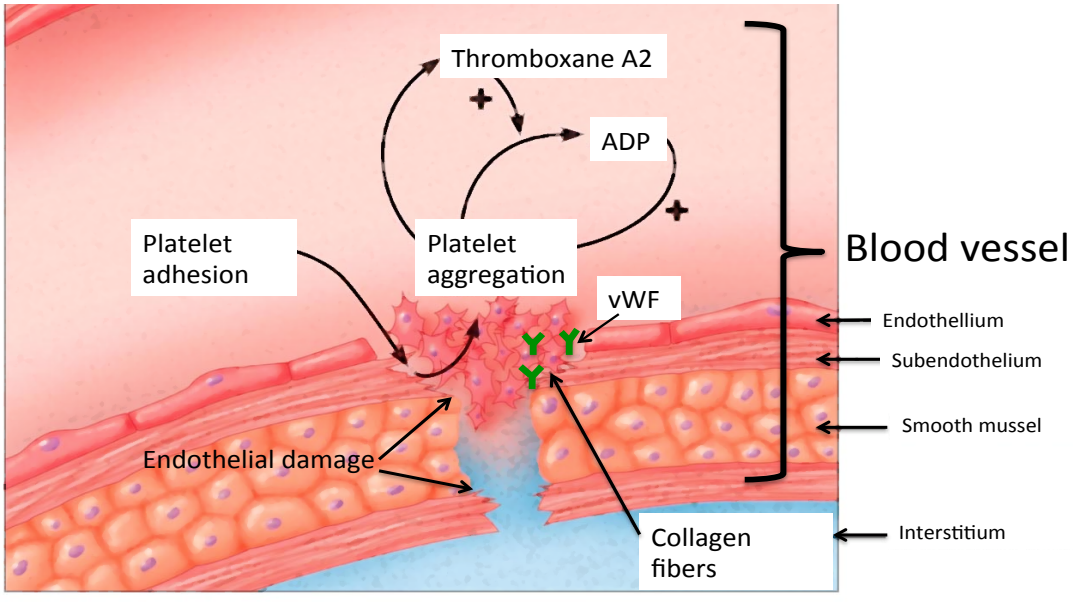
Hemostasis consist of three main steps:[163]

- Primary hemostasis
- Secondary hemostais (or plasmacoagulation)
- Fibrinolysis

### 6.1.1 Primary hemostasis

The primary hemostasis is the result of complex interactions between endothelial proteins and platelets that lead to the formation of a primary platelet plug. It is initially triggered by an endothelial injury to the vascular wall. In contrast to the antithrombotic endothelial lining, the subendothelial layer contains highly thrombogenic substances such as collagen fibers, laminin, vitronectin, and Von Willebrand factor (vWF).[164,165] At the site of the damaged endothelium these thrombogenic substances cause platelet adhesion. The activated platelets change form and release the vasoconstrictive substances thromboxane A2 (TXA2) and serotonin, which in turn cause vasospasm and reduce blood loss. Further platelet aggregation and creation of the preliminary platelet plug is stimulated by secretion of calcium, adenosine diphosphate (ADP), and TXA2 from the activated platelets (Figure 12).[166] On undamaged endothelium, prostacycline ($PGI_2$) and nitric oxide (NO) act as inhibitors of further platelet activation thereby limiting the thrombosis.[167]

Figure 12 Primary hemostasis.



### 6.1.2 Secondary hemostasis

Secondary hemostasis leads to the formation of fibrin by coagulation proteins. This process can be divided into four phases:

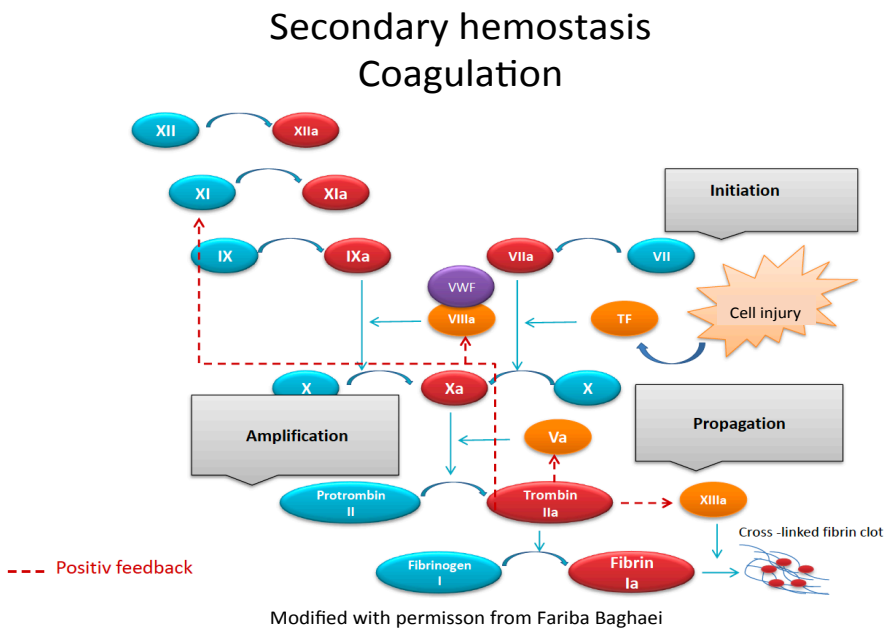
- Initiation
- Amplification
- Propagation
- Termination

In the initiation phase, tissue factor (TF) on the cell surface at the site of injury is exposed to the circulating blood and its components. Activated FVII binds to TF, forming a TF-VIIa complex, which in turn activates FIX and FX. Activated FX (in a complex with FVa) promotes the conversion of prothrombin to small amounts of thrombin.

In the next phase, thrombin not only catalyzes fibrinogen to fibrin but also acts as a promoter in converting FXI to FXIa, which after activation of FIX promotes the further conversion of FX to FXa. This positive feedback of conversion of prothrombin to thrombin in the amplification phase was formerly known as the intrinsic pathway, but is today more commonly described as the ”thrombin burst”.[163]

In the propagation phase, large quantities of thrombin lead to the production of sufficient amounts of fibrin that can form a stabilized platelet plug. Finally, FXIIIa promotes the cross-linking of loose fibrin polymers to create a stable and elastic clot. Secondary hemostasis is summarized in Figure 13.

Figure 13. Secondary hemostasis




Modified with permisson from Fariba Baghaei

During the termination phase the coagulation process is constrained by specific inhibitors, the most important of which are antithrombin (AT), Protein C, Protein S, and tissue factor inhibitor (TFPI).

### 6.1.3 Fibrinolysis

After the damaged blood vessel is healed, fibrinolysis begins and the clot is gradually dissolved. In this process plasminogen is converted to plasmin that in turn resolves fibrin to small protein fragments (D-dimers). Plasminogen is produced in the liver and circulates freely in the plasma. It binds to fibrin and is activated by tissue plasminogen activator (t-PA) and urokinase plasminogen activator on the surface of the fibrin clot. This ensures that the fibrinolysis remains local to the affected area. The main inhibitors of fibrinolysis are antiplasmin and plasminogen activator inhibitor type 1 (PAI-1), and, during pregnancy, also PAI-2 (which inhibits tPA). PAI-2 is synthesized in the placenta and increases with gestational age.[168]

## 6.2 PHYSIOLOGY AND HEMOSTASIS DURING PREGNANCY

### 6.2.1 Physiology during pregnancy

Major physiological changes occur during pregnancy in order to nurture the growing fetus and prepare the mother for the forthcoming delivery, and a possible hemorrhage. These changes involve all organs, but they resolve almost completely after a normal pregnancy. Some of the most important adaptions to pregnancy are mentioned below. Changes in hemostasis are described separately in more detail.

Cardiac output (CO) increases by 40% by means of increased stroke volume and a slightly higher heart rate. It reaches its maximum around 20 to 28 weeks of gestation. This is partly to compensate for a peripheral vasodilatation that causes vascular resistance to fall by 30% and to the increased blood volume.[169] The plasma volume rises progressively by about 50% during pregnancy.[170] This plasma expansion exceeds the increase in red blood cell mass, causing a lower hemoglobin concentration and bringing about the physiological anemia seen in pregnancy. Further changes during pregnancy are an increase in the metabolic rate by 15%, and in the consumption of oxygen by 20%. To compensate, ventilation is increased by

50%.[171] This slight form of hyperventilation causes a physiological compensated respiratory alkalosis in normal pregnancies.[171]

### 6.2.2 Hemostasis during pregnancy

As mentioned above, coagulation is a complex, tightly regulated system. During pregnancy this balance changes to a hypercoagulable state to prepare for potential bleeding at delivery. From an evolutionary perspective, the effect might have been an important advantage for survival.[172] This hypercoagulability may partially explain the increased risk of thromboembolism during pregnancy. It might also explain why some variants of thrombophilia (such as factor V mutation or factor II mutation) only cause a slightly increased risk of thrombosis in non-pregnant women, but they became significant risk factors during pregnancy.

Most coagulation factors increase during pregnancy, especially FVII, FX and FXII. Table 2. Fibrinogen increases by 50% to 3-6g/L.[173] VWF is a protein that carries FVIII, and binds to activated platelets increases significantly as early as the first trimester.[174]

There might be an acquired APC (activated protein C) resistance during pregnancy that is most likely due to an increase in FVIII but also to a decrease in protein S.

Table 2. Coagulation factors and haemostatic changes in pregnancy.

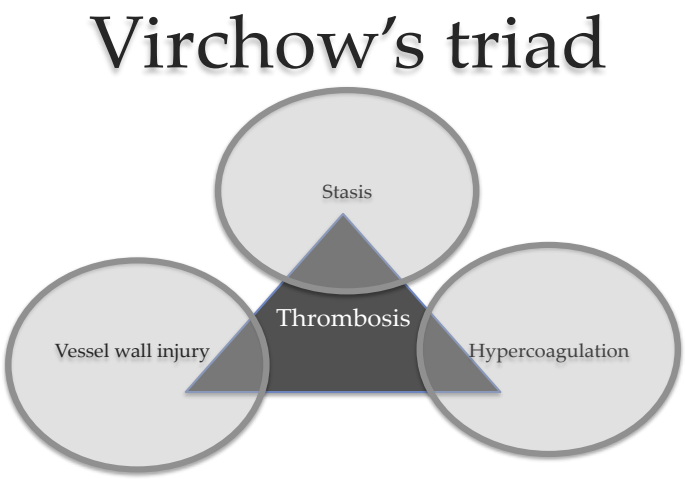
| Factor | Change in pregnancy | Effect on coagulation | Effect on fibrinolysis |
|---|---|---|---|
| FII | Unchanged | ↔ | |
| (FV), FVII, FVIII | Increases | ↑ | |
| FX, FXII, | Increases | ↑ | |
| FXI, FXIII | Decreases | ↑ | |
| VWF | Increases | ↑↑ | |
| PAI-1, PAI-2 | Increases | | ↓ |
| Protein C | Unchanged | ↔ | |
| Protein S | Descreases | ↑ | |
| Antithrombin | Decreases | ↑ | |
| TPFI | Decreases | ↑ | |
| Alfa2-antiplasmin | Unchanged | ↔ | |

The main anticoagulants, antithrombin and Protein S as well as tissue factor inhibitor (TFPI) decreases, which favors coagulation. Finally, fibrinolysis is lowered by a rise in plasminogen activator inhibitor-1 (PAI-1) and PAI-2 from the placenta.

### 6.2.3 Thromboembolism in pregnancy

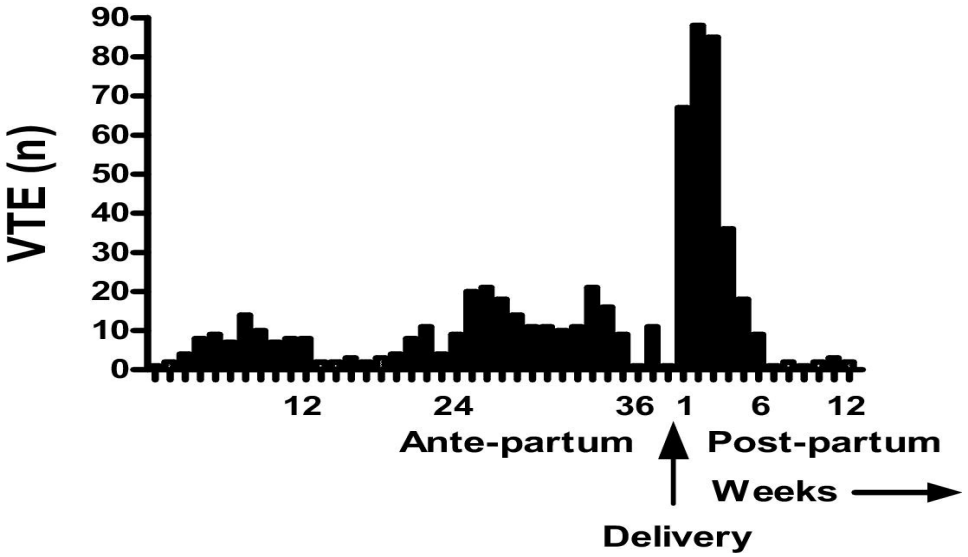
There is a well-known increased risk of venous thromboembolism (VTE) during pregnancy and in the postpartum period. The three main contributors to the formation of thrombosis, venous stasis, endothelia injury and hypercoagulability (Virchow's triad), are all present in pregnancy Figure 14.

Figure 14. Virchow's triad




VTE remains a major cause of maternal morbidity and is responsible for 3% of all maternal mortality worldwide. In high resource countries pulmonary embolism (PE) accounts for 8% to 17% of all maternal deaths.[6] Pregnancy, including the postpartum period is associated with an increased risk of VTE by a factor of 5 to 20, as compared to age-matched non-pregnant women.[28,175,176] In Sweden and other high resource countries the incidence of VTE during pregnancy and the postpartum period is estimated at 12 to 17 per 10,000 pregnancies.[28,175,177] The risk of VTE, especially PE, is highest in the first 6 weeks postpartum (Figure 15).[25,178]

Figure 15. Venous thromboembolic events during pregnancy and postpartum. (Used with permission from ACOG, Jacobsen 2018)




Variations in the reported incidences may be due to differences in data sources, management of VTE cases in outpatient care, misclassification (ICD coding), use of imaging and other diagnostic modalities, as well as the extent of thromboprophylaxis in the cohort studied.

As a consequence of the increased risk of VTE, many countries have guidelines recommending low-molecular-weight heparin (LMWH) as thromboprophylaxis during pregnancy and postpartum. Sweden has a weighted scoring-based thromboprophylaxis algorithm that includes major risk factors that are equivalent to an approximately five-fold increased risk of VTE. By means of this algorithm, women with $\geq 2$ major risk factors (representing approximately 4 % of all deliveries with a 25-fold increased risk) will be recommended postpartum thromboprophylaxis. The efficacy of LMWH prophylaxis during pregnancy has been shown to produce an 88% relative risk reduction.[179] Similarly, there are indications that maternal death caused by PE has decreased by almost 50% after implementing thromboprophylactic guidelines in the UK.[7]

Prophylaxis with LMWH is generally safe but a heightened risk of PPH, hematomas, and skin reactions have been reported.[180] As always there must be a balance between potential harm and benefit.

In order to identify the high-risk group of women who can benefit from LMWH, correct risk factors must be identified.

Prior thrombosis and thrombophilia are two of the most important risk factors for VTE. Other major risk factors are obesity, high maternal age, immobilization, rheumatoid disease, and

inflammatory bowel diseases. Among pregnancy-related risk factors, preeclampsia, multiple pregnancy, placental abruption, cesarean delivery, and ovarian hyperstimulation syndrome (OHSS) have been previously reported.[28,176,181]

Both PPH and blood transfusions have been suggested as risk factors for VTE postpartum. It is still unclear whether either of these risk factors are strong enough by themselves to be implemented in the Swedish risk scoring algorithm, that is, representing at least a five-fold increased risk of VTE. To answer these questiones we conducted a study based on a cohort that existed before general implementation of the thromboprophylactic guidelines.

# 7 TRANSFUSION COMPLICATIONS

Blood transfusions can be life saving and have become one of the most common medical treatments in high resource countries today. In Sweden close to 600,000 transfusions of RBC, plasma, or platelets were administered annually from 2011 to 2013. Modern blood transfusions are safe, but complications do occur. Severe complications after ABO-incompatible transfusions and the risk of transfusion transmitted infections (TTI) such as HIV were major contributors to the development of national surveillance schemes for transfusions that now exist in many countries. TTIs such as hepatitis B, C, and HIV have become rare due to testing, but emerging infections, i.e., Zika and West Nile virus, are not universally tested for and are still a concern.[182]

### 7.1.1 Transfusion reactions (TR)

Complications other than TTI are transfusion reactions (TR) and short- and long-term effects of immunomodulation. TR can be classified based on a) pathophysiology or b) time between transfusion of blood component and clinical sign of a reaction. Early reactions occur in close relation to the transfusion; delayed reactions may produce symptoms days or months after the transfusion. Reactions can be immunologic or non-immunologic, and may vary in severity from mild to fatal.

Blood transfusions may also have a delayed effect on the recipient's immune system. This reaction, transfusion-related immunomodulation (TRIM), involves both immunosuppression and hyperinflammation. It is thought to be associated with an increased risk of recurrence of tumors and infections. However, many clinical aspects of TRIM are uncertain and its

pathophysiology is unclear.[183] The different types of transfusion reactions are summarized in Table 3 below.[184,185]

Table 3. Types of transfusion reactions

| Type of reaction |
|---|
| **Early/acute reactions** |
| Immunologic |
| Mild allergic |
| Anaphylactic |
| Febrile non-hemolytic |
| Acute hemolytic |
| Septic |
| Transfusion related acute lung injury (TRALI) |
| Non immunologic |
| Transfusion-associated circulatory (TACO) |
| **Delayed reactions** |
| Immunologic |
| Delayed hemolytic |
| Transfusion -associated graft-versus-host |
| Post-transfusion purpura (PTP) |
| Immunomodulation |
| Non Immunologic |
| Iron overload |

The true overall incidence of TR is not known (partly due to underreporting), but published incidences lie between 1 and 37 per 1,000 blood transfusions.[186-188] Most TRs are mild, with common symptoms such as fever, chills, itching, and urticaria, that in most cases resolves without any treatment. Mortality due to TRs are rare and occur in one in 100.000 transfusions with TACO and TRALI as major contributors.[189-191] However, there has been an decrease in rate of TRALI after implementing the exclusion of female plasma donors and use of leukodepleted blood components.[190]

HLA and other leucocyte antibodies are associated with increased risk of TR.[192,193] During pregnancy the levels of human leucocyte antigen (HLA) and granulocyte antibodies increase, which may affect the risk of adverse TR.[193,194] Also red blood cell antibodies are increased in a pregnant population and can cause hemolytic transfusion reactions. Very few studies have assessed TR in relation to pregnancy. In a 2014 study by Teofili et al. an association was found between pregnancy-related hypertensive disorders in women with PPH and TRALI (OR = 27).[195] The retrospective study included 14 cases of possible TRALI in women transfused with three or more units of RBC. The potential mechanism for this association is

far from clear, and the results remain to be confirmed by additional research, which was a motivation for our study, "Incidence and risk factors of transfusion reactions in postpartum blood transfusions" (Paper IV).

### 7.1.2 Transfusion related acute lung injury (TRALI)

TRALI is a clinical diagnosis and has symptoms similar to those of acute respiratory distress syndrome (ARDS). They include increased respiratory rate and hypoxia caused by an inflammatory lung injury and increased microvascular permeability. ARDS is associated with sepsis, pneumonia, complicated surgery, and aspiration of gastric fluid in the transfusion recipient. The risk of mortality is considerable, around 40%.[196]

TRALI is also characterized by acute respiratory distress and occur within 6 hours of a blood transfusion. According to the Canadian Consensus Conference on TRALI, the diagnostic critera criteria of diagnosis are the following:[197]

- 1) Acute lung injury, hypoxemia: SpO2 < 90% or PaO2/FiO2 < 300 mm Hg on room air
- 2) No preexisting acute lung injury before transfusion
- 3) Occurs during or within 6 hours of transfusion
- 4) No temporal relationship to an alternative risk factor for acute lung injury (such as pneumonia, sepsis, aspiration, or multiple trauma)

As with all TR, the incidence of TRALI is uncertain, and the previously reported incidence of 1 in 5,000 transfusions has decreased dramatically after introduction of leukoreduced blood products and the exclusion of female plasma donors as mentioned above.[155,198-200]

The etiology of TRALI is not completely understood, but the leading theory consists of a "two-hit model".[201] In the first hit, a clinical condition exists such as major surgery or infection/sepsis leading to sequestration and priming of neutrophils on pulmonary endothelium. In the second hit, these primed neutrophils are activated by a factor in the blood being transfused, causing an inflammatory response that damages the endothelium and results in pulmonary edema.[202] Anti-HLA or anti-human neutrophil antigen (HNA) antibodies as well as bioactive lipids and soluble mediators from stored platelets, are suggested to be responsible for the activation of the neotrophils.[203] The main source of anti-neutrophil and anti-HLA antibodies is blood from women with prior pregnancies. Thus, the exclusion of female plasma donors has reduced the incidence of TRALI.[200]

Pregnancies complicated by fetal growth restriction and preeclampsia are associated with endothelial modulations that may, in theory, be a cause for the priming of neutrophils on the pulmonary endothelium corresponding to the first hit of TRALI described above.

### 7.1.3 Transfusion-associated circulatory overload (TACO)

TACO is a result of hydrostatic transudate accumulation in the lungs. Its etiology is not clear but is also described as a similar two-hit model. Clinical signs are characterized by acute respiratory distress with hypoxia and pulmonary edema within 6 hours of a blood transfusion. It was introduced as a transfusion reaction in 2006. Although its incidence is probably greatly underestimated it is reported to affect between 1% to 8% of all patients receiving blood transfusions.[184,201,204] As with TRALI it is associated especially with plasma and platelet transfusions, but with the important difference that TACO is a hydrostatic and not a permeability edema. Therefore, patients with TACO respond to diuretic treatment in clinical praxis. Still, TACO has a reported mortality rate of 4% and is associated with between 30% and 44% of all transfusion related fatalities.[205-207] As in the case of every TR, the first action taken is to stop transfusion immediately, administer oxygen, and if TACO is suspected, administer diuretics.

### 7.1.4 Amniotic fluid embolism (AFE)

AFE is a rare but serious complication of pregnancy. It is not considered a TR but has clinical features similar to TRALI. Clinical characteristics include sudden dyspnea, low blood pressure, cardiovascular collapse, and coagulopathy (disseminated intravascular coagulation). The incidence in high resource countries is reported to be 1.7 to 6.1 per 100,000 births and a case fatality rate of 13% to 30%.[208-210] The diagnosis of AFE in surviving cases is probably underreported, and so the true incidence is not known. The etiology is also not fully understood and many theories have been proposed. One such theory holds that amniotic fluid and fetal debris cause an anaphylactic/anaphylactoid (not immunoglobulin E mediated) reaction.[211] However, the expected mast cells degranulation seen in anaphylaxis has not been found.[212] In Paper IV we discuss the possibility that AFE, having both similar risk factors and clinical signs as TRALI, might be the result of an incompatible feto-maternal transfusion triggering an acute hemolytic TR and respiratory distress.[213]

# 8 AIMS OF THE STUDIES

The overall aim of this thesis was to explore prevalence, risk factors and complications of massive blood transfusions in relation to pregnancy, with a special focus on abnormally invasive placenta.

The specific aims of the individual studies were as follows:

I. To investigate the epidemiology, outcomes and risk factors for abnormally invasive placenta in the Nordic countries and determine its rate of antenatal detection.

II. To describe the epidemiology of massive transfusion (MT) postpartum regarding incidence, risk factors, and changes over time; and to assess balanced transfusion (plasma/RBC ratio) in relation to MT and peripartum hysterectomy post partum.

III. To explore whether blood transfusion and postpartum hemorrhage are significant independent risk factors for venous thromboembolism, and whether they should be included in the Swedish thromboprophylaxis algorithm during pregnancy.

IV. To assess whether postpartum blood transfusion is associated with an increased risk of a transfusion reaction compared to transfusion in other recipients.

# 9 METHODS

*Study designs*

Table 4. Studies included

| | Study design | Inclusion criteria | Cases | Statistical analysis |
|---|---|---|---|---|
| Study I<br>Accreta | Population-based cohort | Women who gave birth in the Nordic countries, 2009-2012<br>n = 605,362 | 205 | Cross-tabulation, Chi2 test or Fisher's exact test |
| Study II<br>Massive transfusion | Population-based cohort | Women who gave birth in the Stocholm County, 1990-2011<br>n = 517,854 | 277 | Chi2-test, Student's t-test<br>Multivariate regression analysis |
| Study III<br>VTE | Population-based cohort | Women who gave birth in the Stockholm County, 1999-2002<br>n = 82,376 | 56 | Cross-tabulation,<br>Multiple logistic regression in multivariate analysis |
| Study IV<br>TR | Population-based cohort | Women with PP blood-transfusion in Stockholm County 1990-2011<br>n = 11,842 | 96 | Chi2-test, Student's t-test<br>Cross-tabulation and logistic regression in multivariate analysis |

## 9.1 DATA SOURCES

### Swedish Medical Birth Register (MBR)

The Swedish Medical Birth Register (MBR) is a unique database established in 1973. It includes data of the mother, pregnancy, and the perinatal outcome. It covers more than 97 to 99% of all births in Sweden and has been validated in previous publications.[214,215] The data is standardized and prospectively collected from medical records. Demographic data of the mother, including medical conditions and maternal diagnosis before and during the current pregnancy, as well as medical interventions are registered using International Classification of Diseases (ICD) 9 and 10 codes.

### The Stockholm Transfusion Database

In the Stockholm Transfusion Database (ProSang®, Databyran AB, Stockholm, SE), all transfusions of blood components have been registered in the County of Stockholm since the beginning of 1980. The data includes personal identification number (PIN) of donor and

recipient, blood group of donor and recipient, unique serial number of blood component, the time the blood component was issued, and whether it was transfused or returned. According to national regulations, all transfusions are reported and traceable within the system. The data programme has been validated according to quality standards for IT-systems in health care.

### The Swedish Discharge Register

The Swedish Discharge Register, also called The Swedish National Inpatient Register (IPR), was founded in 1964, but complete coverage dates from 1987. The register includes information on dates of admission and discharge and on diagnosis and interventions according to the Swedish International Classification of Disease (ICD) system. More than 99% of all somatic discharges are registered in the IPR, which records nearly all inpatient diagnoses and surgical procedures. The high coverage and quality of the data has been validated in a 2010 study that found an overall positive predictive value (PPV) of diagnoses in the IPR to be 85% to 95%. .[216]

### Specific data forms and medical charts

In paper I, data on cases with abnormally invasive placenta (AIP) was collected by means of a specific data-form (electronic or paper form) directly from the clinicians to a national representative. In cases identified from MBRs data was collected retrospectively from medical charts and inpatient registers. The data-forms were jointly developed by the members of the Nordic Federation of Societies of Obstetrics and Gynecology study group. The data included information on maternal characteristics, previous deliveries, previous postpartum hemorrhage, previous surgery, antenatal suspicion of AIP, blood loss at delivery, amount of blood transfusion, hemostatic treatments, surgical procedures and postoperative complications.

## 9.2 STUDY POPULATION AND DESIGN

To determine causal relationships, prospective controlled studies are preferred. However, to explore rare outcomes, prevalence, and risk factors, large retrospective observational studies are often the best option. In observational studies both random and systematic errors have to

be addressed. Our studies involved very large sets of data, so the impact of random errors was small. Systematic errors of importance would be risk of confounding, selection bias, and information bias. In all of the studies we conducted, measures were taken to reduce risk of confounding by stratifying data and by careful adjustments in the multivariate logistic regression analysis. In Papers II to IV, the cohort studied was pregnant women in Stockholm County. While this may be considered a selection bias the cohort represents approximately one-third of all births in Sweden. Another possible selection bias was missing data, as seen in the BMI variable. As mentioned in the related papers, data on BMI must be interpreted carefully. The BMI variable was also excluded as an adjusting variable in the regression analysis in Paper IV. Misclassification in coding a diagnosis is a possible information bias. The MBR and the IPR have been previously validated and proven to be of high quality. In Paper I, the number of AIPs in the MBR corresponded to the number of AIPs reported directly by clinicians in Sweden. Any eventual misclassification is most likely to be same in both cases, and in the background populations in Papers II to IV. In all the studies above, odds ratio (OR) with 95% confidence intervals (CI) was used as a measure of risk estimation. However, in studying risk factors for rare outcomes, as in the studies included in this thesis, OR will become a proxy for relative risk (RR).

### 9.2.1 Paper I

This study was conducted between 2009 and 2012 as part of collaboration between the Nordic countries called the Nordic Obstetric Surveillance Study (NOSS). It comprised a population-based cohort study of abnormally invasive placenta (AIP), and included 91% (605,362/ 666,306) of all pregnancies in the Nordic countries. The cohort base was made up of the maternities registered in each country's MBR during the study period. The national coverage of participating clinics was 100% in Denmark, Finland, and Iceland; 80% in Sweden; and 88% in Norway.

Clinicians in the maternity wards surveyed reported cases of AIP to a national coordinator on a monthly basis. Regular reminders were sent to the participating clinics to urge full compliance with the survey. Positive or negative answers had to be mailed back. In case of positive findings, the local representative got informed consent from the cases and a more detailed questionnaire was answered by online registry or on paper. The specific data forms were developed by consensus in a working group of the Nordic Federation of Societies of Obstetrics and Gynecology (NFOG). In Sweden, Finland, and Iceland all cases were

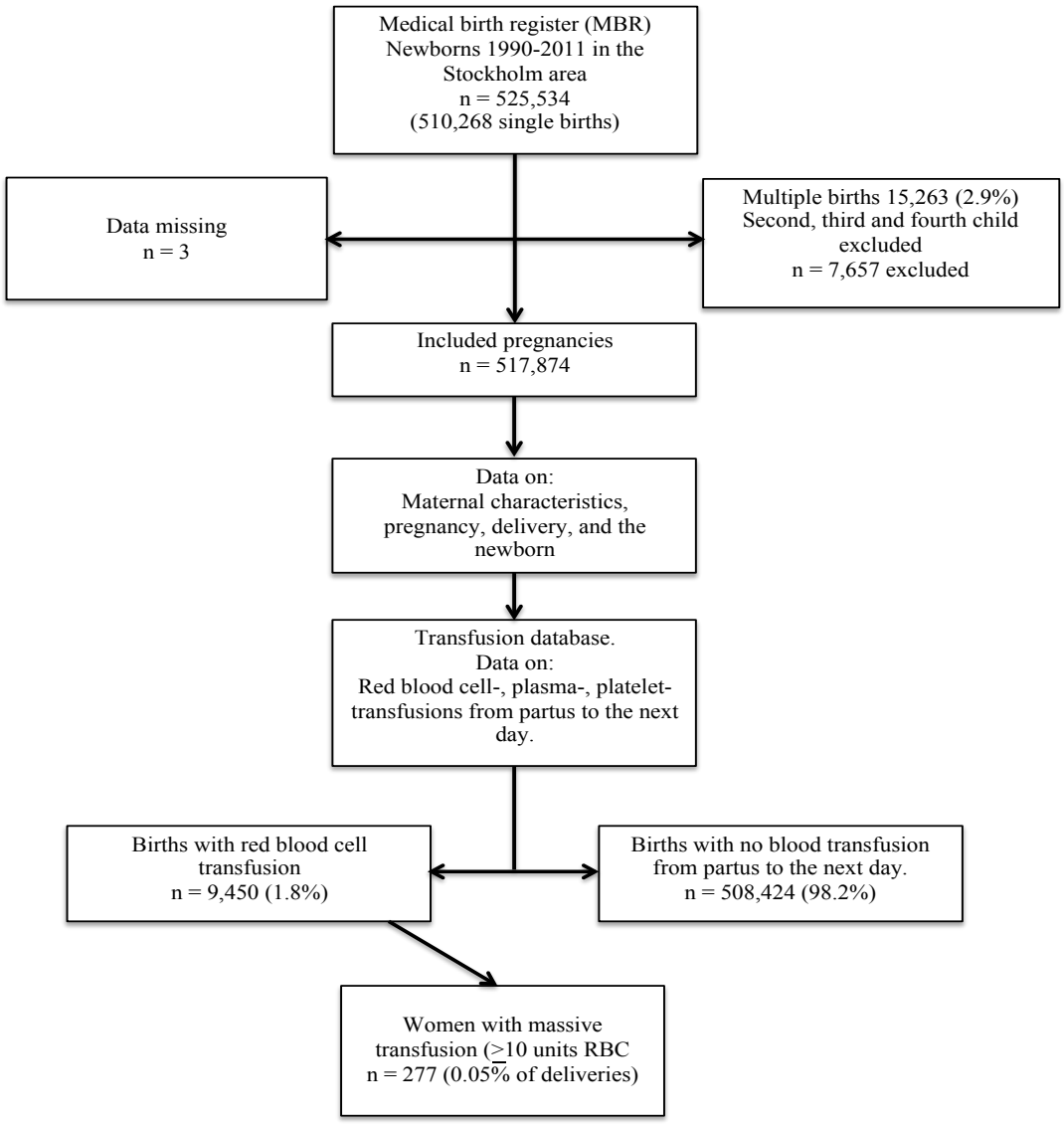
collected prospectively through the reporting system described. The total number of cases was validated against the national MBRs. In Denmark and Norway the majority of the AIP cases (70%) were identified from MBRs and hospital discharge registers. The clinicians responsible verified the cases and reported the information on the data collection forms above. The appropriate international classification of diseases (ICD-10) code (O43.2X) was used.

Cases of AIP were defined as a) women with a cesarean delivery assessed by the attending obstetrician to be AIP, or b) a vaginal delivery in which a laparotomy was needed due to AIP. A total of 205 cases of AIP were identified and included in the analysis. Data collected from Sweden and Finland were stored with the national NOSS representative in each country. Denmark, Norway, and Iceland stored their data in a common database in Denmark. Only aggregated background data from the MBRs were able to be shared in the NOSS studies due to different ethics clearances.

### 9.2.2 Paper II

This is a population-based cohort study including women, whose pregnancy extended over 22+0 gestational weeks and who gave birth in the County of Stockholm between 1990 and 2011. Altogether 525,534 births were registered during the study period, representing about approximately one-third of all deliveries in Sweden. Multiple pregnancies (n = 7,657) were identified and treated as a single pregnancy. Three pregnancies were lacking all data from the MBR and were therefore excluded. The final cohort included 517,854 pregnancies (Figure 16). MT was defined for the purpose of this study as the transfusion of >10 units of RBC within time from partus through the next day. This definition is a modification of the usual definition of MT, i.e., receiving 10 or more units of RBC within 24 hours. The change was due to having the date, but not the exact time, of partus and blood transfusion in the database.

Figure 16. Flow chart of inclusion of pregnancies.




By use of the mother's PIN, data on the mother and the pregnancy could be collected from the MBR and linked to the Stockholm Transfusion Database. The data was merged at the National Board of Health and Welfare (Socialstyrelsen). The final anonymized data included information on maternal characteristics, previous cesarean deliveries, IVF pregnancy, multiple pregnancy, date of delivery, diagnostic and procedural codes during pregnancy and at delivery using ICD 9 and 10 codes, mode of delivery, as well as maternal blood group and number of transfused blood components (RBC, plasma, and platelets).

Characteristics of women receiving between 1 and 9 units of RBC postpartum were compared to women receiving massive transfusion (≥ 10 units of RBC) and to women having no blood transfusion post partum. Risk factors were divided into two categories: a) those apparent before delivery, and b) those evident at delivery.

To determine changes in rate of blood transfusions and rate of peripartum hysterectomy over time, we compared the first 11 years of the study period (1990 to 2000) with the last 11 years (2001to 2011).

### 9.2.3 Paper III

The study was designed as a retrospective cohort study. It included all women who gave birth in the County of Stockholm between 1999 and 2002. We chose a time period before the implementation of the national guidelines for thromboprophylaxis in pregnancy in order to avoid ongoing and unregistered thromboprophylaxis as a confounding factor in assessing venous thromboembolic events (VTE). At that time, only women with a prior VTE, estimated to be 0.3% of all pregnancies, were considered for this prophylaxis.[217] A total of 82,376 deliveries were included, and 56 cases of postpartum VTE were identified in the study.

By means of the unique PIN of the mothers, data from the MBR was linked to the transfusion database (previously described in Paper II) and to the National Discharge Registry (NDR). Women who are hospitalized at least overnight are registered in the NDR with the corresponding diagnoses (ICD-10 codes). To locate cases with VTE at time of delivery the ICD-10 codes O871, O873, and O882 were used. In the study we identified women with a VTE diagnosis from date of delivery through the next six weeks.

Postpartum hemorrhage was defined according to the Swedish ICD-10 criteria as a blood loss of >1000 ml within 24 hours from partus. Finally, women receiving a blood transfusion at the time of delivery were identified by linking the MBR to the transfusion database. Outpatients were not included for two main reasons: At the time the majority of the VTEs were diagnosed by imaging methods such as ultrasound, phlebography or lung scintigraphy and treated in hospital care. The risk for misclassification is reported to increase when outpatient cases are included.[218]

To analyze PPH and blood transfusion postpartum as independent risk factors for VTE, we used multiple logistic regression analysis in consecutive models.

### 9.2.4 Paper IV

This population-based cohort study is used the same cohort as Paper II and included all women who gave birth in the County of Stockholm between 1990 and 2011. Data on

pregnancies and deliveries were linked to the Stockholm Transfusion Database. The merged data included information on maternal characteristics, pregnancy data, blood group of donor and recipient, the time of issue of blood component, number of transfused blood components, and whether a TR occurred or not.

Altogether 517,854 pregnancies were included among which, 11,842 (2.3%) women with a blood transfusion within 7 days of partus were identified. Multiple pregnancies were treated as one case.

Blood components with a recorded TR in women with a postpartum blood transfusion were identified. Maternal characteristics and pregnancy complications in women with a TR were compared to women with a postpartum blood transfusion without a TR. Cases of TR were also compared to the background population of non-pregnant women who had received blood transfusion during the same time period.

In cases of multiple blood transfusions it was not always possible to identify the specific blood component that caused the reaction. Therefore, we chose to analyze incidence of TR as well as rates of TR per transfused blood component (RBC, plasma, and platelets).

The registration of transfusions and TR are regulated by The National Board of Health. After 2005, registration of severe TRs to a National Hemovigilance Register became mandatory. However, since the beginning of 1980 TRs have been registered in the Stockholm County. The clinicians responsible reported unexpected reactions that occurred in relation to a blood transfusion. The involved blood product was returned to the blood bank where the TR was recorded in the transfusion database. Almost 50% of all TR in this study are from 2005 to 2011.The change in registration policy however, should have equal effect on cases and control group.

The TRs were registered as Yes or No data, since we did not have information of the different types of TR.[184]

## 9.3 STATISTICAL METHODS

The statistical calculations in all studies were performed using IBM SPSS v22.0 (SPSS Inc., Chicago IL, US). Continuous data was checked for normal distribution (Shapiro-Wilk test plots) and presented as means with standard deviation (SD). Variables not normally

distributed were presented as medians with interquartile range (IQR). Student's t-test or Mann-Whitney U test were used as appropriate. When possible, continuous variables were categorized and Pearson's Chi-square test or Fisher's exact test was used to investigate differences in proportion. Risk associations were presented as odds ratios (OR) with 95% confidence intervals (CI). Logistic regression was used to control for potential confounders and presented as adjusted risk estimates (OR with 95% CI). Statistical significance was defined as *P*-values < 0.05.

### 9.3.1 Paper I

Frequencies and rates were given per 10,000 deliveries. Risk estimations, expressed as OR, were calculated by cross tabulation with 95% CIs. In this study with a relatively rare outcome, OR will be almost the same as relative risk (RR). Risk profiles for AIP were compared with background population data obtained from the MBRs during the study period. Dichotomous data was analyzed using Chi-square test or Fisher's exact test where appropriate. The different ethical permissions obtained permitted only aggregated data and stratified analysis.

### 9.3.2 Papers II and IV

Normally distributed continuous data were presented as means with +/- SD and not normal distributed data as medians with an IQR expressed as the $25^{th}$ and $75^{th}$ percentiles. Continuous variables were categorized where possible. Discrete data was summarized into frequencies and percentages. Risk estimations were expressed as crude and adjusted OR with 95% CI and were calculated using cross-tabulation and logistic regression. In the multivariate analysis we included variables with $p < 0.1$ from the bivariate analysis.

Data on BMI was incomplete in almost one-third of the cases and was included in the background data but excluded in the multivariate analysis.

### 9.3.3 Paper III

Continuous variables were, where possible, categorized and presented as frequencies and percentages, and normally distributed continuous variables as means and SDs. Not normally distributed variables were presented as medians with its corresponding IQRs.

Associations between a VTE and possible risk factors were calculated in the bivariate analysis by using cross tabulations and presented as OR with 95% CI.

In the multivariate analysis, variables with a *p*-value < 0.1 from the bivariate analysis were included. Absolute risks for main risk factors were presented from the analysis.

RBC transfusions and postpartum hemorrhage are dependent on each other in their association with pregnancy complications (including VTE). For this reason these variables should not be evaluated in the same adjusted analysis in order to avoid over or under estimation of the true OR.

In order to eliminate as far as possible the interactions between the related variables, we created appropriate dummy variables and used different logistic regression models in a step-by-step manner.[219] In each model we included a "dummy variable" in which the variables investigated in the model were excluded. This variable was then used as a reference when adding "step-by-step" variables that might be dependent on each other.

## 9.4 ETHICAL CONSIDERATIONS

All four studies included in this thesis were approved by appropriate national or regional ethics committees. Study I was approved by the Swedish Central Ethics Board for Medical

Research; in Norway by Regional Ethics Committees; in Denmark by the Danish Data Protection Agency; in Iceland by the Directorate of Health and the National Bioethics Committee; and in Finland by the Ministry of Social Affairs and Health. Studies II to IV were approved by the regional ethic committee in Stockholm.

Medical data registers contain sensitive personal information and the use of this data in research might be considered an invasion of privacy. In all research it is important to weigh the risk of harm against the benefits of the research. In the included research presented here the benefits were considered to outweigh the risk of harm.

In very rare outcomes identification might be possible without personal identification number (PIN), but no data was presented on an individual basis.

In Study I the different ethics approvals from the Nordic countries did not allow individual data to be shared between the researchers. Therefore only aggregated background data was

used in the analysis. All the material presented is at the group level and without any possibility of identifying any unique patient.

In studies II-IV data from the MBR and the Stockholm Transfusion Database was cross-linked at the Swedish National Board of Health and Welfare and delivered as anonymized data. All data was presented in aggregated form. All data was kept within the research group of four researchers. Outcomes with very few numbers were excluded. Personal identification was not possible.

# 10 RESULTS AND DISCUSSION:

## 10.1 SUMMARY OF MAIN RESULTS/CONCLUSIONS

Paper I

- The rate of abnormally invasive placenta (AIP) in the Nordic countries is 3.4 per 10,000 deliveries.
- Main risk factor for AIP is placenta previa. Prior CS is associated with a progressively incresed risk of AIP and prior PPH was found to be a novel riskfactor.
- Antenatal detection in the Nordic countries is a low 30% and a focused ultrasound assessment of women at high risk might allow improved predelivery preparations and reduce morbidity.

Paper II

- The rate of massive transfusion (MT) postpartum is 5.3 per 10,000 deliveries.
- Placental abnormalities (placenta previa/AIP) is the major risk factor evident before delivery (adjusted OR = 41).
- Uterine rupture, uterine atony and cesarean delivery are major risk factors evident at delivery (adjusted OR = 38, 17, and 3 respectively).
- Increased awareness of riskfactors for MT and lowering the rate of CS might be the best way to reduce rate of MT postpartum.

Paper III

- Blood transfusion is an independent risk factor for VTE postpartum, but postpartum hemorrhage (PPH) alone is not.
- Blood transfusion should be implemented as a risk factor in the score-based thromboprophylactic algorithm during pregnancy.

Paper IV

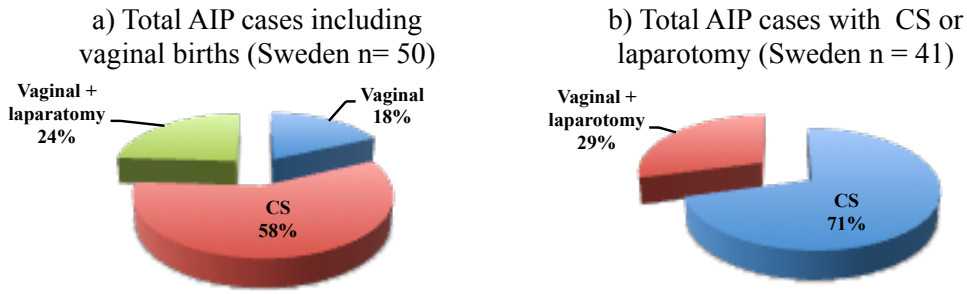
- Transfusion reactions are twice as common in women receiving bloodtransfusions postpartum compared to not-pregnant women.
- Women with preeclampsia have the highest risk (OR = 2) of a TR during pregnancy.
- Blood products should only be administered when necessary and when alternative options have been considered, especially in women with preeclampsia.

## 10.2 PAPER I ABNORMALLY INVASIVE PLACENTA (AIP)

### 10.2.1 Prevalence

Altogether 91% (605,362) of all deliveries in the Nordic countries during the study period from 2009 to 2012 were included in the study. A total of 205 cases of AIP were identified which corresponds to a prevalence of 3.4 per 10,000 deliveries. Only cases with CS or a laparotomy were included in order for the prevalence to represent only severe clinical cases that were assessed to be AIP. When cases with vaginal births without laparotomy were included the prevalence increased to 4.6 per 10,000 deliveries but resulted in a much wider spread in the individual rate of AIP among the participating countries suggesting differences in the interpretation of the case definition.[220] In Sweden, 29% (12/41) of the included AIP cases underwent a laparotomy after vaginal delivery. Nine cases that were assessed to be AIP after vaginal birth, but did not need a laparotomy, were excluded in the final cohort, Figure 17. One case diagnosed in gestational week 13 resulting in termination of pregnancy was also excluded.

Figure 17 (a + b). Cases of AIP in Sweden a) including CS and all vaginal deliveries b) including CS and vaginal deliveries with a laparotomy.




In the Nordic countries, hysterectomy was performed in an average of 47% of the cases, but with a considerable spread (19% to 100%) between the countries. Mean blood loss was 4.6 L and blood transfusion of more than 5 units of RBC occurred in 44% of all AIP cases, suggesting that mostly severe cases of AIP were identified and included in the analysis.

**Table 5. Background data from the Nordic countries and summary of outcomes**

| | Denmark | Finland | Iceland | Norway | Sweden | Total |
|---|---|---|---|---|---|---|
| Data collection period | 4/09-12/11 | 4/09-8/11 | 9/09-8/11 | 9/10- 8/12 | 9/09-8/11 | |
| Months of collection | 33 | 29 | 24 | 24 | 24 | |
| Parturients included | 168,170 | 145,546 | 9,540 | 106,531 | 175,575 | 605,362 |
| Participating clinics | 30 | 31 | 11 | 24 | 40 | 136 |
| Coverage parturients | 100.00% | 100.00% | 100.00% | 87.60% | 79.30% | 90.80% |
| Cesarean section (%) | 21.20% | 16.20% | 14.70% | 16.60% | 16.50% | 17.80% |
| *Outcome study population* | | | | | | |
| Placenta accreta (n) | 85 | 52 | 1 | 26 | 41 | 205 |
| Antenatal awareness (%) | 25% | 42% | 0% | 8% | 34% | 29% |
| Hysterectomy (%) | 19% | 62% | 100% | 54% | 67% | 47% |
| Blood loss mean (L) | 3.5 | 6.8 | 6 | 3.3 | 5 | 4.6 |
| Blood loss $\geq$ 5L (%) | 21% | 37% | 100% | 27% | 39% | 30% |
| Blood transfusion $\geq$ 6 units (%) | 32% | 60% | 100% | 42% | 49% | 44% |
| Maternal death (n) | 0 | 0 | 0 | 0 | 0 | 0 |

### 10.2.2 Risk factors

The main risk factors for AIP were, as expected, placenta previ and prior cesarean delivery. As the different ethical approvals we received only allowed aggregated background-data to be shared between countries solely stratified analysis was performed. Risk of AIP increased 290-fold in the presence of placenta previa. The greatest increased risk (OR = 640) was seen in women over 35 years and older who had a placenta previa and a previous CS. The absolute risk of AIP in this high group was 10%. The number of prior CSs progressively increased the risk of AIP from 7-fold after one CS to 56-fold after 3 or more CSs. This supports findings from other authors that also demonstrate AIP to have a dose-dependent association with prior SC.[32,43,46] We identified a novel risk factor, prior postpartum hemorrhage, which was associated with a more than 6-fold increased risk of AIP. The reason might be occurrence of an abnormally adherent placenta in a previous pregnancy, resulting in manual or instrumental evacuation that caused myometrial damage. Senthiles et al. has reported a recurrence risk of AIP in a future pregnancy to be as high as 30%.[131] High BMI ($\geq$ 30) was more common among cases with AIP than in the background population. The risk of a cesarean delivery is increased in women with a high BMI, which may partly explain this relationship.[79] However, a considerable proportion of cases had no major risk factor and one-fifth of AIP cases were primiparous and with no placenta previa.

### 10.2.3 Antenatal detection

Surprisingly only 29% of all AIP cases were detected antenatally. Finland had the highest rate of antenatal detection, 42%; in Sweden 34% were suspected before delivery. All cases were identified by means of ultrasound. There was no improved maternal outcome among women with antenatal detection, which contradicts what other authors have reported. This may be because only the more severe cases of AIP were detected antenatally. Unfortunately, we could not differentiate the cases into accreta, increta, and percreta. Peripartum hysterectomy was performed more often when AIP was suspected (65%) as compared to cases where AIP was not suspected (45%), ($p = 0.001$).

Among cases with AIP that were not detected antenatally, one-third had a placenta previa and 40% a previous CS. In the Swedish cohort, vaginal bleeding before delivery was present in 42% (17/41) of women with AIP, and in this group AIP was suspected only 41% of the time (7/17).

### 10.2.4 Conclusions

The overall prevalence of AIP in the Nordic countries was 3.4 per 10,000 deliveries, using a strict clinical definition that included only cases with CS or laparotomy after vaginal birth. Prior PPH was a novel major risk factor (OR = 6.5) that should be considered in risk assessments for AIP. We found that placenta previa is the single most important risk factor, with the number of prior CS progressively increasing the risk of AIP.

It is a concern that more than two thirds (70%) of all AIPs are not identified before delivery. A screening policy, with a focused ultrasound on a well-identified risk group for AIP might allow better planning and surgical preparation of the delivery, hence improve outcomes. However, the most effective way to decrease the occurrence of future AIPs appears to be by lowering the rate of cesarean deliveries.

### 10.2.5 Discussion

There is a wide spectrum of reported incidences of AIP, ranging from 2 to 90 per 10,000 deliveries. This can be accounted for because of a lack of uniformity in definitions of AIP, varying study designs, and possible differences in maternal characteristics. The prevalence of AIP in the Nordic countries was 3.4 per 10,000 deliveries, which is at the lower end of what has been reported previously. This might reflect the fact that for the last few decades the

Nordic countries have had lower rates of cesarean deliveries than many other high resource countries. Our study showed a difference in observed prevalence of AIP between the participating countries ranging from 1.1 to 4.9 per 10,000 deliveries (Table 5). In Denmark the prevalence of AIP was twice as high as Sweden, which might in part be explained by a higher rate of prior cesarean deliveries in Denmark. Also, despite our efforts to minimize inclusion bias (and to exclude vaginal births with potential cases of placental retention), there might have been differences in interpreting the definition of AIP. However, the study was not designed to explain differences between countries, since the frequencies of AIP were too small to accomplish this. For example, Iceland contributed with only one case of AIP. A limitation of our study might be the lack of histopathological results. However, our purpose was to use a definition that reflected the most clinically severe cases. Histopathological examinations are only possible in cases of hysterectomy, partial resections, or death. Today, great effort is being made to preserve the uterus and fertility, which makes histopathological examinations difficult and would exclude severe cases of AIP from the study. Also, there have been reports of normal histopathological findings in cases with clinically verified cases of placenta accreta at time of delivery.

A major finding was the surprisingly high proportion of cases (70%) not diagnosed antenatally. Although our study did not show that early detection of AIP led to an improved outcome several other studies have reported less complications, especially if patients were referred to a specialized center.[69] One reason for this discrepancy might be that only the worst cases of AIP were detected antenatally, or that early detection did not lead to a referral to a dedicated medical center with multidisciplinary team care. In order to improve the rate of antenatal detection, well-defined criteria for an AIP are needed. Women with a placenta previa (about 0.3% of the pregnant population) or women with a previous CS (about 10% of the pregnant population in Sweden) and low-lying placenta over the uterine scar (about 0.5% of the pregnant population) would adequately define a high-risk group.[221] Antenatal detection of AIP using ultrasound has demonstrated with high sensitivity and specificity (70% to 90%).

If a focused ultrasound addressing AIP were to be performed on this subgroup of women during gestational weeks 24 to 28, antenatal detection of AIP would most likely increase and allow pre-delivery planning with a multidisciplinary team. Such precautions might decrease the rate of maternal morbidity, such as severe blood loss, excessive blood transfusion, and surgical complications.

Assuming that ultrasound in assessing AIP has 80% sensitivity and 90% specificity on a subgroup of pregnant women with a placenta previa and previous cesarean delivery with

placenta over the uterine scar (approximately 0.8% of pregnant population). A focused ultrasound on these high-risk women would almost double the rate of AIPs detected before delivery, compared to the detection rate in the present study. In the studied cohort constituting of approximately 600,000 pregnancies, 4800 women would be assessed for AIP using ultrasound. Theoretically, out of the expected 141 (205-64) cases of AIPs in this group, 113 (141 x 0.8) cases of AIP would be detected antenatally, compared the total of 60 (29%) cases that was suspected before delivery in our study. An almost doubling (88%) of suspected AIP cases.

The major strengths of this study are its large size (the largest of its kind at the time); its design, which prospectively collected data directly from the responsible clinicians; and the ability to use the medical birth registries for background data and verifying number of AIP cases. There was a difference between the countries in data collection (described above), which might have caused an underestimation of the prevalence of AIP. Due to ethics constraints and restricted data access, we were limited to using aggregated data and could not perform adjusted analysis. However, by employing stratified analysis, risk factors with odds ratios and risk groups could be described.

## 10.3 PAPER II MASSIVE TRANSFUSION (MT) IN OBSTETRIC PATIENTS

### 10.3.1 Prevalence and trends

In total 517,874 pregnancies were included in the study and we found that among them a blood transfusion of at least one unit of RBC was administered in 9450 women (1.8%) from partus through the next day. MT occurred in 5.3 per 10,000 deliveries (277 women). The median number of transfused RBC units was 2 and the highest number of transfused units was 73. Among women receiving MT, plasma was transfused in almost all of the cases (276/277), as compared to platelets which were administered in only 67% of cases with MT.

To discover changes in rate of RBC, plasma and massive transfusion over time the first 11 years was compared to the last 11 years of the study period. The prevalence of RBC transfusion and MT both increased significantly by 40% and 30%, respectively (Table 6). During the study period a total of 110 (2.1 per 10,000 deliveries) peripartum hysterectomies were performed and a hysterectomy was performed in 17% of women with MT; (Table 6). Notably, the rate of hysterectomies did not increase over time. However, the proportion of

MT among cases with hysterectomy did increase dramatically from 24% in the first eleven years to 60% in the last eleven years ($p < 0.001$).

Table 6. Transfusion of blood components and hysterectomies over time comparing the first eleven years with the next eleven years

| Event | 1990-2000 Cases (n) | (%) | 2001-2011 Cases (n) | (%) | Total (n) | Trend (%) | P-value |
|---|---|---|---|---|---|---|---|
| Total deliveries | 240,934 | 100.00% | 276,940 | 100.00% | 517,874 | 115% | n/a |
| Delivery with CS | 27,336 | 11.35% | 54,542 | 19.69% | 81,878 | 174% | < 0.001 |
| Previuos CS | 15,798 | 6.56% | 27,190 | 9.82% | 42,988 | 150% | < 0.001 |
| RBC transfusion | 3,645 | 1.51% | 5,805 | 2.10% | 9,450 | 139% | < 0.001 |
| Plasma transfusion | 959 | 0.40% | 1,331 | 0.48% | 2,290 | 121% | < 0.001 |
| Platelets transfusion | 71 | 0.03% | 340 | 0.12% | 411 | 417% | < 0.001 |
| RBC ≥10 units | 110 | 0.05% | 167 | 0.06% | 277 | 132% | 0.003 |
| Hysterectomies | 50 | 0.02% | 60 | 0.02% | 110 | 104% | n/s |
| Hysterectomies with MT | 12 | 24.00% | 36 | 60.00% | 48 | 250% | < 0.001 |
| Uterine rupture | 104 | 0.04% | 306 | 0.11% | 410 | 256% | < 0.001 |
| PPH* | 15,414 | 6.40% | 21,971 | 7.93% | 37,385 | 124% | < 0.001 |

n/a = not appliable; CS = Cesaerean Section; RBC = Red blood Cell; n/s = not significant

MT = Massive blood transfusion; PPH = Postpartum Hemorrhage

* 1990-1996 PPH dignosed as estimated hemorrhage >500ml and from 1997 and forward >1000ml

### 10.3.2 Risk factors

Risk factors were divided into risks those apparent before delivery and those evident only at the time of delivery. Major risk factors detectable before delivery were the placental complications; AIP and placenta previa. These complications combined showed a 41-fold adjusted increased risk for MT. This is especially important, since only 30% of all cases of AIP are identified antenatally, according to the study in Paper I.[222] Other major antenatal risk factors with at least a 3-fold increased risk were prior cesarean delivery, preeclampsia/abruption, and age > 40 (adjusted OR = 4, 4, and 3, respectively).

Major risk factors for MT at delivery with a more than 3-fold increased risk, were uterine rupture (adjusted OR = 38), atonic uterus (adjusted OR = 17), and cesarean delivery (adjusted OR = 3).

### 10.3.3 Balanced transfusion (plasma/RBC ratio)

Balanced transfusion is described as a high plasma/RBC ratio or a high rate of plasma and platelets transfusion. A recent review of MT protocols in obstetrics by Tanaka et al. found a

plasma/RBC ratio ≥ 1 associated with an improved maternal outcome.[162] In our study we found the overall plasma/RBS ratio to be 0.7 in women with MT. There was no difference between the two decades we compared. Plasma transfusion occurred in all but one case of MT. Only 15% had a plasma/RBC ratio above 1.0. The transfusion of platelets in cases with MT increased from 40% in the first half of the study period to 80% in the second half. The effect of the higher platelet rate on outcomes could not be evaluated further in this study.

### 10.3.4 Conclusions

The prevalence of MT postpartum is 5.3 per 10,000 deliveries and has shown an increasing trend. Major risk factors that can be identified antenatally are abnormal placentation and prior cesarean section (OR 41 and 4, respectively). Identifying women at risk and lowering the rate of CS might be the most effective way to reduce the frequency of MT postpartum. In women receiving MT, the plasma/RBC ratio was 0.7 and did not increase during the study period. A higher plasma/RBC ratio (> 1.0) has been suggested as potentially improving outcomes in cases with MT postpartum. Finally, the increase of MT in cases involving peripartum hysterectomy is a concern that might be associated with higher frequency of placental abnormalities and obstetricians having less surgical training. However, this theory, remains to be explored in future studies.

### 10.3.5 Discussion

The reported incidences of MT postpartum vary widely and ranges from 2.3 to 9.1 per 10,000 deliveries. The use of different definitions and reporting systems makes direct comparisons difficult. A prospective study from the UK reported the lowest incidence of 2.3 per 10,000 deliveries.[136] However, they defined MT as transfusions of 8 or more units of RBC within 24 hours as compared to the definition of 10 or more units of RBC from partus to the next day in our study. Both studies could link data directly to a high-quality transfusion register, which represents major strength in comparison to voluntary reporting system used in other studies.[8]

In comparing results from two recent Dutch studies (2004 to 2006 and 2011 to 2012) they could report a decreasing trend in the rate of MT (9.1 to 6.5 per 10,000 deliveries) using the same definition as in the UK study.[223] Interestingly the also reported an increase in the case fatality rate from a low 0.9% to 2.3%. In our Study the transfusion rate of 8 or more units of RBC postpartum was 8.5 per 10,000 deliveries. The reported difference in incidence of MT is

most likely due to a more liberal transfusion policy in the Netherlands and Sweden than in the UK.[158,223] Finally, our findings are in agreement with a 2013 US study that found rate of massive transfusion (defined as transfusion of 10 or more units of RBC) in obstetric patients to be 5.9 per 10,000 deliveries. The best clinical definition of MT is still unresolved. The definition of MT should reflect clinically acute and life-threatening hemorrhages. Therefore a more appropriate definition might be the transfusion of 4 or more units of RBC within 4 hours, a definition proposed by Morena et al.[150]

In order to prevent unnecessary bleeding and take early hemostatic action it is important to identify risk groups for MT. It has been reported that 54% to 93% of maternal deaths due to hemorrhage in the US was associated with suboptimal medical care.[145] By separating risk factors before and at delivery it becomes more evident in a clinical situation what should be focused on in the risk assessment during pregnancy and at delivery. In this study we found that the single most important risk factor was abnormal placentation, (OR=41) a condition that is known to increase with the number of previous CSs.[32] Uterine atony is still the major cause of ordinary PPH. In our study we found uterine atony as a cause of MT in only 18% of all cases, far less than the 65% reported for ordinary PPH.[34] We conclude that uterine atony is the major risk factor for PPH and placental complications are the major risk factor for MT. Women with PPH and women receiving MT seem to have different risk profiles.

Rate of peripartum hysterectomy was 2.1 per 10,000 deliveries, which is lower than the average rate reported from the 2015 Nordic Obstetric Surveillance Study (NOSS) (3.5 per 10,000 deliveries).[37] NOSS described a broad span in incidence between countries, ranging from 2.0 to 5.1 per 10,000 deliveries. The variations in incidence suggest differences in policy towards peripartum hysterectomy. They also studied a later time period, 2009 to 2012, which may include higher frequencies of women with prior CS and pregnancies complicated with AIPs, which may partly explain their higher rate in peripartum hysterectomy.

Although the rate of peripartum hysterectomy did not increase over time during the study period, the fact that the proportion among women with a hysterectomy who needed MT increased by 150 % in the last decade of the study period is troublesome. The reason for this is not evident. Hysterectomies might have become more complicated due to an increasing rate of placental abnormalities such as AIPs and placenta previa.[32,45,51] This is supported by a Nordic study from 2015 that found AIP to be the major cause for acute peripartum hysterectomy.[37] Another reason could be that obstetricians have become more reluctant to perform a hysterectomy because of a patient's wish to preserve the uterus; or it might even be due to a lack of surgical training among obstetrician because of early specialization in

gynecology or obstetrics as was suggested in a recent study from France.[224] The UK study reported a much higher rate of hysterectomies among women with MT, 45 %, compared to 17 % in our study, which is difficult to explain but might have contributed to their lower rate of MT.[136]

Plasma is not an internationally standardized product; different preparations, such as fresh frozen plasma (FFP), thawed plasma, never-frozen liquid plasma, and pathogen inactivated plasma are used. In each of these preparations the methods and quality differ, e.g., the volume of a plasma unit and the preparation method differs, and thawed and liquid plasma may be stored for different periods of time. In addition, cryoprecipitate is used in many hemorrhage protocols. It is, therefore important to be careful when interpreting the reported plasma/RBC ratios from different studies. During the first 10 years of the study period liquid plasma, stored up to 14 days, were most often administered, but today, FFP is the dominant plasma product transfused in Sweden. Internationally, FFP is also most commonly used. FFP and stored plasma have a volume of about 270ml. FFP contains a higher level of labile coagulation proteins, such as factor VIII and FV, compared to stored plasma. SD plasma is a pooled product from > 1000 donors. It is not used routinely in Sweden, but used on specific indications. In the US and in the UK cryoprecipitate is in general use. Cryoprecipitate is prepared by precipitation of the large coagulation factors in a plasma unit. These are fibrinogen, factor VIII, factor XIII, and von Willebrand factor (vWF). Normally one cryoprecipitate transfusion is made from a pool of 5 units of FFP. Most guidelines concerning severe obstetric hemorrhage recommend that the plasma/RBC should be at least 1:1. Our results show that only 15% of the cases with MT had a plasma/RBC ratio > 1 which suggests that the bleeding protocols may be improved. The optimal rate of platelet transfusion is not known, but in Sweden a 4/4/1 ratio of plasma/RBC/platelets is recommended in the bleeding protocols.

## 10.4 PAPER III BLOOD TRANSFUSION AND POSTPARTUM HEMORRHAGE (PPH) AS RISK FACTOR FOR VENOUS THROMBOEMBOLISM (VTE)

### 10.4.1 Prevalence

A total of 82,376 women were included in this study, among whom 56 suffered a venous thromboembolic event (VTE). A pulmonary embolism (PE) was identified in 21 (38%) of the

cases. The prevalence of postpartum VTEs of 0.7 per 1,000 deliveries is similar to what has been reported from Norway by Jacobsen et al. (0.5 per 1,000), from Sweden by Lindqvist et al. (0.6 per 1,000), and from the US by James et al. (0.9 per 1,000).[25,28,176] The rate of PE was 0.25 per 1,000 in our study, compared to 0.22 per 1,000 reported by Jacobsen. The Norwegian study was a register-based case-control study and included 600,000 pregnancies. The characteristics of the pregnant populations in Norway and Sweden are likely to be similar, and one would expect to find analogous prevalence of VTE.

### 10.4.2 Risk factors

In the initial bivariate analysis, BMI $\geq$ 30, multiple pregnancy, preeclampsia, placental complications, postpartum anemia, cesarean delivery, postpartum hemorrhage, red blood cell transfusion, plasma transfusion, and platelets transfusion were associated with an increased risk of VTE. In multivariate analysis, different adjustments significantly influence the estimated ORs.

In all of the adjustments made in the analysis, cesarean delivery (OR = 3) and preeclampsia (OR = 6) remained as significant and independent risk factors for VTE in the postpartum period. These findings confirm the findings of several previous authors.[27,225,226] Among women with VTE in our study, 16% had RBC transfusion and 20% had PPH. There were no significant differences between the RBC and the PPH groups regarding age > 40, BMI > 30, IVF, cesarean delivery, or preeclampsia.

By performing different regression analysis in a consecutive manner, we systematically evaluated a) RBC transfusion, and b) PPH as independent major risk factors for VTE.

In the first model assessing RBC transfusion, adjusting for age (> 40 years), BMI > 30, multiple pregnancy, blood group non-O, CS, and placental retention, we found RBC transfusion and preeclampsia/abruptio to be 5-fold and 7-fold increased risks (OR) for postpartum VTE. The combination of these risk factors was related to a 15-fold increased risk. Preeclampsia and placental abruption are measures of the same entity and were for this reason combined into one variable (preeclampsia/abruption). If divided into separate variables their risk might be underestimated and the analysis less stable due to few cases.

In the second model assessing PPH, adjusting for age (> 40 years), BMI > 30, multiple pregnancy, blood group non-O, CS, and placental retention, we found PPH and preeclampsia/abruptio to be 2-fold and 8-fold increased risks for VTE. However, the

combination of these two risk factors did not increase the risk of VTE more than preeclampsia/abruptio alone. Thus the addition of PPH did not improve the risk estimate.

In the third model we showed that the risk of VTE increased 3-fold with transfusion of 1 to 3 units of RBC and 5-fold when > 3 units were transfused.

In the fourth model, *representing the main outcome*, assessing both PPH and RBC transfusion for the risk of VTE, adjusting for age (> 40 years), BMI > 30, multiple pregnancy, blood group non-O, CS, placental retention and preeclampsia/abruptio, we found that PPH alone (without RBC transfusion) was not a significant risk factor for VTE, but transfusion of RBC was. Thus, of the two possible risk factors measuring a similar cause, only RBC transfusion was a valid risk factor for VTE.

In the fifth model assessing RBC and plasma transfusion we show that the combination of RBC and plasma transfusion seems to lower the risk of VTE, as compared to RBC transfusion alone.

In summary, we found that PPH was not an independent risk factor for VTE while RBC transfusion was related to a five-fold increased risk (OR = 5), when confounding for placental complications (preeclampsia/abruptio placenta). The risk increased by the number of transfused units (Table 7). The estimated absolute risk of postpartum VTE in women with a transfusion of > 3 units of RBC was almost ten times higher than the background risk (6.0 compared to 0.7 per 1,000 deliveries).

Table 7. Risk (OR) of VTE by number of transfused units of RBC.

| Amount of RBC Transfusion | Control group n=82320 | VTE group n=56 | OR | 95% CI |
|---|---|---|---|---|
| none | 80353 | 47 | 1 | reference |
| 1-3 units RBC | 1340 | 5 | 3.1 | 1.1-8.4 |
| >3 units RBC | 627 | 4 | 4.9 | 1.6-15.2 |

### 10.4.3 Conclusions

A transfusion of RBC at delivery is an independent major risk factor for postpartum VTE and thus should be included in thromboprophylactic guidelines during pregnancy. PPH without RBC transfusion, on the other hand, was not an independent risk factor for VTE.

### 10.4.4 Discussion

The primary aim of this study was to assess blood transfusion and PPH as independent risk factors for PPH. To evaluate the true risk of VTE, we required a study population that existed before the introduction of thromboprophylaxis guidelines in Sweden, and we therefore chose a study period from 1999 to 2002.

In the study we clearly show the impact of different adjustment models. If common pregnancy complications, such as preeclampsia and abruptio placenta, were not adjusted for, PPH alone (no blood transfusion) would still be considered a major risk factor for VTE.

RBC transfusions and the association of PPH with VTE have been investigated by previous authors. They have all reported increased risk of PPH, but different ORs, depending on study design and inclusion criteria.[176,225,227,228] They did not, however, consider the confounding effect of the RBC transfusion or, in some studies, the effect of cesarean delivery, preeclampsia, and placental abruption on the risk of VTE.[178,225 226] By performing the systematic step-by-step logistic regression analysis described above, we were able to explain that the major part of the heterogeneity in risk estimates (OR) depends on which factors are included in the adjustments.

Blood group non-O is associated with higher levels of factor VIII and vWF factor, and it has been suggested that individuals with these blood groups have an increased risk of VTE and preeclampsia.[229] However, blood group non-O showed a non-significant increased risk of 70% in the crude estimations and was therefore, not included in the adjusted analysis that followed.

## 10.5 PAPER IV RISK OF TRANSFUSION REACTIONS DURING PREGNANCY.

### 10.5.1 Incidence

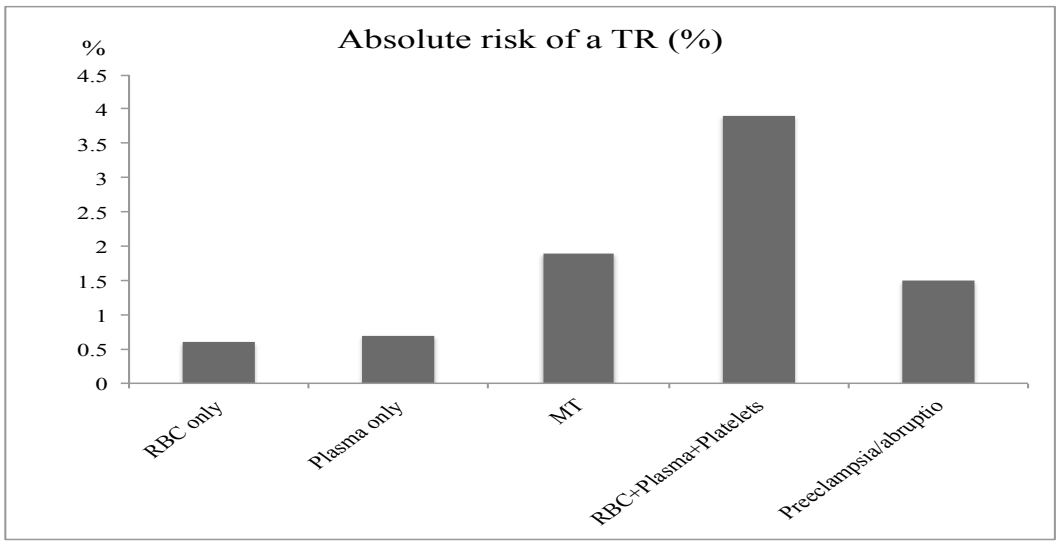
The cohort studied included 517,854 pregnancies, the same as in Paper II. A total of 12,183 women were identified who received at least one unit of RBC, plasma, or platelets from the time of partus through the next seven days. This corresponds to an incidence of 2.3% and is at the higher end of what has been reported from other high resource countries.[8,9,26]

The risk of a TR was more than doubled in women with a blood transfusion postpartum, compared to the background population consisting of age-matched non-pregnant women (OR = 2.0, 95% CI 1.6 – 2.5). In total 96 women (0.8%) were identified with a TR postpartum, compared to 3,436 (0.4%) in the background population.

There was no difference in the rate of female RBC or plasma donors (47.1% with no TR and 52.2% with a TR, *p*-value = 0.147) or in the proportion of plasma transfused in the two groups.

A TR occurred in almost 2% (6/309) of women receiving MT (≥ 10 units of RBC within 2 days from partus). Surprisingly, the highest rate of TRs, (5,5%) was seen in women who received just one unit of RBC, probably because further transfusions that were planned were cancelled when an adverse reaction occurred. After the first unit was transfused, the risk of a TR increased with the number of RBC units being transfused, and with the addition of plasma and platelets. When a combination of RBC, plasma, and platelets were transfused, the absolute risk for a TR was 4% (Figure 18).

Figure 18. Absolute risk of TR in women receiving blood transfusion postpartum.



### 10.5.2 Risk factors

Significant risk factors among women with postpartum blood transfusion were preeclampsia, induced labor, and premature delivery < 34 gestational weeks.

After adjustments in a multivariate logistic analysis, preeclampsia remained as the dominant risk factor and was associated with a two-fold increased risk of a TR postpartum (OR = 2.0, 95% CI 1.2–3.5).

The increased risk due to induced labor or premature delivery was OR = 1.7 in either case.

Other significant risk factors from the initial bivariate analysis did not remain after adjusting for confounders. In these variables the increased risk most likely stands for their association with hemorrhage and blood transfusion, not TRs.

### 10.5.3 Conclusions

Pregnancy seems to be associated with an increased risk for TRs. The awareness of this risk might contribute to considering alternative options to administering blood products to women postpartum and an overall reduction of blood transfusions.

In women with preeclampsia and postpartum blood transfusion, particular attention to clinical signs of a TR is recommended.

### 10.5.4 Discussion

Prevalence estimates of TR vary widely based on reporting systems and study design. An active reporting system has higher reported rates than systems with passive reporting. [230] There is also a risk of comparing different form of rates as rates can be reported per patient, per unit, or per hospital. Moreover, most TRs are underreported. Therefore, the true prevalence of TR is not known, and comparisons between studies must be interpreted with caution. Other authors have reported a prevalence between 0.1% and 4%, which renders the background rate of 0.4% in our study acceptable.[230,231]

A major strength of our study is the ability to compare the rate of TR in postpartum women to a large background population of non-pregnant women using the same system of registration and definitions. We found that women with postpartum blood transfusion were associated with a two-fold increased risk (OR = 2.0) of TR, compared to non-pregnant women. The two

groups were age-matched but the background population probably included severely ill persons who might have had an affect on the rate of TRs. On the other hand, symptoms in healthy young women were more unexpected and therefore might have been more likely recorded than similar TRs in the background population.

Unfortunately, we were not able to divide the TRs into different pathophysiological subtypes. In Sweden registration of transfusion of blood components are regulated by the Swedish National Board of Health. In Stockholm County, TRs have been registered since1980 and it has been mandatory since 2005 to report severe cases of adverse TRs to a National Hemovigilance Register. This is probably the main reason for the increased rate of TR seen during the last years of the study period. Almost half (47%) of all TRs in our study period were registered between 2005 and 2011.

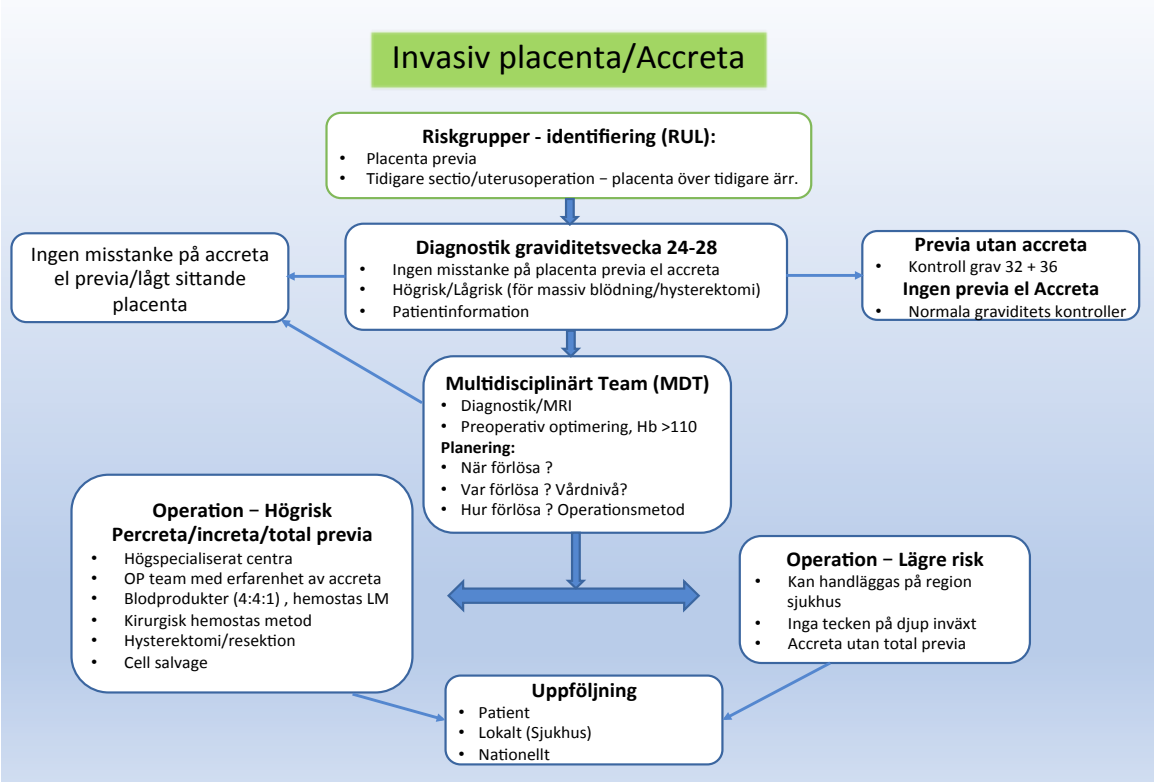
Few studies have investigated TR in relation to pregnancy. Among women with a postpartum blood transfusion, we found that those with preeclampsia had a two-fold increased risk of TR. This is in agreement with a study by Teofili et al. They found that women with gestational hypertension had an increased risk of TRALI (OR = 28). However, they retrospectively diagnosed possible TRALI from medical charts among women who had received 3 or more units of RBC postpartum. This might have caused the higher OR. However, even though the specific ORs cannot be directly compared, both studies found preeclampsia to be a major risk factor for TRs, which should be considered in clinical praxis concerning blood transfusion postpartum. The etiology of TRALI is far from clear, but the two-step theory with the initial priming of neutrophils on the pulmonary endothelium by an illness could well apply to preeclampsia. A pregnancy complicated by severe preeclampsia has an endothelial dysfunction.[232]

We also speculate that the amniotic fluid embolism syndrome could, in fact, be a TR caused by a fetomaternal transfusion with a similar mechanism as in TRALI. Induced labor seems to be associated with TRs and with the risk of a fetomaternal transfusion, which is in congruence with this theory.

# 11 MAIN CONCLUSIONS – CLINICAL IMPLICATIONS

AIP, massive postpartum blood transfusions, VTEs postpartum, and adverse TR are all potential severe complications of pregnancy. As shown in the research supporting this thesis, they are all directly or indirectly associated with one another. Together they stand for approximately half of the maternal mortality in high resource countries.[7] A major risk factor for VTE and TR is MT, and the single most important risk factor for MT is abnormal placentation. These complications also share an association with prior CS. A long-term strategy that is highly likely to help reduce the rate of AIP and, as a consequence, MT is to avoid unnecessary cesarean deliveries. A further critical strategy to reduce morbidity in relation to pregnancy is to institute improved risk assessment and identification of certain high-risk groups. As an example of this, the results from Study I on AIP, describing the very low rate of antenatal detection (< 30%) of AIP in the Nordic countries, has motivated and contributed to the Swedish national guidelines on diagnosing AIP (produced by the national working group of obstetric ultrasound (Ultra-Arg) in 2018). This work has further led to Swedish guidelines on management of AIP (to be published in 2020). A flowchart summarizing suggested management of AIP is presented in Figure 18.

Figure 19. Management of AIP in Swedish (by permission of the Swedish National Working-Group on Management of AIP)



Blood transfusions can be lifesaving, and in developing countries lack of blood transfusions cause maternal death. At the same time, all blood transfusion should be well motivated and alternatives to blood transfusion should be considered whenever possible. Most blood transfusions today are safe; but, as shown in Papers III and IV, there are concerns about VTE and adverse TRs. Especially in women with preeclampsia, heightened attention to the risk of TR is advisable.

As a member of the National Working Group for Hemostasis in Obstetrics and Gynecology, I have participated in many discussions on how to improve the prophylaxis of pregnancy-related VTEs. One frequently asked question was whether hemorrhage or blood transfusion should be considered major risk factors. Previous studies have indicated an increased risk, but whether this applied to all PPH or only to large hemorrhages following blood transfusion was unclear.[225,227] Such uncertainties motivated our study. In it we showed that PPH alone was not an independent major risk factor for VTE. RBC transfusion, however, *was* a major risk factor, bringing with it a 5-fold increased risk for VTE, and a risk which increased by the number of transfused RBCs. Today blood transfusion is implemented as a major risk factor in the Swedish thromboprophylactic algorithm during pregnancy. Remarkably, the transfusion of plasma seems to lower the risk of VTE. In the study we speculate that early plasma transfusion might retain the balance between coagulation and fibrinolysis, hence reduce the risk of VTE.

The trend toward increasing blood transfusions is of concern. It is costly and might have both short and long term consequences as described above.

Awareness of the increased risk of a TR might help the clinician opt for alternative treatments. Especially in pregnancies complicated by preeclampsia. In women with a combination of preeclampsia and certain erythrocyte antibodies (Anti-Lea), rare but severe reactions have been described.[233] An increased awareness of TRs could lead to reduced morbidity by heightening early detection and treatment, i.e. stopping the transfusion, administering oxygen, and also diuretics in cases of TACO.[195,233] TRALI is a clinical diagnosis with uncertain etiology that used to be one of the leading causes of transfusion related mortality but after implementing the use of only male plasma-donors and leukodepletion it is now much more scarce. Never the less, the inflammatory process plays an important role in the development of TRALI. Recent research has indicated that an anti-inflammatory cytokine, interleukin-10, might be a possible future treatment.[234] Another anti-inflammatory substance is ASA, commonly used as prophylaxis for severe preeclampsia. Whether the anti-inflammatory drugs, such as ASA and hydroxychloroquine, could lower the

risk of TRs in women with preeclampsia has not been investigated; but it may be a topic for future studies and could perhaps complement the ongoing Impact trial on preeclampsia in Sweden.

# 12 FUTURE PERSPECTIVES

The purpose of the present research has been to contribute to the understanding and medical care of rare obstetric complications. It is hoped that the papers included here have added to the accumulated knowledge of AIP, massive blood transfusions and complications of blood transfusions, in relation to delivery. They have also attempted to raise new questions and indicate areas that need to be addressed by future research.

- Management of AIP changes over time. During the past decade, diagnostics have improved and new surgical techniques have been introduced. National guidelines suggesting more standardized care protocols using a multidisciplinary approach have been published. How these changes in approaches to treatment of AIP have been implemented and how they may have affected outcomes in Sweden and in the Nordic countries is not fully known. The management of AIP today differs from clinic to clinic, partly due to a lack of consensus on what constitutes best medical practice.

  To further improve clinical management and be able to make recommendations on ultimate levels of care and best surgical approaches, it would be of great value to conduct a follow-up study on detection rate, management, and outcomes of women with AIP in Sweden and the Nordic Countries. The study design of Paper I, which used a prospective obstetric surveillance system together with data from the National Birth Register, attempted to insure high quality data and a low level of missing cases. To add data from the National Transfusion Database would have further increased the data quality. Lessons learned from the previous study (Paper I) include maintaining close contact with all involved centers on a regular basis, and assigning specific clinicians the responsibility for reporting cases at each clinic. There should be complete agreement on a strict definition that has clear clinical relevance. In diagnosing AIP, the use of three-dimensional power doppler ultrasound should be incorporated and further evaluated.[235] A standardized protocol (clinical grading system), as suggested by Collins et al., would be the most preferable method to ensure a uniform definition of the AIP cases included and to separate the percretas from the

less severe forms of AIPs. Morevover, the percretas should be analyzed separately, since they require special resources and have the highest risk of severe complications.

Further, ethics permission should be obtained to allow adjusted regression analysis to go beyond aggregated data and stratified analysis. Finally, data on histopathological findings should be included. Steps have already been taken in a Nordic collaboration and in the Swedish working group to begin a follow-up study in the Nordic countries.

Another study of interest would an investigation of best surgical techniques and the best method for devascularisation when performing a hysterectomy or local resection of the uterine wall. Endovascular procedures have not been compared to extravascular techniques in prospective randomized trials. The trend towards uterine-saving techniques, such as local resection, or leaving part or the entire placenta in situ to give women a chance for future pregnancies rather than performing a hysterectomy, has been investigated in observational studies, but multicenter RCTs are needed to be conclusive. Studies addressing these issues are needed in order to provide women with reliable information and recommend evidence-based treatment.

- Amniotic fluid embolism (AFE) is a rare obstetric condition with an unclear etiology. As described in Paper IV, its symptoms are similar to those of TRALI and of acute hemolytic transfusion reactions. In fatal cases, arrhythmia, sudden hypotension, disseminated intravascular coagulopathy, pulmonary edema, and cardiovascular collapse have been reported. Hemolysis often leads to high potassium levels that may contribute to disturbances in the heart rhythm and cause cardiac arrest. In Paper IV we propose that AFE might be the result of an incompatible feto-maternal blood transfusion. We have shown that preeclampsia and induction of labor are risk factors for TR postpartum. The same risk factors are known to be associated with both feto-maternal blood transfusion and AFE.[236] Due to its rarity, AFE is difficult to study, and retrospective observational studies would not answer questions of causality. A suggested study design would be to prospectively identify possible cases of AFE by use of a multicenter obstetric surveillance system, as described above, and then carry out specific blood tests on both newborn and mother in suspected cases. Blood testing should include blood group, fetal hemoglobin fraction, erythrocyte antibodies, HNA- and HLA-antibodies, and potassium levels.

In theory, AFE cases with suspected hemolysis and acute high levels of potassium could be treated with intravenous calcium (Calciumglukonat) to decrease the risk of arrhythmia. However, to establish effectiveness on mortality large international RCTs will be needed.

- Women with massive transfusion at delivery constitute a heterogeneous group. The different causes of hemorrhage are likely to have differing impacts on future well-being. Few, studies have been published regarding the long-time consequences of MT. In 2011 Sentilhes et al. reported that women with severe PPH and uterine preservation had adverse long-term psychological outcomes.[237] After MT at delivery, women may face extended periods of sick leave, unemployment, and are likely to be prescribed antidepressant drugs. Those with a spared uterus might have fewer future pregnancies compared to women without MT at delivery. These are issues among women who received MT that have not been previously studied. A qualitative pilot study has already begun to address this. After obtaining ethics permission, 50 out of 277 women with MT postpartum have been contacted by mail. The response has been overwhelming. Several women have described how they suffer from depression or have other health issues as a result of circumstances surrounding delivery. In their initial written replies, many state that they felt neglected by the healthcare system and, twenty years later, still live with many unanswered questions. They had expected that their medical care would include better follow-up. The importance of the subject, based on the response from these women, is a strong motivation to continue the study.

# 13 SUMMARY IN SWEDISH - POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA:

Blödning i samband med förlossning är fortfarande den vanligaste orsaken till att kvinnor dör i samband med graviditet. Ur ett globalt perspektiv står blödning för ¼ av den totala maternella mortaliteten och drabbar enligt WHO mer än 100,000 gravida kvinnor varje år. I Sverige och andra hög inkomstländer är mortalitet i anslutning till graviditet ovanligt, men oroande är att andelen förlossningar med stor blödning och behov av blodtransfusion har ökat de senaste åren. En av orsakerna till detta anses vara en stegrad kejsarsnitts frekvens. I Sverige har andelen förlossningar med kejsarsnitt ökat från 5 % i början på 1970-talet till 18 % idag. Blodtransfusion är idag i de allra flesta fall en säker och nödvändigt åtgärd, med det finns allvarliga komplikationer såsom transfusionsreaktioner och infektioner. Massiv transfusion innebär att man ger ett stort antal enheter blod under en begränsad tid. Vi har definierat detta som transfusion av 10 eller fler enheter inom 24 timmar. Dessa mycket allvarliga tillstånd förekommer oftast inom kirurgi eller trauma sjukvård men även inom förlossningsvården. En av orsakerna till stora blödningar med stort transfusions behov vid förlossning är att moderkakan har vuxit fast på ett onormalt sätt i livmoderns vägg. Detta tillstånd kallas placenta accreta och är starkt kopplat till förekomst av en föreliggande moderkaka och antalet tidigare kejsarsnitt eller annan kirurgi på livmodern. Förekomsten av placenta accreta varier kraftigt från land till land och rapporteras vara mellan 2 och 90 per 10,000 förlossningar. För att kunna ta hand om dessa förlossningar på ett optimalt sätt och därmed minska risken för komplikationer krävs en noggrann planering och att tillståndet blir upptäckt under pågående graviditet. Förekomsten av och hur väl omhändertagande av dessa patienter fungerat i Sverige och i de Nordiska länderna har inte varit känt.

En annan allvarlig komplikation under graviditet och efter förlossning är blodproppar (trombos) i venerna i benen, bäckenet och i lungan. Risken för blodpropp är ökad 10-20 gånger i anslutning till graviditet jämfört med icke-gravida kvinnor i motsvarande ålder. För att förhindra att blodproppar uppstår ges idag blodförtunnande medicin till gravida kvinnor med hög trombos risk. Kännedom om riskfaktorer är därför av stor vikt.

Denna avhandling består av fyra delarbeten som alla berör olika aspekter av blodtransfusion i samband med förlossning. Syftet med arbetet har varit att öka kunskapen och identifiera riskfaktorer för invasiv moderkaka, massiv blodtransfusion samt komplikationer till blodtransfusion i anslutning till förlossning. Delarbete I och II berör orsaker och riskfaktorer

för stort transfusionsbehov medan delarbete III och IV berör potentiella komplikationer till blodtransfusion.

I *delarbete I* studeras förekomst av och riskfaktorer för placenta accreta samt till vilken grad dessa graviditeter kunde identifieras innan förlossningen startade. Studien, som var ett Nordiskt samarbete, pågick under åren 2009 till 2012 och inkluderade 605,000 graviditeter, vilket motsvarar 91% av alla förlossningar i de Nordiska länderna under denna tidsperiod. Fall med placenta accreta rapporterades direkt från ansvariga klinker på förlossningsenheterna till en nationell representant i respektive land. Bakgrunds data hämtades från de Nationella födelseregistren från respektive land. Totalt identifierades 205 fall med placenta accreta, vilket motsvarar en förekomst på 3,4 per 10,000 förlossningar. För graviditeter med placenta accreta var genomsnittsblödningen 5 L och 44% fick minst 6 enheter blod. Mest betydelsefulla riskfaktorer var föreliggande moderkaka (placenta previa) och tidigare kejsarsnitt som ökade risken för placenta accreta med 290 respektive 7 gånger. Överraskande nog var en majoritet av placenta accreta fallen (70 %) inte upptäckta före förlossningsstart. Av dessa odiagnostiserade fall hade 40% en föreliggande moderkaka och 1/3 av mödrarna hade genomgått ett tidigare kejsarsnitt.

**Slutsats:** Graviditeter som kompliceras med placenta accreta orsakar stora blödningar och förekommer vid 3.4 av 10,000 förlossningar i Norden. En minskning av andelen kejsarsnitt är troligen den mest effektiva åtgärden för att minska andelen framtida graviditeter med placenta accreta. En ultraljudsundersökning av gravida kvinnor med tidigare kejsarsnitt och en lågt sittande moderkaka skulle förbättra andelen med placenta accreta som upptäcks innan förlossning och därmed möjliggöra ett planerat omhändertagande och mindre risk för komplikationer och sjuklighet för dessa kvinnor.

I *delarbete II* studerades riskfaktorer för och förekomst av massiv blodtransfusion i anslutning till förlossning. I studien inkluderas alla kvinnor som fick barn i Stockholmregionen under åren 1990 till 2011. Data från det medicinska födelseregistret (MFR) länkades till Stockholms transfusionsdatabas. Cirka 517,000 kvinnor kunde inkluderas i studien. Massiv blodtransfusion förekom i 5.3 per 10,000 förlossningar och visade en utmed tiden ökande trend. Störst risk förelåg vid föreliggande eller invasiv moderkaka (OR = 41) samt vid tidigare förlossning med kejsarsnitt (OR = 4).

**Slutsats:** Massiv blodtransfusion förkommer vid ca. 5 av 10,000 förlossningar och har en ökande trend. Genom att innan -eller tidigt i förlossningsförloppet- identifiera de gravida kvinnor som har riskfaktorer för stor blödning och genom att minska andelen förlossningar med kejsarsnitt skulle troligen förekomsten av massiv blodtransfusion minska.

I *delarbete III* studerades om blodtransfusion och stor blödning efter förlossning är oberoende riskfaktorer för tromboembolism (blodpropp). Vi samanställde data från MFR, Patientregistret och Stockholms transfusionsdatabas på 82,376 graviditeter för åren 1999 till 2002 (innan införandet av blodproppsprofylax till gravida). Blodpropp i anslutning till förlossning förekom hos 56 kvinnor. Förekomst av blodtransfusion efter förlossning innebar en femfaldigt ökad risk för blodpropp medan blödningar över 1000ml utan blodtransfusion inte innebar en riskökning för blodpropp. Risken ökade med antalet enheter blod som transfunderades.

**Slutsats:** Blodtransfusion är en oberoende riskfaktor för blodpropp efter förlossning och bör ingå i den nationella riktlinje som idag finns för blodproppsförebyggande behandling under graviditet, medan risken för blodpropp efter stor blödning utan transfusionsbehov är låg.

I *delarbete IV* studerades risken för transfusionsreaktion (TR) vid blodtransfusion i anslutning till förlossning. I denna studie användes samma population av gravida kvinnor som i delarbete II. Information från MFR och Stockholms transfusions databas samanställdes. Kvinnor med blodtransfusion och TR under den första veckan efter förlossning identifierades. Bland 12,183 kvinnor med blodtransfusion noterades 96 med en TR. Gravida kvinnor som erhöll blodtransfusion hade en dubbelt så hög risk för TR som icke-gravida jämnåriga kvinnor. Bland gravida kvinnor innebar preeklampsi (tillstånd med förhöjt blodtryck under graviditet) en fördubblad risk för TR när blodtransfusion gavs post partum. Induktion av förlossning och prematur förlossning innebar en 70% ökad risk för att utveckla en TR vid blodtransfusion direkt efter förlossning.

**Slutsats:** Risken för transfusionsreaktion är dubblerad under graviditet och en ökad observans är speciellt indicerad när blodtransfusion ges till kvinnor med preeklampsi i anslutning till förlossning.

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