DEPARTMENT OF WOMEN´S AND CHILDREN´S HEALTH
Karolinska Institutet, Stockholm, Sweden

NEONATAL COMPLICATIONS FOLLOWING BIRTH BY VACUUM EXTRACTION

Katarina Åberg

Karolinska Institutet

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Neonatal complications following birth by vacuum extraction

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By

Katarina Åberg

Principal Supervisor:
Associate Professor Cecilia Ekéus
Karolinska Institutet
Department of Women´s and Children´s Health
Division of Reproductive Health

Co-supervisor(s):
Professor Mikael Norman
Karolinska Institutet
Department of Clinical Science, Intervention and Technology

Associate Professor Karin Pettersson
Karolinska Institutet
Department of Clinical Science, Intervention and Technology

Opponent:
Associate Professor Lars Ladfors
University of Gothenburg
Sahlgrenska Academy
Department of Obstetrics and Gynecology

Examination Board:
Professor Anna-Karin Dykes
Lunds Universitet
Department of Health Sciences
Medical Faculty

Associate Professor Marie Blomberg
Linköpings Universitet
Department of Clinical Science and Experimental Medicine

Associate Professor Kristina Thorngren-Jerneck
Lunds Universitet
Department of Clinical Sciences
Division of Pediatrics

ABSTRACT

Background: Vacuum extraction is a common method of delivery presently accounting for approximately 7 percent of all deliveries in Sweden. It is considered an important and safe obstetric procedure, although both maternal and neonatal complications exist. There is a lack of knowledge about if and how specific risk factors contribute to neonatal complications after vacuum assisted delivery. Therefore, the aim of this thesis was to identify risk factors for neonatal complications following vacuum assisted delivery, ultimately in order to increase infant safety.

Methods: Study I, II and IV were population-based cohort studies with data from the Swedish Medical Birth Register. In the first study we investigated neonatal outcomes after preterm delivery by VE. The outcomes were extracranial hemorrhage, intracranial hemorrhage, convulsions, encephalopathy and brachial plexus injury. In the second study, we investigated the relationship between birthweight at increasing levels and neonatal complications of infants delivered by vacuum extraction at term. The following outcomes were assessed: five minute Apgar score <7, convulsions, intracranial hemorrhage and brachial plexus injury. In the fourth study, maternal and obstetric risk factors for nonhemolytic hyperbilirubinemia in term newborn infants were assessed. The exposures were a large number of maternal and obstetric factors, including country of birth, mode of delivery and gestational age. The outcome was neonatal hyperbilirubinemia. In the third study, a matched case-control design was used to investigate the association between characteristics of the extraction and intracranial hemorrhage. Cases diagnosed with intracranial hemorrhage after delivery by vacuum extraction at term were included and compared to controls without intracranial hemorrhage delivered by vacuum extraction. The exposure was protracted vacuum extraction, defined as vacuum duration > 15 min, > 6 pulls or > 2 cup detachments.

Results: The rates of serious neonatal complications were low in all studies, although some risk factors were identified. Firstly, preterm infants delivered by vacuum extraction had the highest adjusted odds ratios for the outcomes studied, compared with infants delivered by spontaneous vaginal delivery or caesarean section during labor. Secondly, the rates of complications increased with increasing birthweight among term infants delivered by vacuum extraction. Thirdly, protracted extractions occurred more often among cases diagnosed with intracranial hemorrhage than among controls. Compared to extractions adhering to guidelines, the risk of intracranial hemorrhage was nine-fold among infants exposed to a protracted extraction. And lastly, the risk of nonhemolytic neonatal hyperbilirubinemia varied substantially depending on maternal and obstetric risk factors.

Conclusions: Easy-available maternal and obstetric risk factors can be used to predict large variations in the risk of hyperbilirubinemia, information that is useful in timing of hospital discharge and follow-up. We also identified some situations that call for cautious use of vacuum extraction: preterm deliveries, including 34-36 gestational weeks, and deliveries with clinical suspicion of a large fetus. Furthermore, the importance of abandoning a difficult extraction in time is emphasized by the strong association between protracted extractions and intracranial hemorrhage.

LIST OF SCIENTIFIC PAPERS

I. **Preterm birth by vacuum extraction and neonatal outcome: a population-based cohort study**
Katarina Åberg, Mikael Norman and Cecilia Ekéus
BMC Pregnancy & Childbirth 2014, 14(42)

II. **Vacuum extraction in fetal macrosomia and risk of neonatal complications: a population-based cohort study**
Katarina Åberg, Mikael Norman, Karin Pettersson, Cecilia Ekéus
Acta Obstet Gynecol Scand 2016, 95:1089-1096

III. **Protracted vacuum extraction and neonatal intracranial hemorrhage among infants born at term: a case-control study**
Katarina Åberg, Mikael Norman, Karin Pettersson, Hans Järnbert-Pettersson, Cecilia Ekéus
In manuscript

IV. **Predicting nonhemolytic neonatal hyperbilirubinemia**
Mikael Norman, Katarina Åberg, Karin Holmsten, Vania Weibel and Cecilia Ekéus
Pediatrics 2015, 136(6):1087-94

CONTENTS

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CI	Confidence Interval
CS	Cesarean Section
CTG	Cardiotocography
EDA	Epidural Analgesia
ICD	International Classification of Diseases
ICH	Intracranial Hemorrhage
LGA	Large for Gestational Age
MRI	Magnetic Resonance Imaging
OR	Odds Ratio
RCT	Randomized Controlled Trial
RR	Risk Ratio
SGA	Small for Gestational Age
SMBR	Swedish Medical Birth Register
VD	Vaginal Delivery
VE	Vacuum Extraction

1 INTRODUCTION

Vacuum extraction (VE) is never a first choice route of delivery beforehand, but can be one of the options when shortening of the second stage of labor is necessary, in case of non-reassuring fetal or maternal status or when progress is poor. Sweden is one of the countries with the highest rates of VE for assisted vaginal birth, and among Swedish obstetricians and midwives, it is considered an important and safe procedure that reduces maternal and neonatal morbidity.

During the last decade though, there has been a decrease in the use of VE in many countries, and consequently, an increase in cesarean section rates. Some argue that this trend is due to an increased fear of serious neonatal complications. Reports describing complications after VE are numerous, although there is a lack of studies investigating specific risk factors for adverse outcomes in VE deliveries. One way to improve the safety of VE and to address the fear of complications is to increase the knowledge of risk factors for complications related to VE deliveries. Therefore, this thesis will cover different aspects of possible risk factors for neonatal complications following birth by VE.

2 BACKGROUND

2.1 OPTIONS FOR SHORTENING THE SECOND STAGE OF LABOR

VE is one of the methods for shortening of the second stage of labor. When discussing vacuum assisted delivery, it is important also to mention the alternatives: forceps or second stage cesarean delivery. Unfortunately, there is not a clear answer to which alternative to prefer, and therefore, the choice of method is influenced by custom and practice, clinical circumstances, operator preferences and availability of specific education and equipment.

Forceps delivery is the alternative method for operative vaginal delivery. VE and forceps both need fulfillment of similar prerequisites, and therefore, several randomized controlled trials (RCTs) (1-4), have compared the two methods. The RCTs, summarized in meta-analyses, have shown that forceps are more likely than VE to achieve vaginal delivery. However, forceps delivery is associated with an increased risk of perineal trauma and need for analgesia, compared with vacuum delivery. VE, on the other hand, is associated with increased risk of cephalohematoma and retinal hemorrhage in the newborn, compared with forceps, although serious neonatal complications are rare with either instrument (2, 5, 6). In Sweden, forceps are currently used in 0.1 percent of all deliveries (7).

A cesarean section does not need fulfillment of the same prerequisites as VE or forceps, and can be performed at any stage of labor and in any fetal presentation. However, a second stage cesarean section when the fetal head has descended deeply into the pelvis, can also be difficult and traumatic for both the mother and the fetus. Recent studies comparing second stage cesarean section with forceps and vacuum delivery show that VE was associated with the lowest frequency of postpartum infection and postpartum hemorrhage. The frequency of severe perineal lacerations was lower after VE compared with forceps, but higher compared with cesarean section. No difference in the composite neonatal outcome was observed between the groups (8, 9). Cesarean deliveries also increase the risks of complications in subsequent pregnancies and previous cesarean section is associated with placenta previa, placental abruption, invasive placenta and uterine rupture (10, 11). These long-term consequences are the main reason for the concerns about increased cesarean rates and the efforts to keep cesarean rates at acceptable levels.

In some cases, when the progress is judged inadequate but there is no concern for the fetal or maternal well-being, there is also a fourth option: expectant management. Several studies show that extending the time limit for prolonged second stage of labor may decrease the incidence of cesarean delivery, compared with usual management (12, 13). However, there is also evidence showing that, as the duration of the second stage increases, the likeliness of a vaginal delivery decreases, while maternal and neonatal complications increase (14, 15). Thus, the issues of if, when and how to intervene, have no easy answers.

2.2 THE HISTORY OF VACUUM EXTRACTION

The first successful vacuum instrument for obstetric use was introduced in 1849 by the Scottish Professor James Young Simpson. His rubber cup extractor had some technical difficulties and forceps continued to be the first instrument of choice for operative vaginal delivery. It would take another century, until the introduction of stainless steel cup devices, for VE to gain popularity (16). The steel cup was first developed and introduced in the 1950s by the Swedish obstetrician Tage Malmström (17). Compared with previous devices, the advantage of the Malmström cup was its hollow design, that, once the negative pressure was applied, filled the cup with caput succedaneum, and thereby made it attach firmly to the fetal head (16). Malmström´s cup was further developed over the following decades and in the 1960s and 70s, Geoffrey Bird improved the metal cup instrument by moving the suction tube laterally from the center towards the brim. This improvement enabled a more correct placement of the Bird cup, allowing for flexion of the fetal head, also in occiput posterior positions (18, 19). In the 1970s, the soft and semi-soft cups were introduced and in the 1980s, disposable cups and handheld pumps became popular. Today, there are numerous types of cups from different manufacturers and of different materials, from rubber, silastic, polyethene and plastic, to metal devices (18).

2.3 TRENDS IN THE USE OF INSTRUMENTAL DELIVERY

There are large variations between and within countries in the use and preferences of instrumental deliveries. In the early 1990s, Hillier and Johanson (20) conducted a worldwide survey to investigate which instruments were most frequently used for assisted vaginal delivery in different parts of the world. In summary, they found that VE was the most popular instrument in northern Europe, Africa and China, while forceps delivery was more common in South America and eastern Europe. The exact rates, however, could not be determined.

The Scandinavian countries have a long tradition of VE and relatively low cesarean section rates, compared with many other western countries. In Sweden, the rates of instrumental vaginal delivery increased from 4.5 percent in 1973 to 9.7 percent in 2007. Since then, there has been a decrease, and in 2014, VE was surpassed by both elective and emergency cesarean sections (7) (Figure 1). In Sweden, VE accounts for more than 99.5 percent of the instrumental vaginal deliveries. In Norway, 2.6 percent of all deliveries were assisted by VE in 1973, and in 2015, VE accounted for 8.5 percent of the deliveries, while 16.6 percent were cesarean sections (21). In Denmark, the rates are similar.

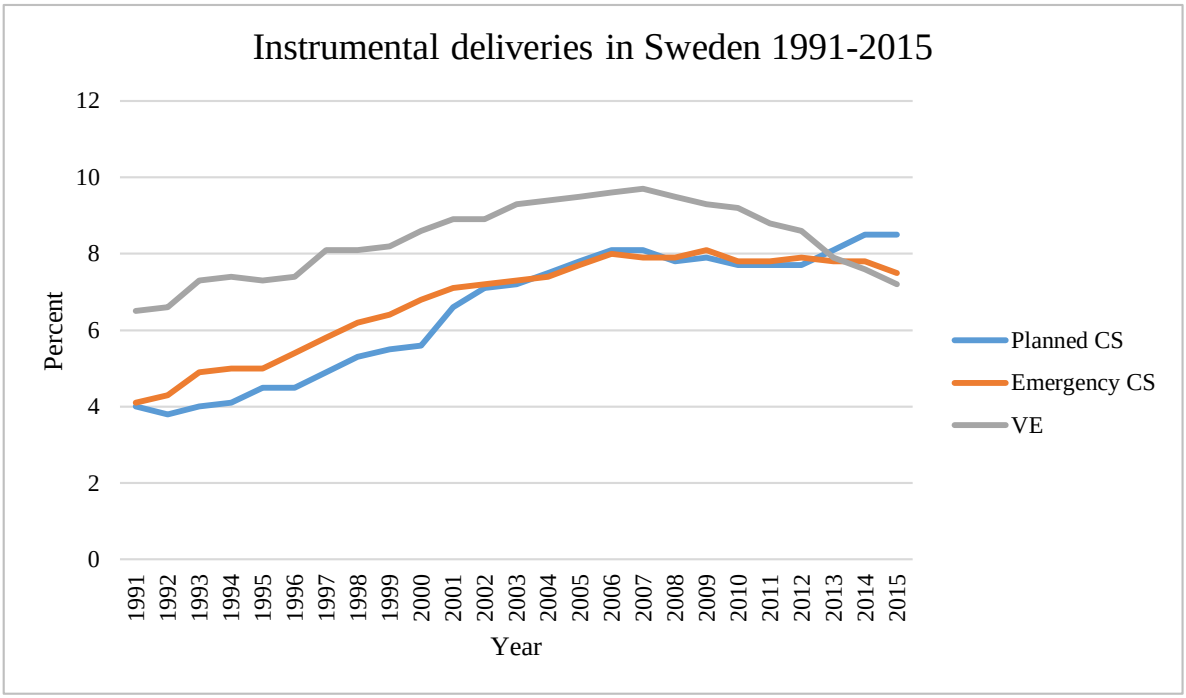


Figure 1. Instrumental deliveries in Sweden from 1991-2015

In the United Kingdom, VE accounted for only 0.7 percent of all deliveries in 1980, while 11.5 percent were forceps deliveries. In 2000, the VE rate had increased to 7.4 percent, however, decreased to 6.5 percent in 2012. Here, forceps continue to be as popular as VE, with a forceps rate of 6.5 percent in 2012 and a total cesarean section rate of 25 percent (22).

In the United States, both VE and forceps decreased during the last decade. In 2001, 9 percent of all deliveries were assisted by VE and in 2015, the rate had declined to 2.58 percent. Meanwhile, the cesarean section rate increased from 20 percent in 1996 to 32.9 percent in 2009, although declined in recent years to 32.0 percent in 2015 (23, 24).

2.4 RISK FACTORS FOR VACUUM EXTRACTION

There are several factors associated with increased risk of instrumental vaginal delivery. The most important is a non-modifiable risk factor: nulliparity. In Sweden, approximately 14 percent of nulliparous and less than three percent of parous women deliver by the assistance of VE (7). Other factors associated with VE are increasing maternal age (25-27), epidural analgesia (EDA) (26, 28-30), labor induction (26, 30), maternal pre-gestational diabetes and preeclampsia, gestational length > 41 weeks, short maternal stature, increasing birthweight (26), fetal head circumference $\geq$ 36 cm (31) and continuous use of cardiotocography (CTG) (32). In parous women, additional risk factors include previous cesarean section or VE and an interpregnancy interval of >4 years (33).

2.5 FACTORS THAT DECREASE THE NEED FOR VACUUM EXTRACTION

Continuous support during labor and birth has several beneficial effects for women and infants, including decreased risk of cesarean and instrumental vaginal delivery. A large meta-analysis (34), including 22 RCTs, reported that the relative risk of instrumental vaginal delivery was 0.90 (95% CI 0.85-0.96) among women receiving continuous support, compared with those who did not. Furthermore, another large meta-analysis suggests that avoiding EDA could reduce the need for VE (28). When EDA is used, delayed pushing, i.e. no pushing until strong urge to push is felt, or more than two hours of the second stage has passed, has been shown to decrease the need for VE (35, 36).

2.6 INDICATIONS FOR VACUUM EXTRACTION

To avoid unnecessary complications associated with VE, it is important that VE is only performed on acceptable indications. There are three major indications for VE recognized in national guidelines by the American College of Obstetricians and Gynecologists (ACOG) (37), the Royal College of Obstetricians and Gynaecologists (RCOG) (38), and the Swedish colleges of obstetricians and gynecologists (SFOG) and midwives (SBF) (39):

- Fetal indication
- Prolonged second stage of labor
- Maternal indication

Fetal indication refers to situations of suspected fetal distress or non-reassuring fetal status. This is often the case when cardiotocography (CTG) shows fetal heart rate abnormalities in the second stage of labor. Unfortunately, CTG has a low specificity for detecting hypoxia and non-reassuring patterns occur in approximately 15 % of all deliveries and the false positive rate is around 60 % (40, 41). There is also a high inter-observer variability in CTG interpretation (42). Therefore, CTG is sometimes combined with fetal scalp-blood sampling, pH or lactate. If the blood sample is abnormal, standard practice is to expedite delivery (43). Neonatal outcome has been compared between VE and cesarean section for deliveries that were shortened due to suspected fetal distress. No difference was found in umbilical artery pH at birth between the groups, suggesting that no option is superior to the other for expediting delivery in case of non-reassuring fetal status (44).

Prolonged second stage of labor refers to inadequate progress and is a relative indication for operative delivery. For nulliparous women, inadequate progress is usually defined as no descent or rotation for >2 h without and >3 h with epidural analgesia (45). However, more recent recommendations are to individualize decisions of intervention and allow longer duration in some cases (43, 46). Several studies of length of the second stage of labor show that the likeliness of spontaneous vaginal delivery decreases as the duration increases (14, 47). Furthermore, prolonged second stage of labor is associated with increased risk of

maternal infections, postpartum hemorrhage and severe perineal lacerations (13, 14, 47, 48). Studies of the effect of prolonged labor in the newborn show conflicting results. One RCT investigated the effect of extending the time limit for intervention and found no increase in neonatal morbidity (12), although several studies indicate that prolonged second stage of labor is associated with birth asphyxia, and that the risk gradually increases with duration of second stage (49, 50). A recent study of deliveries complicated by prolonged second stage compared perinatal outcomes of second stage cesarean sections with vacuum assisted deliveries and found that the neonatal outcome was poorer after cesarean section than after VE (51).

Maternal indication refers to situations where elective shortening of the second stage of labor is required, for instance in case of maternal exhaustion or, in rare cases, when maternal pushing efforts are contraindicated (cerebrovascular or cardiac disorders) or impossible (neuromuscular disorders) (18).

2.7 GUIDELINES, PREREQUISITES AND RECOMMENDATIONS

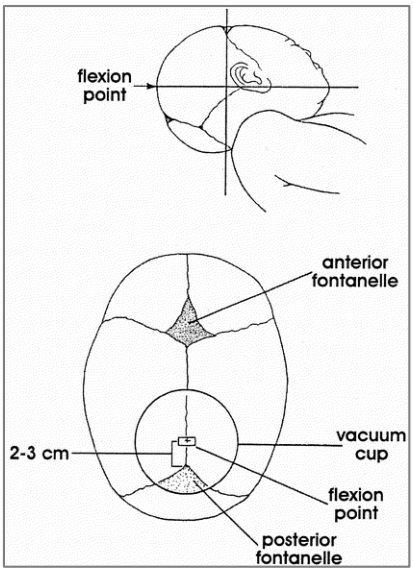
To minimize the risks of complications after VE, guidelines for the performance have been developed (37-39, 52, 53). A safe VE requires careful selection of patients, correct technique and adherence to guidelines. First, a number of prerequisites, listed below, need to be fulfilled before a safe vacuum assisted delivery can be performed:

- Acceptable indication for VE
- Cephalic presentation
- Informed patient
- Full cervical dilatation and retraction
- Ruptured membranes
- Engaged fetal head, station at or below maternal ischial spines (exceptions can be made for second twin)
- Bladder care
- Adequate analgesia
- Willingness to abandon the procedure

Contraindications for VE are:

- Non-cephalic presentation
- Unknown fetal station or vertex above maternal ischial spines
- Preterm delivery (<34-36 weeks)
- Incomplete cervical dilatation
- Known/suspected fetal coagulopathy
- Suspected feto-maternal disproportion

Once decision is made and prerequisites are fulfilled, recommendations aim to make sure that the VE technique is correct and optimal. The correct point for placing the cup, called the flexion point (Picture 1), is located on the center of the sagittal suture, approximately three centimeters in front of the posterior fontanelle. When the cup is placed over its center, the fetal head keeps flexed when traction is applied, making the diameters optimal for delivery, regardless of the position of the fetal head. Incorrect placement of the cup is highly associated with detachments and failure of vacuum attempt (54).



Picture 1. Correct placement of the vacuum cup on the flexion point. Reprinted with permission from Miksovsky & Watson (18)

Successful vacuum technique further depends on correct vector of traction, following the direction of the pelvic curve (55). Traction should be simultaneous with uterine contraction and maternal pushing efforts, and no rocking movements should be used. Ideally, descent of the fetal head should begin with the first traction. If no descent can be confirmed by the first traction, the operator needs to make sure that the second traction results in progress. Moreover, successful extraction depends on a number of factors, such as quality of contractions, maternal pushing efforts, use and type of analgesia and operator training, experience and skills (56). Guidelines recommend that the vacuum attempt is re-evaluated and that the procedure is abandoned and converted to a cesarean section if:

- Traction does not result in progress
- Two cup detachments occur
- Fetal head has not reached the pelvic floor after three pulls
- More than six pulls are needed
- Delivery is not completed within 15 (-20) minutes

2.8 FAILURE TO DELIVER BY VACUUM EXTRACTION

Most VEs are successful, although sometimes the method fails to achieve vaginal delivery. As mentioned above, appropriate management includes abandoning the VE procedure when difficulties occur, and for that reason, unsuccessful extractions should not always be considered failed VEs. The rate of unsuccessful vacuum attempts in Sweden is approximately five percent (57), which is low compared to other studies that report failure rates around ten percent (58-60). There are several risk factors associated with unsuccessful vacuum attempts, for instance high birthweight, occipitoposterior position (61), mid-pelvic fetal station, short maternal stature, epidural analgesia, induction of labor (57), increased maternal age, high body mass index (BMI), diabetes, dysfunctional labor and prolonged labor (49). Furthermore, soft cups and hand-held devices are more likely to fail than metal cups (6).

When VE is abandoned, it is usually followed by sequential cesarean section or, in rare cases, a forceps attempt. Cesarean delivery after failed VE has been associated with increased risk of neonatal complications, including intracranial hemorrhage and seizures, compared with either VE, forceps or cesarean delivery alone (62). Sequential use of forceps after failed VE is associated with the highest risk of neonatal complications (62, 63).

2.9 MATERNAL COMPLICATIONS ASSOCIATED WITH VACUUM EXTRACTION

The most frequent maternal complication after instrumental vaginal delivery is perineal injury. Instrumental vaginal delivery is also one of the most important risk factors for severe perineal lacerations, i.e. anal sphincter tears (third- and fourth-degree lacerations) (48, 64). The reported rates of anal sphincter tears after VE vary from less than one percent to 15 percent, compared with spontaneous vaginal delivery with rates varying from less than one to 4 percent (65). The associations are complicated, since several factors are related both with instrumental delivery and with perineal injury, such as nulliparity, prolonged duration of second stage of labor, fetal size and occiput posterior position (48). The rates of severe perineal injuries are, however, lower after VE, compared with forceps. A Cochrane review compared maternal outcomes between forceps and VE (6). The authors found that there were significantly more third- or fourth-degree tears, vaginal trauma and flatus incontinence at long term follow-up, among women in the forceps group. Some suggest the rates of perineal injuries could be reduced by routine mediolateral or lateral episiotomy in primiparous women having vacuum assisted deliveries (66, 67), although others disagree (68).

Operative vaginal delivery is also associated with a lower frequency of postpartum infection, compared with cesarean section (9). Women giving birth by the assistance of VE are at increased risk of postpartum haemorrhage compared with spontaneous vaginal delivery. Several factors are likely to be associated with this increased risk: bleedings from lacerations, dystocia and prolonged labor (69, 70).

Furthermore, a negative birth experience and secondary fear of childbirth is more common among women giving birth by VE (71-73). The birth experience can leave an impression on women lasting more than a decade after delivery (74). Women who had their first delivery by VE also had a reduced probability of subsequent childbearing, although this probability was even more reduced if the first delivery was an emergency cesarean section (75).

2.10 NEONATAL COMPLICATIONS

There are several neonatal complications associated with vacuum extraction: pain, scalp lacerations, cephalo- and subgaleal hematoma, retinal haemorrhage, jaundice, brachial plexus injury and intracranial hemorrhage (76-82). Some are of minor concern while others are severe with potential to cause permanent injury or death. It has therefore been suggested that complications should be classified according to their clinical significance into (56, 83):

- Cosmetic effects: chignon, bruising and discolouration of the scalp
- Clinically non-significant injuries: superficial scalp injuries, cephalhematoma, retinal hemorrhage
- Clinically significant injuries: subgaleal hemorrhage, intracranial hemorrhage, skull fractures
- Indirect injuries/effects: brachial plexus injury, clavicular or humeral fracture, jaundice

Scalp injuries

Superficial scalp injuries are common in infants delivered by VE with reported frequencies around 10 percent (84). Scalp injuries are associated with difficult extractions, durations longer than ten minutes (83, 85) and are more common with the use of metal or hard plastic cups, compared with soft cups (6).

Retinal hemorrhage

Retinal hemorrhage, a bleeding in the membrane in the back of the eye, is a frequent finding in newborns that occurs more often after vacuum assisted delivery (5). Reported incidence of moderate to severe retinal hemorrhage is 18 percent in infants born by spontaneous vaginal delivery, 28 percent after VE, and 50 percent in infants born after sequential use of forceps after vacuum extraction has failed (86). Follow-up studies of infants with retinal hemorrhage show that the hemorrhages resolve within days to months, depending on severity, and that retinal hemorrhage does not cause permanent damage.

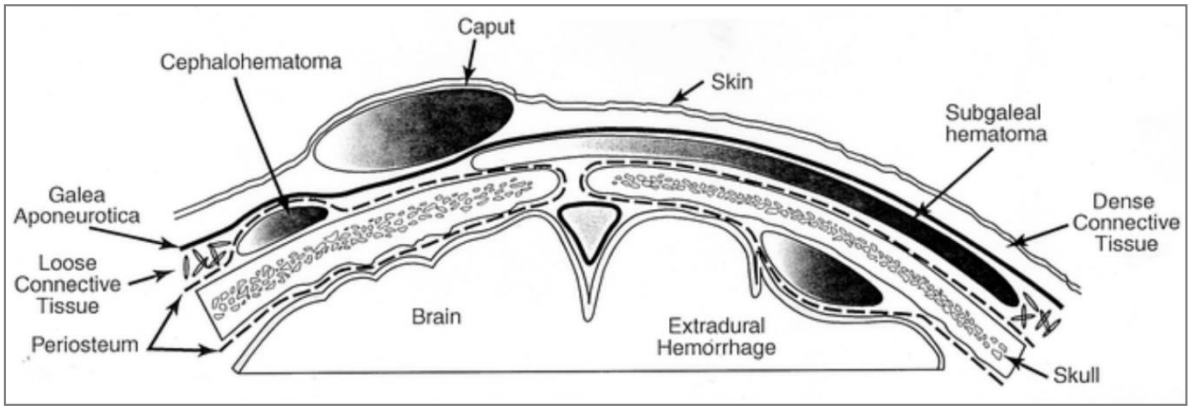
Cephalohematoma

Cephalohematoma is an extracranial bleed located between the skull and the periosteum (Picture 2). The periosteum is attached at the suture lines of the bone plates of the skull and the potential amount of blood that can fill this space is thereby limited. The incidence varies from 1 to 26 percent (83, 87). Cephalohematomas are more common when metal cups are

used, compared with soft or plastic cups (87). Clinically, these hematomas are recognized by not crossing the suture lines, which differentiate them from the far more serious subgaleal hemorrhages. Cephalohematomas are rarely causing complications such as hypotension or anemia, and no treatment is indicated for otherwise uncomplicated cephalohematoma. However, they contribute to an increased risk for neonatal hyperbilirubinemia due to excessive hemolysis and bilirubin formation during the first postnatal days.

Subgaleal hemorrhage

Subgaleal hemorrhage (Picture 2), also called subaponeurotic hemorrhage, is an extracranial bleed into the potential space between the periosteum and the galea aponeurotica. These bleedings are not limited by the suture lines, as they are in cephalohematomas, and the subaponeurotic space has a potential volume of up to 260 milliliters (88). A blood loss of that amount could result in hypovolemic shock or even death. The mortality associated with subgaleal hemorrhage is around 14 percent (80), although, for survivors, the long-term prognosis is good (80, 88). There is a strong association between VE and subgaleal hemorrhage. Reported incidence varies from 3-7.6/1000 VE-deliveries in retrospective studies, to 210/1000 VE-deliveries in prospective studies (89). In spontaneous vaginal delivery, the rate of subgaleal hemorrhage is around 0.4/1000 (90). The proposed mechanism of how VE contributes to subgaleal hemorrhage involves strong traction, especially traction that does not cause descent of the head, and that pull the aponeurosis from the cranium, resulting in tear of the underlying veins (90).



Picture 2: Schematic picture of the five anatomic layers of the scalp and their relationship to various hemorrhages that may develop within these tissue planes. Reprinted with permission from Amar et al. (91)

Intracranial hemorrhage

Intracranial hemorrhage (ICH) is defined as any bleeding within the cranial vault. Based on anatomy, ICH can be classified as epidural, subdural, subarachnoid, intraventricular or intraparenchymal (92). Intraventricular hemorrhage is the most common type in preterm infants, but in term infants, symptomatic ICH is rare and has a different etiology. In term infants, this complication is associated with birth trauma (63, 93), hypoxia (94, 95) and with coagulative disorders (94, 96). In recent years, improved neuroimaging techniques such as magnetic resonance imaging (MRI), have revealed that small intracranial hemorrhages are common findings, even in asymptomatic infants born at term, and regardless of mode of

delivery (97, 98). Symptomatic ICH, however is very rare in infants born at term with reported incidence around 3-8/10 000 live births. In preterm infants the incidence of intraventricular hemorrhage range from more than 30 percent among infants with a birthweight of 401-1500 grams to 3 percent among preterm infants with a birthweight of 1251-1500 grams (99).

The association between VE and ICH is debated. There are several case-reports of ICH after vacuum extraction deliveries (100-102), although most large studies have found increased rates of ICH after all methods for operative delivery, except elective cesarean section (62, 103, 104). Consequently, the authors have assumed that a dysfunctional labor and the indication for operative delivery, rather than the extraction itself, is a cause of ICH in term infants. These studies have all lacked information about the indication for operative delivery. Contradictory to these studies, a large Swedish register-based study (105) reported an excess risk of ICH after VE, even after adjusting for the indication for the operative delivery, suggesting that the association is not solely reflecting confounding by indication.

Only one study have previously investigated long-term outcome among infants delivered by VE and diagnosed with neonatal ICH (106). The authors reported poor neurodevelopmental outcome in 50 percent of the afflicted children.

Brachial plexus palsy

Obstetric brachial plexus palsy is a neurologic injury to the network of nerves that originate from the cervical and thoracic roots: C5-8 and Th 1. Depending on localization of the injury, it may affect the shoulder, arm and hand. Reported incidence varies about 0.13-3.6/1000 births (107-109) and the main causes of this injury are strain or compression of the brachial plexus (110). Risk factors for brachial plexus injury are shoulder dystocia, high birthweight, maternal diabetes and instrumental vaginal delivery. In VE deliveries, a vacuum duration of more than ten minutes and a high number of pulls to deliver the infant, increases the risk for brachial plexus injury (111). Most children with obstetric brachial plexus injury recover completely (107, 112), although the injury can be irreversible in some cases. Of infants followed up to at least 12 months, 10 percent had permanent injury (113).

Nonhemolytic neonatal hyperbilirubinemia

Neonatal hyperbilirubinemia is a common finding in the newborn´s first week of life and more than 60 percent of term infants have visible signs of transient hyperbilirubinemia that require no further treatment, physiologic jaundice (114, 115). In some infants, there is a pronounced imbalance between bilirubin production and excretion, resulting in bilirubin levels that rise rapidly and become pathologic. Unconjugated bilirubin is neurotoxic and exaggerated levels of bilirubin could potentially cause brain damage and therefore, neonatal jaundice above certain age-specific limits is treated with phototherapy or in rare cases with blood exchange transfusion. There are several factors that are associated with nonhemolytic hyperbilirubinemia, for instance low gestational age, maternal diabetes mellitus, ethnicity, genetic factors, enzymatic defects, hematomas, and vacuum assisted delivery, explained by the break-down of accumulated blood in chignons and cephalohematomas (116, 117). The

long term outcome of treated neonatal non-hemolytic hyperbilirubinemia is good, with no impact on adult neurodevelopment or cognitive performance (118).

2.11 LONG-TERM OUTCOMES IN CHILDREN DELIVERED BY VACUUM EXTRACTION

A few years ago, Ahlberg and co-workers (119) investigated long-term outcomes of VE deliveries in Sweden by studying school performance at 16 years of age in relation to mode of delivery. They reported that children born by VE or by unplanned cesarean section had slightly lower grades in mathematics, compared with those born by spontaneous vaginal delivery. However, the difference was so small that it was considered clinically insignificant.

Several other studies on long-term outcomes after different modes of delivery have compared physical and intellectual outcomes in children and adolescents born by VE, forceps, cesarean section and spontaneous vaginal delivery. Their results are reassuring and no differences have been found (120-123).

2.12 BENEFITS OF VACUUM EXTRACTION

The focus of this thesis is complications associated with VE. However, as important as the risks of VE are the benefits of the procedure. VE prevents injuries from birth asphyxia and in that respect, it can be considered life-saving. It also prevents injuries and complications associated with a prolonged second stage of labor. Moreover, VE is an important intervention that helps keep the cesarean rate on an acceptable level.

3 AIMS

Overall aim

The overall aim of this thesis was to improve the safety of vacuum assisted deliveries by identifying and defining clinically important risk factors for neonatal complications following vacuum extraction.

Specific aims

Study I

To describe the use of VE in preterm deliveries in Sweden and to study the risk for adverse neonatal outcomes among preterm infants delivered by VE.

Study II

To investigate the relationship between birthweight at increasing levels and neonatal complications of infants delivered by vacuum extraction at term.

Study III

To investigate if and how characteristics of the extraction is related to the risk for intracranial hemorrhage among term infants.

Study IV

To assess maternal and obstetric risk factors for clinically significant nonhemolytic hyperbilirubinemia in term newborn infants.

4 SUBJECTS AND METHODS

A brief overview of the subjects and methods of the four studies is presented in the table below.

Table 1. Overview of the studies included in the thesis

Paper	Aim	Design	Exposure	Outcome	Statistics
I	To describe the use of VE in the preterm period and study neonatal outcomes of preterm infants delivered by VE	Population-based cohort study	Mode of delivery	Cephalohematoma, subgaleal hemorrhage, intracranial hemorrhage, convulsions, encephalopathy, brachial plexus injury	Descriptive statistics (frequencies and proportions) and logistic regression analysis
II	To investigate the association between birthweight, mode of delivery and neonatal outcome among term infants with birthweight $\geq$ 3000g	Population-based cohort study	Mode of delivery and birthweight	5 min Apgar score <7, convulsions, intracranial hemorrhage and brachial plexus injury	Descriptive statistics and logistic regression analysis
III	To investigate the impact of protracted vacuum extractions on the risk for neonatal intracranial hemorrhage in term infants.	Case-control study based on medical records	Protracted extraction: duration > 15 min, > 6 pulls, > 2 cup detachments	Intracranial hemorrhage	Descriptive statistics and conditional logistic regression analysis
IV	To assess maternal and obstetric risk factors for nonhemolytic neonatal hyperbilirubinemia in term infants	Population-based cohort study	Maternal country of birth, age, anthropometrics, parity, induction of labor, mode of delivery, gender, birthweight, gestational age	Nonhemolytic neonatal hyperbilirubinemia	Descriptive statistics and logistic regression analysis

4.1 DATA SOURCES

The retrospective cohort studies (I, II and IV), were all based on data from the Swedish Medical Birth Register (SMBR), held by the National Board of Health and Welfare. The SMBR was established in 1973. The quality of the SMBR for the years 1973-1998 was evaluated in 2002 and was found to be high with a coverage of 97-99,5 percent of all births. Most variables, such as birthweight, gestational age and mode of delivery, were found very reliable. However, infant diagnoses were missing to a varying degree during the evaluation period (reasons and consequences will be further discussed in Methodological discussion, section 7.1). Infant diagnoses are recorded in the Swedish Medical Birth Register from birth until the baby is discharged from hospital. There is no time limit for diagnoses to be recorded in this register, but there is a maximum of 12 diagnoses for each baby. Diagnoses are not reported to the register in case of readmission to hospital in the neonatal period.

Also for Study III, we used the SMBR to identify the study population, that was based on ICD-10 codes for neonatal intracranial hemorrhage, reported to the register. Information on personal identification number of the mother and her infant, hospital and year of birth was retrieved from the SMBR. However, detailed data on the extraction, which was the main exposure in this study, are not available in the SMBR. Therefore, data for Study III was mainly collected from medical records from antenatal care and delivery. The medical records were scrutinized in a systematic manner by the author of this thesis (KÅ) and the same protocol was used for cases and controls.

4.2 EXPOSURES

In Study I and II, the main exposures were mode of delivery: spontaneous vaginal delivery (VD), cesarean section after the onset of labor (CS), VE and CS after failed VE. We chose not to include forceps deliveries since they only accounted for 1/1000 deliveries in 2012. Furthermore, when forceps are used in Sweden it is often secondary to a failed vacuum attempt and in one third of all forceps deliveries, use of vacuum extraction was also reported. In Study II, we also used birthweight at increasing levels, as exposure.

In Study III, the main exposure was protracted extraction, defined as extractions exceeding safety recommendations for VE, including: duration >15 minutes, >6 pulls or >2 cup detachments.

In Study IV, we investigated multiple exposures. Maternal factors included region of birth, maternal age, weight, height, BMI, parity and diabetes. Obstetric factors included mode of delivery and induction of labor. Infant characteristics included gestational age, gender, birthweight and being born small or large for gestational age (SGA/LGA).

4.3 OUTCOMES

The outcomes investigated in the four studies are neonatal complications based on the ICD-10 diagnostic codes for intracranial hemorrhages, extracranial hemorrhages, brachial plexus injury, convulsions and hyperbilirubinemia. All ICD-codes assessed in Study I-IV are presented in the appendix. Furthermore, low Apgar score, defined as <7 at five minutes was used as an outcome in study II and as a secondary outcome in study III.

Intracranial- and extracranial hemorrhages, brachial plexus injury and hyperbilirubinemia are all known complications associated with VE and has already been described in section 2.10 of this thesis. Therefore, only neonatal convulsions and Apgar score will be described in this section.

Neonatal convulsions is the most frequent neurological symptom in the neonatal period and usually indicates serious neurological complications, for instance hypoxic ischemic encephalopathy (HIE), intracranial hemorrhage, cerebral infarctions, meningitis, sepsis, and metabolic disorders (124). Approximately one third of neonatal convulsions occur during the first day of life, and another third within the first week of life (125). The clinical manifestations vary and can be categorized into subtle (e.g. apnea or eyelid fluttering), clonic (rhythmic jerking), myoclonic (rapid, non-rhythmic isolated jerks) and tonic (increased muscle tonus, e.g. extension of limbs) and can be focal, multifocal or generalized (126).

The Apgar score is a standardized method for assessing the condition of newborns immediately after birth. Different definitions of low Apgar score are used, although the most common definitions are < 7 or < 4. The Apgar score is often used as an indicator of birth asphyxia, although the appropriateness of this has been questioned. Low Apgar score at one minute is most often due to temporary depression. A low five minute Apgar score is associated with birth asphyxia, although asphyxia is not present in all cases with low Apgar score. In a Swedish study, acidemia (pH $\leq$ 7.15) at birth, was present in 54 percent of newborns with Apgar scores of 4-6 at five minutes, and in 69 percent of newborns with score 0-3 at five minutes (127). Low Apgar score is associated with increased risk of minor motor impairments and epilepsy and with an increased risk of mortality within the first year after birth (128, 129). However, 20 percent with Apgar score 0 at 10 minutes survive without disability (130, 131). Thus, Apgar score alone has limited value as evidence of hypoxia and is not a good predictor for individual neonatal mortality or neurologic outcome (132).

4.4 STATISTICS

Statistical Methods

In all four studies, logistic regression analysis was used: unconditional logistic regression in Studies I, II and IV. In Study III, we used conditional logistic regression analysis, a type of logistic regression that takes the matching of controls into account.

Regression techniques are commonly used to measure strengths and directions of associations, predict outcomes and control for confounding. Logistic regression is one such method that is used to analyse the effect of one or several independent variables on a binary outcome by quantifying each independent variable´s contribution. Like in linear regression, the association between a dependent variable or outcome (y) and one or a group of independent variables (x), are calculated. The main difference of logistic regression is that the outcome, y, is binary and can only take two values: 0 or 1. The independent variables can be either binary, categorical or continuous. Since the dependent variable is binary, it is not possible to estimate a certain value of the dependent variable y, like in linear regression. Instead, the predicted probability of the outcome is estimated for each given value of the independent variable x. The variables in the model are transformed to logits to avoid that the estimated probability takes a negative value or a value >1. The result of the equation is then transformed back and is expressed as odds ratios (ORs).

Odds is the ratio of two probabilities, i.e. the probability of an event to occur divided by the probability of the event not to occur, which can be expressed as: (p/1-p). An odds ratio is the ratio of the odds in an exposed group divided by the odds in an unexposed group. Odds ratios are frequently used as risk estimates and are good approximations of the relative risk (RR) when the outcome is rare, the so called “rare disease assumption”(133).

Power calculation

To ensure statistical power and calculate an adequate number of controls for the case-control study, we used preliminary data from a descriptive study of VE management (134), that was ongoing at that time. Based on discussions with experienced obstetricians and based on safety recommendations in guidelines for VE, we assumed that an extraction requiring more than six pulls was a good proxy for a difficult or protracted extraction. The proportion of extractions using more than six pulls was nine percent in the preliminary data, which we assumed would correspond to the proportion among the controls. Furthermore, we approximated the proportion of such extractions to be at least 20 percent among the cases. Derived from these assumptions, a 1:3 relation between cases and controls would give an 88 percent power to detect a significant difference, with odds ratios >2, in the proportions of protracted extractions between cases and controls.

5 ETHICAL CONSIDERATIONS

Before the studies were initiated, ethical approval was obtained from the Regional Ethical Board in Stockholm, DNR 2008/1322-31 and DNR 2013/1922-31/4. All studies included in this thesis were performed without participants' informed consent, an otherwise essential part of research ethics. The principle of informed consent is non-negotiable in intervention studies, although, for large, registry-based studies, it is generally not required. Instead, it is assumed that the study participants do not object to registry-based research, provided that the research project is approved by the ethical committee. The main purpose of registry-based health data is to enable health care quality improvement and a requirement of informed consent would carry several disadvantages, for instance introduction of severe selection bias, exclusion of vulnerable groups unable to consent (children, severely ill, etc.) and make large-scale studies impossible (135). The risks for the study participants are very few in register-based research, since it is based on data that already exists and does not involve any intervention or interaction between researchers and participants. However, there is always a risk that individuals are uncomfortable with their involuntary participation in register studies. Therefore, to protect personal integrity, it is important that data is stored, used and published without any risk of possible identification of participants.

Also Study III was performed without obtaining informed consent, despite much fewer participants. The main reason for abandoning this important principle was that such process would reduce the number of participants, resulting in substantial loss of important information. Moreover, we feared that the consenting families, whose children were deceased or disabled, would be further traumatized or possibly expect personal feed-back regarding their own VE-delivery and its possible relation with ICH in their infant, which was not the intention of the study. With studies where medical records are scrutinized, the risk of trespassing participants' personal integrity is greater than with register data and we do recognize that data collected from medical records are of sensitive character. However, we believe that the benefits of increased knowledge on risk factors for ICH, by using previously collected information in medical records, overweighs the risk of breaches of integrity. For all studies of this thesis, safety measures to protect the participants' personal integrity included: safe storage, access to datasets only by the main supervisor and the doctoral student, anonymized data and lastly, that results were exclusively reported on a group level.

6 SUMMARY OF THE FINDINGS IN STUDY I-IV

In this section, only a condensation of the results is presented. For the complete results, please see the full reports at the end of the thesis.

Study I: Preterm birth by vacuum extraction and neonatal outcome: a population-based cohort study

A total of 40 764 preterm deliveries were included in the study population. Of these, 2 319 infants were delivered by VE, corresponding to a rate of 5.7%. Very few VEs were performed in the most preterm period although the rate increased with every gestational week (Figure 2). Less than one percent were delivered by VE in week 22-27, 2.5 percent in week 28-31 and 6.1 percent in week 32-36. Before 34 gestational weeks, 3.3% of all deliveries were assisted by VE, despite recommendations of no VE-use before this limit.

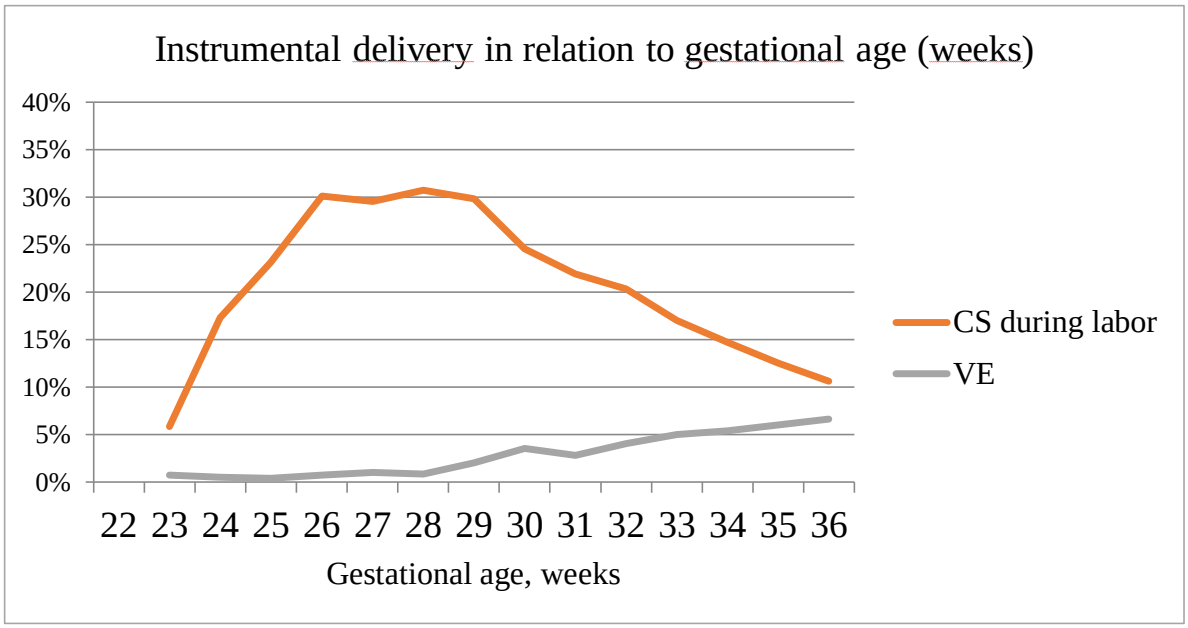


Figure 2. Preterm instrumental delivery (%)

The rates of complications were generally low, regardless of mode of delivery. Infants born by VE in gestational week 34-36 had the highest rates of ICH, convulsions, extracranial hemorrhages and brachial plexus injury, compared with spontaneous vaginal delivery or cesarean section during labor. A total of 617 infants were diagnosed with ICH. Of these, 88% were intraventricular hemorrhages, the most common type in preterm infants. Among all infants born before 34 gestational weeks, the rate of ICH was 75/1000 and in infants born in gestational weeks 34-36, the corresponding rate was 1.6/1000.

The crude model of the logistic regression analysis (Table 2) showed increased ORs after VE for all complications studied, except ICH. However, in the adjusted models preterm infants delivered by VE had increased ORs for intracranial hemorrhage (aOR 1.84, 95% CI 1.09-3.12), extracranial hemorrhage (aOR 4.48, 95% CI 2.84-7.07), and brachial plexus injury (aOR 6.21, 95% CI 2.22-17.4), while infants delivered by cesarean section had no increased risk for these complications, compared with infants born after spontaneous vaginal delivery.

Table 2. Logistic regression for neonatal outcomes in preterm infants exposed to different modes of delivery

Mode of delivery	N	n	1/1000	Crude OR (95% CI)	*Adjusted OR (95% CI)
Intracranial hemorrhage					
Vaginal	32,938	486	14.8	1.0	1.0
CS during labor	5,507	105	19.1	1.30 (1.05-1.61)	0.76 (0.58-0.98)
VE	2,319	26	11.2	0.76 (0.51-1.13)	1.84 (1.09-3.12)
Total	40,764	617	15.1		
Subgaleal- and/or cephalhematoma					
Vaginal	32,938	166	5.0	1.0	1.0
CS during labor	5,507	10	1.8	0.36 (0.19-0.68)	0.36 (0.18-0.70)
VE	2,319	83	35.8	7.33 (5.61-9.57)	4.48 (2.84-7.07)
Total	4,0764	259	6.4		
Neonatal convulsions					
Vaginal	32,938	109	3.3	1.0	1.0
CS during labor	5,507	45	8.2	2.48 (1.75-3.52)	1.42 (0.92-2.17)
VE	2,319	15	6.5	1.96 (1.14-3.37)	1.48 (0.73-3.01)
Total	40,764	169	4.1		
Plexus brachialis injury					
Vaginal	32,938	37	1.1	1.0	1.0
CS during labor	5,507	2	0.4	0.32(0.08-1.34)	0.29 (0.07-1.26)
VE	2,319	14	6.0	5.40 (2.92-10.00)	6.21 (2.22-17.4)
Total	40,764	53	1.3		

* Adjusted for year of birth, gestational age, parity, maternal age, height, BMI, infant birthweight and indications for operative delivery.

Study II: Vacuum extraction in fetal macrosomia and risk of neonatal complications: a population-based cohort study

This study included 1 030 775 term births of infants with a birthweight of $\geq$ 3000g. Also here, we found that the rates of serious complications were low after all modes of delivery. However, our results showed that the rates of all outcomes studied, increased by increasing birthweight after non-instrumental vaginal delivery, and even more after VE/VE+CS (including emergency CS after failed VE).

Among infants delivered by cesarean section, the rates decreased by increasing birthweight (Figure 3).

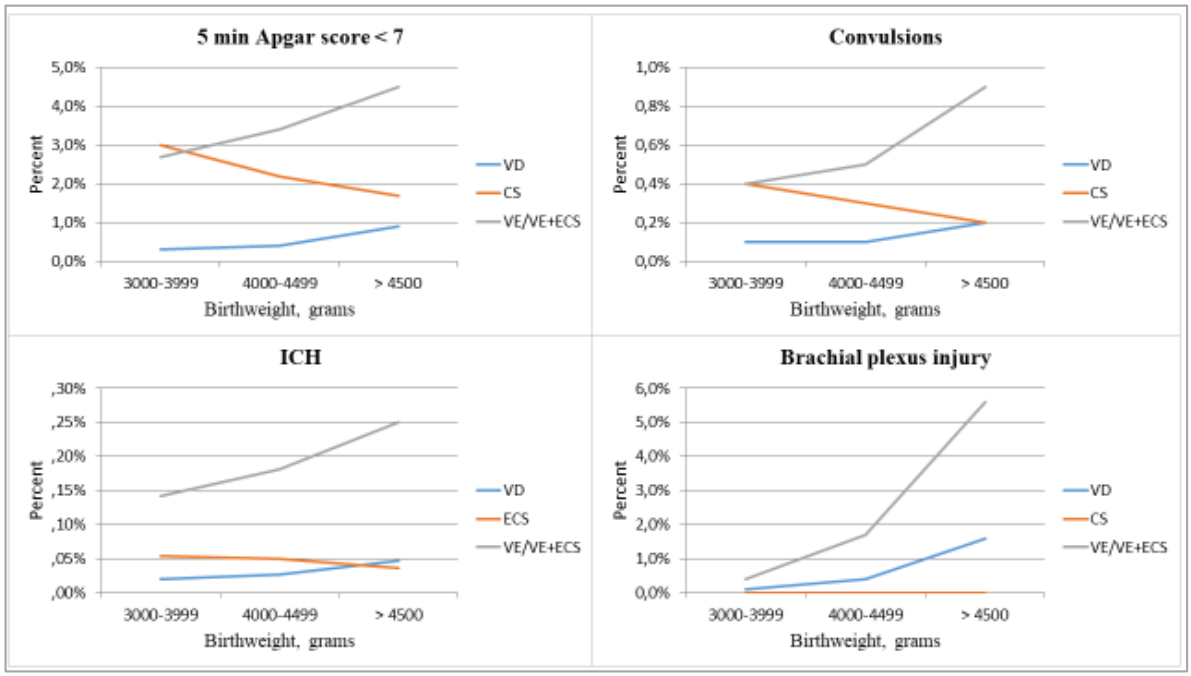


Figure 3. Neonatal complications in relation to mode of delivery and birthweight

The logistic regression analysis of outcomes in relation to mode of delivery and birthweight, showed that the odds ratios for low Apgar score, convulsions, ICH and brachial plexus injury, increased with increasing birthweight among infants delivered by VD and VE/VE+ECS. The highest ORs were seen among macrosomic infants born after VE/VE+CS (Table 3).

Table 3. Logistic regression (adjusted odds ratios) for neonatal outcomes by mode of delivery and birthweight

Mode of delivery	**Birthweight 3000-3999g**	**Birthweight 4000-4499g**	**Birthweight ≥ 4500g**
*AOR (95% CI)			
Neonatal convulsions			
VD	1.0	1.53 (1.26-1.85)	2.85 (2.16-3.76)
Emergency CS	2.50 (1.97-3.17)	1.64 (1.13-2.37)	1.24 (0.65-2.37)
VE/VE+CS	2.62 (2.12-3.24)	3.63 (2.77-4.74)	6.28 (4.29-9.20)
ICH			
VD	1.0	1.68 (1.17-2.41)	2.82 (1.63-4.89)
Emergency CS	1.02 (0.58-1.78)	0.91 (0.39-2.21)	0.83 (0.20-3.46)
VE/VE+CS	2.59 (1.74-3.86)	4.15 (2.55-6.76)	6.70 (3.31-13.57)
Brachial plexus injury			
VD	1.0	7.33 (6.42-8.37)	36.64 (31.97-41.99)
Emergency CS	0.33 (0.18-0.59)	0.33 (0.12-0.89)	0.46 (0.11-1.84)
VE/VE+CS	4.04 (3.31-4.93)	23.51 (19.44-28.42)	88.35 (71.98-108.44)

*Adjusted for maternal age, height, BMI, parity, diabetes, induction of labor, epidural anesthesia, fetal presentation, gestational age and indication for operative delivery

Study III: Protracted vacuum extraction and neonatal intracranial hemorrhage in infants born at term: a nationwide case-control study

This case-control study included all term VE-delivered newborns with a diagnosis of neonatal intracranial hemorrhage from 1999-2013. A total of 654 deliveries were included in the final study population (167 cases with ICH and 487 controls without ICH). Protracted extractions, i.e. extractions including vacuum duration >15 min, > 6 pulls or > 2 cup detachments, were more common among cases with ICH (Figure 4) Conditional logistic regression analysis was used to study the association between protracted VE and ICH. Compared to extractions adhering to guidelines, the risk of ICH was nine-fold (OR 8.91 95%, CI 5.22-15.20) among infants exposed to a difficult extraction. After adjustments for potential confounders, the aOR increased further to 9.27 (95 % CI 4.87-17.63).

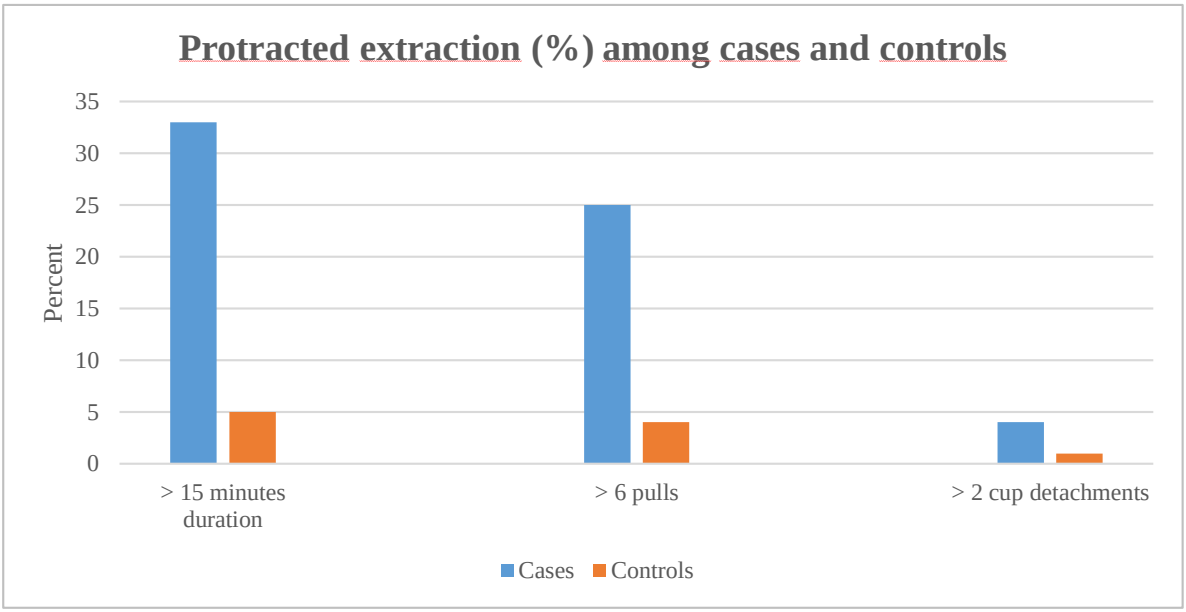


Figure 4. Proportion (%) of protracted extraction among cases with ICH and controls

Study IV: Predicting nonhemolytic neonatal hyperbilirubinemia

A total of 1 261 948 term infants were included in the study population. Of these, 2 711 (1.88%) received a diagnosis of nonhemolytic neonatal hyperbilirubinemia. Risk factors (aOR $\geq$ 1.5) for hyperbilirubinemia were: gestational age 37-38 weeks (aOR 2.83), failed VE (aOR 2.79), VE (aOR 2.22), Asian mother (aOR 2.09), primiparity (aOR 2.06), infant large-for-gestational-age (aOR 1.84), obese mother (aOR 1.83) and infant small-for-gestational-age (aOR 1.66).

Planned cesarean section was associated with a reduced risk (aOR 0.45). In relation to the combined load of different risk factors, the rates of hyperbilirubinemia varied from 0.2% to 25%. Combinations of these risk factors can be used to predict the individual risk of hyperbilirubinemia.

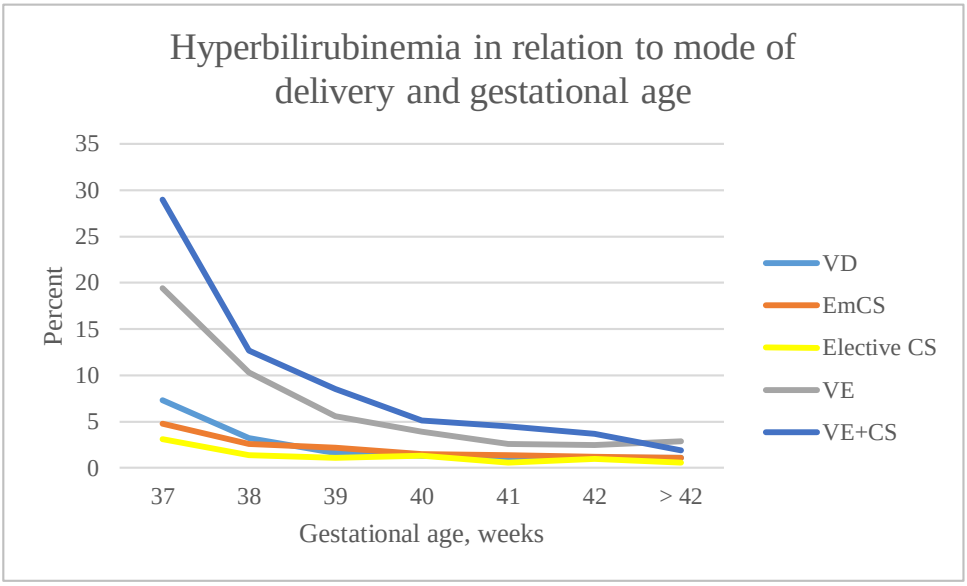


Figure 5. Variations in nonhemolytic neonatal hyperbilirubinemia in relation to mode of delivery and gestational age

7 DISCUSSION

7.1 METHODOLOGICAL DISCUSSION

Internal validity: Internal validity refers to the question of whether the study was performed in a reasonable way, i.e. if it measured what was intended to be measured with as few errors as possible. If the internal validity is low, conclusions on causal inference of the relation between exposure and outcome, may not be correct. There are two major types of errors that can affect the internal validity of a study: random errors and systematic errors. With large study populations, such as the studies of this thesis, random errors are not a problem. Systematic errors, however, are not affected by the size of the study. Systematic errors include selection bias, information bias and confounding (133). In observational research, like the four studies of this thesis, bias and confounding is always present to some degree and may decrease the internal validity of the study (136).

Selection bias: For the three cohort studies of this thesis, the intention was to compare neonatal outcomes after different modes of delivery. Here, selection bias can occur if other factors, affecting the neonatal outcome, were not equally distributed among the groups being compared. In an attempt to decrease the risk of selection bias, we choose only to include preterm deliveries in the first study, since preterm deliveries are more often complicated by maternal or fetal illness and since preterm infants are at significantly increased risk of ICH, compared with term infants. Furthermore, in study I and II, we included only deliveries with a spontaneous or induced onset of labor in an attempt to include only planned vaginal deliveries, since elective cesarean deliveries can be assumed to comprise the most complicated pregnancies. Still, a major limitation with our group comparisons are the lack of information about labor duration and about at what stage of labor the cesarean sections were performed. Very few studies that are large enough to detect differences in rare outcomes have access to such detailed information. In 2013, Walsh and colleagues (104) compared outcomes after different modes of delivery in 65 000 deliveries that had all reached the second stage of labor. They found that the rates of serious neonatal complications were similar after instrumental vaginal delivery compared with cesarean delivery at full dilatation. Therefore, we cannot exclude the possibility that the poorer outcomes after VE, compared with cesarean section in our Studies I and II, could be explained by unknown differences between the groups, for instance that infants born by VE in our studies might have been exposed to longer durations of labor than infants born by cesarean section.

For the case control study, we used a matched design to control for confounding. Paradoxically, matching can result in selection bias, since the matching is made for possible confounding factors related to the exposure. Thereby, the distribution of the exposure in the control group may not reflect the distribution in the source population for cases. In the case-control study of this thesis, the controls were matched for two variables: hospital and year of birth. These matching variables were chosen for two main reasons. Firstly, the exposure, protracted extraction, might have differed over time, since clinical practice and guidelines develop and change over time. There are also local variations in safety limits of guidelines for

VE as previously described in a Swedish study (134). Secondly, the diagnostic tools and procedures have developed over time and may still differ between hospitals. We considered both factors to be indirectly related to exposure and outcome, and a selection bias arising from these two variables would not be a serious threat to the internal validity. A non-matched design, however, could have decreased the validity of the inter-group comparisons due to detection bias, for instance if a larger proportion of cases were born at university hospitals with more diagnostic resources, or were born in the later part of the study period, compared with controls.

Information bias: The cohort studies (I, II and IV), were based on register data from the SMBR. The data is prospectively collected during pregnancy, delivery and the postpartum period and then reported to the SMBR. The risk of information bias due to maternal recall bias, is thereby avoided. However, another source of information bias may be under-reporting of infant diagnoses. The evaluation of the SMBR in 2002 (137) showed that infant diagnoses were missing to a varying degree during the evaluation period. The major explanation for missing diagnoses was problems with the introduction of new computerized delivery records in the latter evaluation period, but diagnoses were also missing more often when infants had been transferred between clinics. According to the Swedish National Board of Health and Welfare (personal communication), the quality of the infant diagnoses has been improved over time but no later evaluation has been published. Infant diagnoses from the register are however frequently used for research. In this case, missing diagnoses due to the initial problems with the extraction of information from computerized delivery records are mainly non-systematic errors and can thus be classified as non-differential misclassification. Such misclassification could decrease the prevalence of a diagnosis, but will have no or very little impact on the risk estimates, since all compared groups would be affected by some dilution of diagnoses. Missing diagnoses in infants who have been transferred between clinics is a more serious problem, since these infants may have been the most severely ill. Such differential misclassification might decrease the association between exposure and outcome.

Confounding: A confounder can be defined as a factor affecting both the exposure and the outcome, without being part of the causal pathway. In the studies of this thesis, several factors are associated with both the exposure, VE, and the outcome, neonatal complications. When confounding factors are known and measured, they can be controlled for in several ways, namely by: randomization (with a large enough sample), restriction, matching, stratification, and multivariate statistical analysis (136). In study I, analyses were restricted to preterm deliveries only. In study II, we stratified the population into different birthweight categories, and the outcomes after different modes of delivery could then be compared both within and between categories. This approach also showed that there was an interaction between birthweight and VE, since the risk estimates after VE multiplied as birthweight increased, suggesting effect modification. In study III, matching was used to control for confounding. Furthermore, we adjusted for possible confounders in multivariate logistic regression models in all four studies.

Still, there might be some residual confounding, since not all possible confounding factors are known, measured or they are not available in the SMBR, for example duration of labor and use of oxytocin.

A certain type of confounding that is most relevant in this thesis is *confounding by indication*. This occurs when the clinical indication for selecting a particular treatment or intervention, also affects the outcome. For example, more severe cases are likely to receive more intensive treatment and when comparing treatments, the more intensive treatment will appear to result in worse outcomes. Several previous studies comparing outcomes after VE with other modes of delivery have concluded that the increased risk seen after VE, might result from confounding by indication. The confounding would be that infants born by VE have been exposed to a more complicated labor, and that the complicated labor, rather than the extraction itself, results in poorer outcomes. For the studies of this thesis we have tried to adjust for the indication for the operative delivery.

External validity

External validity refers to generalizability and the question of whether it is possible to apply the results of one study to a different population. High external validity requires high internal validity, although high internal validity does not guarantee external validity. To increase external validity, the study population should be as similar as possible to the population you want to make inference on. It is further dependent on the environment and specifics of the situations. Study I, II and IV are population-based studies, which minimizes the risk of selection bias and we have no reason to believe that women giving birth by the assistance of VE in Sweden would differ much from women in other countries where VE is used on the same indications. However, it is possible that clinical performance differs between settings where VE is frequently used, such as the Nordic countries, and settings where VE is less common, for instance the United States. Very little has been published on management and performance of the actual extraction in VE deliveries and available reports are limited to specific regions and of limited size, and therefore, comparisons are difficult. Some differences between Sweden and the United States can be assumed, however. Such disparity can be illustrated by differences in the choice of instruments. A Swedish study investigated characteristics of 600 consecutive VE deliveries (134) and found that metal cup was used in 74 percent, Omnicup in 21 percent and soft rubber cup in only 0.8 percent. This is in contrast to a cohort study from the United States that investigated characteristics of 515 VEs in relation to neonatal outcome (138). Here, the authors reported that Omnicup was used in 96 percent and in the remainder, a similar cup called Mitysoft was used. Thus, such differences might decrease the applicability of our findings on settings very different from Swedish obstetric care.

Statistical vs clinical significance.

With a large study sample size, even the smallest differences become statistically significant. Statistically significant difference alone, simply means that the difference was unlikely to have occurred by chance, and is dependent by the level of significance chosen by the

researchers (α-level). It does not, however, tell us whether the difference is important or meaningful from a clinical perspective. Instead, this is up to the clinician to decide.

For the three register studies of this thesis, the study samples are large enough to produce statistically significant results on differences that are in fact very small. As an example, the individual contribution of some of the statistically significant risk factors for hyperbilirubinemia may have very little clinical significance. For instance, infants with overweight mothers had a 2.2 percent rate of hyperbilirubinemia, compared with 1.6 percent in the normal weight group. A very small difference, perhaps not of great clinical significance. However, when combined with other risk factors, the contribution of maternal overweight is clinically important. Furthermore, most of the outcomes studied in this thesis are very rare, regardless of mode of delivery, and for that reason, the clinical importance of our results may be questioned. We think that with such rare outcomes, the clinical importance is dependent on the severity of the outcomes. Thus, if we could reduce even a small number of serious cerebral and other neurological complications, it would be clinically important.

7.2 DISCUSSION OF FINDINGS IN STUDY I-IV

General discussion

This thesis includes four studies investigating different risk factors for neonatal complications following birth by VE: prematurity in Study I, high birthweight in Study II, characteristics of the extraction in Study III, and different combinations of maternal and obstetric risk factors in Study IV. Most of these factors were previously recognized clinically as risk factors for complications after VE, although not studied scientifically. Of course several other factors are also likely to affect the neonatal outcomes after VE, apart from those investigated in this thesis. Factors often mentioned in this context are for instance: unfavorable cup applications, e.g. deflexing and paramedian (59), traction force (60), condition of the fetus at the beginning of the extraction (139) and operator skills and experience (61).

Considering the widespread use of VE, it is most important that the method is evaluated, that risk factors for complications are investigated and that recommendations and guidelines for VE are evidence-based and up to date. Several aspects of current guidelines are still insufficiently studied, for instance maximum duration and number of pulls. Moreover, a previous study by Ahlberg and co-workers (134) demonstrated that several Swedish local clinical guidelines for VE lacked recommendations for gestational length and limits for duration and number of pulls. It is possible that the lack of evidence reduces the motivation to use and comply with guidelines. Our results from Study I and III also indicate that it is rather common to disregard safety recommendations and guidelines for VE. One third of cases with ICH and five percent of the controls were exposed to extractions exceeding safety limits and thus exposed to potentially harmful extractions. Among preterm infants, more than three percent were delivered by VE before 34 gestational weeks, despite recommendations of no use before this limit. Our studies cannot answer whether or not the operators were aware of

these safety recommendations, although it is possible that this reflects insufficient knowledge on indications, contra-indications, technique and principles for abandoning a difficult extraction. Furthermore, guidelines are not absolute, and in some situations, a deviation from the common recommendations may be the least bad option.

In all four studies, we present risk estimates expressed as odds ratios for complications after VE and compare to spontaneous vaginal delivery or cesarean section. It needs to be emphasized that serious complications after vacuum assisted deliveries are very rare and the absolute risk of the complications studied in this thesis is minimal. Nevertheless, we confirm and quantify the impact of these risk factors for neonatal complications following VE and point out risk factors and situations that calls for caution. Moreover, even if reported rates of complications associated with VE are generally low, they also differ between different reports and different populations. As an example, we noticed that the rates of ICH after VE was higher in the high birthweight groups in Study II, compared with the rates among preterm infants delivered by VE in gestational week 34-36 in Study I. Another example from other studies is that failure rates of the same device (Kiwi Omnicup), differed from eight percent (140) in one setting to 30 percent (141) in another setting. Such variations suggest there is room for improvement.

There is no question that inappropriate use of VE has the potential to cause both maternal and neonatal complications. A few studies have shown that prolonged extractions are associated with scalp injury and subgaleal hemorrhage (85, 142) and high number of pulls and cup detachments were associated with skull fracture and intracranial hemorrhage (81). A review of intrapartum deaths associated with cranial injury in the UK revealed that these injuries were strongly associated with difficult extraction and continued attempts at instrumental vaginal delivery, despite lack of progress (143). Also the results of Study II and III of this thesis indicate that poorly judged situations, resulting in protracted and difficult extractions is a major cause of serious complications following VE deliveries. VE is a complex procedure and our results indicate that improvements of guidelines, education, training and supervision, is required if we want to minimize the risks of complications associated with the procedure.

Study I: Preterm delivery by VE

The findings of this study have contributed to increased knowledge on the use of VE and the neonatal outcomes of VE in the preterm period. Previous research on preterm VE was very sparse and only three studies were published on this topic. One was done more than 40 years ago, one compared VE with forceps in the preterm period (144) and one compared neonatal morbidity in only 61 preterm infants with birth weights of 1,500-2,499 who were delivered by vacuum extraction and compared with 122 matched controls delivered by spontaneous VD (145). Neonatal morbidity was not significantly different between the different modes of delivery and the authors concluded that VE did not seem to increase neonatal morbidity in preterm infants with birthweights of 1,500-2,499 grams. Yet, current clinical guidelines

recommend that VE is avoided before 34 gestational weeks, since preterm infants may be more susceptible to ICH, cephalo- and subgaleal hematomas and jaundice (38).

Study I of this thesis was the first population-based study on VE in the preterm period, providing a large enough population to detect possible differences even in rare outcomes. Our results showed that VE was used, although infrequently, before 34 weeks, despite recommendations of no use before this limit. The rates of neonatal complications were generally low after all methods for delivery, except for ICH in the earliest gestations. When all gestational ages were included in the analyses, the rates of ICH were higher (1.91%) among infants born by CS during labor and by spontaneous vaginal delivery (1.48%), compared with VE (1.12%). However, among all infants born in gestational week 22-28, more than 20 percent were diagnosed with ICH, a rate that gradually decreased for each gestational week. In the earliest gestations most deliveries were spontaneous vaginal or cesarean. Very few VEs were performed in the gestational weeks when ICH due to prematurity occur, and the majority of all ICHs in this study population were intraventricular hemorrhages (88%), that occurred in the earliest gestations. Therefore, when the regression analysis was adjusted for confounders, including gestational age, the results were inverse. Compared with infants born after spontaneous VD or CS during labor, preterm infants delivered by VE had increased aORs (1.84) for ICH. The aORs for ICH was decreased among infants born by CS (0.76) in the adjusted models.

This study did not compare outcomes of VE in preterm infants with those in term infants. However, we note in retrospect that the rates of intracranial hemorrhage in preterm infants born by VE at gestational weeks 34-36 were significantly higher, compared with term infants born by VE in Sweden during the same period: 3.9/1000 and 3.8/10 000, respectively (105).

Study II: High birthweight and VE

It has previously been confirmed that high birthweight increases the risk of perinatal morbidity (146), that it is associated with increased risk of instrumental delivery (147) and that it is an important risk factor for failed VE (61). This study adds information about the specific impact of increasing birthweight in vacuum assisted deliveries. Our results showed that high birthweight has a stronger impact on the neonatal outcome after VE than previously known, with rates and odds ratios for complications that multiplied as birthweight increased among infants born by VE.

Even if our results show that high birthweight is a significant risk factor for complications in VE deliveries, the clinical importance of our findings may be limited. The weight is unknown until the infant is born and unfortunately, birthweight estimations are insufficient in detecting macrosomia. Hoopman and colleagues (148) compared the accuracy of 36 commonly used weight estimation formulas in suspected macrosomic fetuses and found that none predicted fetal macrosomia with sufficient accuracy for clinical use. Some formulas had advantages,

but none was reliable enough for fetuses of ≥4 500 g, and the larger the fetus, the more errors in estimations.

Furthermore, it is not solely the actual weight or size of the fetus that causes the complications. Among infants born by emergency CS the rates of complications were low and even decreased with increasing birthweight. However, in vaginal deliveries, spontaneous as well as vacuum assisted, high birthweight can contribute to a relative disproportion between the fetus and the maternal birth canal, causing prolonged second stage of labor and prolonged pushing. In VE deliveries, such disproportion could also result in difficult and protracted extractions. If there is a significant resistance in each pull and when the pulls do not result in descent, then injury is more likely to occur (90). There is also a strong association between VE and shoulder dystocia (61). Altogether 928 cases of shoulder dystocia were reported in the VE group of our study, corresponding to a total rate of one percent, and a rate of 7.5 percent among infants with a birthweight of ≥ 4500 g. A previous study reported that the rates increased in VE deliveries from 8.6 percent in infants weighing 4000-4250 g to 29 percent in infants weighing 4750-5000g (149).
The most important message of this study may be to consider an alternative method in case of a combination of suspected macrosomia and poor progress, and to discontinue a vacuum attempt early, in case traction does not result in descent.

Study III: Protracted and difficult VE
The question of whether VE as a method increases the risk of ICH has been debated. Previous well-known cohort studies of mode of delivery and risk for ICH (62, 103) have concluded that increased risk of ICH after VE most likely reflects confounding by indication, and that complicated labor, rather than the extraction itself, is the cause of ICH. In this study, we addressed the question by using a design different from previous studies: case-control design, which is efficient for studying rare outcomes. By collecting information from delivery records, we were able to assess details on factors during pregnancy, labor and the actual extraction. We found a strong association between protracted extractions and ICH with an adjusted OR of 9.27. Our result thereby gives little support for the hypothesis that complicated labor, rather than the method, causes ICH. Instead, we demonstrated that the most important differences between the cases with ICH and the controls were differences in the characteristics of the extractions.

Our result strengthens the advice not to exceed 15 minutes, not to use more than six pulls and to abandon the procedure if more than two cup detachments occur. However, this study does not answer the question of a safe limit for vacuum duration or number of tractions. Moreover, it gives very limited information on the mechanism involved and we cannot tell whether it is a mechanical effect of the actual vacuum duration, number of pulls and detachments, or whether it is just the time itself passing from decision to delivery. A delay in delivery, due to for example difficult or failed vacuum delivery could result in hypoxic injury (150). The increased risk could also be explained by unmeasured factors such as traction

force, that might correlate with protracted extractions. A recent Swedish study investigated traction force in 200 VE deliveries. The authors reported that higher than expected levels of traction force was used, and that traction force was often underestimated by operators (151). However, they found no association between traction force and neonatal complications.

We were also surprised by the frequent use of fundal pressure, in almost half of the cases and in one fourth of the controls. Fundal pressure is an intervention used to increase the progress of the second stage of labor. To our knowledge, fundal pressure is no longer taught or recommended by the formal educations of midwives and obstetricians, although obviously still a part of clinical practice. Few studies have investigated the use and consequences of the intervention, although existing studies show an association with shoulder dystocia (152).

Study IV: Risk factors for hyperbilirubinemia

In the fourth study, we showed that the risk of nonhemolytic neonatal hyperbilirubinemia varies substantially depending on a number of easily available risk factors. This was the first population-based study investigating risk factors for neonatal hyperbilirubinemia. The three most important risk factors were: gestational age 37-38 weeks, failed VE and VE. Several risk factors identified here had previously been described as significant contributors to non-hemolytic hyperbilirubinemia. This study confirmed the impact of these factors, added a few new risk factors, and questioned one previously described factor, increasing maternal age, since we found only a weak association between maternal age and hyperbilirubinemia. Unlike previous smaller studies, we showed that early term birth, i.e. gestational length 37-38 weeks, had a strong impact.

Earlier, most infants were diagnosed and treated for hyperbilirubinemia before hospital discharge. With a trend towards shorter postpartum stay at hospital, many infants reach their peak serum bilirubin concentration after discharge from hospital. Hyperbilirubinemia has also become the most frequent reason for readmission to hospital in the neonatal period (153). The results from this study can be used as a basis for individual risk assessment before hospital discharge and provide guidance for timing of hospital discharge and follow-up.

8 CONCLUSIONS AND CLINICAL IMPLICATIONS

- The rates of serious complications after VE were generally low, in all groups studied, meaning that the absolute risk of these complications is very small.

- Higher rates and increased adjusted odds ratios for complications after VE, compared with spontaneous vaginal delivery or cesarean section during labor, strenghtens the evidence behind the recommendation of careful use of VE in preterm deliveries. Our results support a continued cautious use, also at 34-36 weeks of gestation.

- High birthweight had a strong impact on the risk of neonatal complications following vacuum assisted delivery. Therefore, in deliveries with a clinical suspicion of a large fetus, the operator should be prepared that the extraction may be difficult and abandon the procedure in time, if traction does not result in adequate progress.

- The strong association between protracted extraction and ICH indicates that adherence to guidelines may prevent ICH in some infants born by vacuum assisted delivery. However, a significant proportion of cases suffering from ICH were exposed to extractions approaching the limits in guidelines, although not exceeding them. This indicates that also extractions adhering to guidelines can be harmful and that the safe limit for duration and number of pulls is unknown.

- Combinations of easily available maternal and obstetrical risk factors can be used for individual risk assessment for neonatal hyperbilirubinemia. Predicting the individual risk for this complication is important for the planning of both postpartum in-hospital care and follow-up after hospital discharge.

9 FUTURE PERSPECTIVES

- Besides studying risk factors for adverse neonatal outcomes after vacuum extraction, it is important to study long-term outcomes of ICH after vacuum extraction. At this point we do not know whether these ICHs had any impact on the long-term outcomes and previous follow-ups of ICH after VE are few. Therefore, we are planning to make a follow-up study of the children with ICH from Study III.

- There are large variations in complication rates between individual operators and between groups. These variations imply that there is room for improvements of both maternal and neonatal outcomes by theoretical education and practical skills training. Future studies should investigate whether such VE training could reduce maternal and neonatal complications related to VE deliveries.

- There is still a lack of knowledge regarding some aspects of a safe VE performance. For instance, we still have no answer to what is a safe vacuum duration or a safe number of pulls. Moreover, the impact of traction force needs to be further investigated.

- A frequent use of fundal pressure was noted during the work with the case-control study. More knowledge is needed on the use and consequences of this intervention.

- We found a higher than expected incidence of the serious complication kernicterus. Detailed investigation on background, clinical management and outcome of these cases would add information that could possibly be used to prevent future cases of kernicterus.

10 SVENSK SAMMANFATTNING

Sugklocka är ett instrument som används för att avsluta det sista skedet av en vaginal förlossning då det finns misstanke om hotande syrebrist hos barnet, då förlossningen går långsamt framåt, eller då mamman inte på egen hand kan eller orkar krysta ut barnet. I Sverige används sugklocka vid ungefär sju procent av samtliga förlossningar, vilket gör det till en vanlig förlossningsmetod. Riskerna för mor och barn är små men det är sedan tidigare känt att förlossning med sugklocka kan öka risken för vissa komplikationer. Hos barnet handlar det exempelvis om skador på huvudet, skador på nerver i skuldra, arm och hand, samt gulsot. De specifika riskfaktorerna för att dessa komplikationer ska uppkomma vid förlossning med sugklocka är däremot mycket lite studerade. Det övergripande syftet med denna avhandling var därför att identifiera riskfaktorer för komplikationer hos nyfödda barn som fötts med hjälp av sugklocka, för att därigenom ytterligare förbättra säkerheten vid denna typ av förlossning.

I avhandlingens första delstudie undersökte vi användandet av sugklocka vid förlossning före fullgången tid (<37 graviditetsveckor) och jämförde risken för komplikationer hos för tidigt födda barn som fötts med hjälp av sugklocka, med vanlig vaginal förlossning och med akut kejsarsnitt. Vi använde registerdata som rapporterats till Medicinska födelseregistret för åren 1999-2010 och drygt 40 000 förlossningar inkluderades i analyserna. Resultaten visade att sugklocka används vid nära sex procent av de prematura förlossningarna (kejsarsnitt före värkstart var exkluderade). De komplikationer som studerades var ovanliga, men risken att drabbas var något större efter förlossning med sugklocka, jämfört med spontan vaginal förlossning eller förlossning med akut kejsarsnitt.

I avhandlingens andra delstudie var syftet att undersöka vilken betydelse storleken på barnet hade för komplikationsrisken vid förlossning med sugklocka och jämföra den med spontan vaginal förlossning eller kejsarsnitt efter värkstart. Även denna studie baserades på data från Medicinska födelseregistret för åren 1999-2012 och här inkluderades endast fullgångna graviditeter (≥37 graviditetsveckor) och barn med en födelsevikt på 3000 gram eller mer. Våra resultat visade att andelen komplikationer ökade med stigande födelsevikt hos barn som fötts med hjälp av sugklocka, men även bland barn som fötts spontant vaginalt. Hos barn födda med akut kejsarsnitt var förhållandet det omvända och andelen barn med komplikationer minskade med stigande födelsevikt.

I den tredje studien ville vi undersöka om faktorer vid själva extraktionen påverkar risken för intrakraniell blödning hos barn som fötts med hjälp av sugklocka. Studien var en fall-kontrollstudie baserad på data från förlossningsjournaler. Fallen utgjordes av samtliga fullgångna barn som fötts med hjälp av sugklocka under åren 1999-2013 och som drabbats av intrakraniell blödning i samband med förlossningen. Kontrollerna, matchade för födelseår och sjukhus, var också födda med hjälp av sugklocka, men var inte diagnosticerade med intrakraniell blödning. Detaljerad information om graviditet, förlossning och det första omhändertagandet i samband med födelsen inhämtades genom systematisk granskning av mödravårds- och förlossningsjournaler. Resultaten visade att betydligt fler barn som drabbats

av intrakraniell blödning hade exponerats för "svår extraktion", vilket definierades som extraktionstid mer än 15 min, mer än sex dragningar med sugklockan eller mer än två ofrivilliga klocksläpp, alltså extraktioner där säkerhetsrekommendationerna för sugklockeförlossning överskridits. Risken att drabbas av intrakraniell blödning ökade med nio gånger bland de som exponerats för "svår extraktion", jämfört med sugklockeförlossning där säkerhetsrekommendationerna följts.

Den fjärde delstudien var en registerbaserad kohortstudie med data från Medicinska födelseregistret för åren 1999-2010. Syftet var att studera hur risken för behandlingskrävande gulsot förändrades beroende på olika faktorer hos mamman, vid förlossningen och hos barnet. Resultatet visade att risken för gulsot varierade kraftigt utifrån de studerade riskfaktorerna. De enskilt starkaste faktorerna var kort graviditetslängd (37-38 veckor), förlossning med kejsarsnitt efter misslyckat sugklockeförsök, förlossning med sugklocka, asiatisk härkomst hos modern, att modern var förstföderska, att vara född stor för graviditetslängden (LGA), fetma hos modern, samt att vara född liten för graviditetslängden (SGA). Genom att kombinera dessa riskfaktorer kunde risken för gulsot individuellt beräknas. Störst risk att utveckla behandlingskrävande gulsot hade barn som fötts med hjälp av sugklocka två till tre veckor före fullgången tid.

Sammanfattningsvis visar våra studier att den absoluta risken för komplikationer hos barnet efter förlossning med sugklocka är mycket liten. Dock pekar våra resultat på några situationer som bör uppmärksammas extra: Barn som är födda med hjälp av sugklocka i graviditetsvecka 37-38 har stor risk att utveckla behandlingskrävande gulsot. Riskfaktorer för komplikationer vid förlossning med sugklocka är: för tidig födsel, hög födelsevikt, lång extraktionstid, många drag och att sugklockan lossnar under dragning.

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