Kati Ojala

MODERN METHODS IN THE PREVENTION AND MANAGEMENT OF COMPLICATIONS IN LABOR
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Academic dissertation to be presented with the assent of the Faculty of Medicine of the University of Oulu for public defence in Auditorium 4 of Oulu University Hospital, on 7 May 2010, at 12 noon

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Abstract

Although in Finland the incidence of maternal and neonatal mortality in labor is very low, labor carries some risks. This study focused on two major complications in labor: fetal asphyxia and maternal hemorrhage. The roles of fetal electrocardiographic ST-analysis (STAN) and pelvic artery embolization in the prevention and management of these complications were investigated.

Intrapartum fetal monitoring aims at a timely detection of fetal hypoxemia. When non-selected parturients were randomly assigned to be monitored during labor either by STAN or conventional cardiotocography, no differences between the groups were detected in terms of neonatal outcome and operative delivery rates. Only the incidence of fetal blood sampling was lower in the STAN group. In the interpretation of the STAN tracings according to the guideline matrix provided by the STAN manufacturer, the interobserver agreement was moderate; in terms of clinical decision-making as to whether to intervene in the labor, this agreement varied from moderate to good among STAN-trained obstetricians.

The aim of prophylactic pelvic artery occlusion balloon catheterization, with or without embolization, is to reduce hemorrhage in elective cesarean operations in patients with placenta accreta. Furthermore, pelvic arterial embolization may be performed post partum if bleeding continues after cesarean hysterectomy, or may serve as an alternative to hysterectomy. In the present study, pelvic artery catheterization and embolization did not reduce blood loss during cesarean delivery, nor did it decrease the need to perform hysterectomy in patients with placenta accreta. In the management of massive postpartum hemorrhage, pelvic artery embolization was most successful in patients with uterine atony, with a success rate of 75% in achieving hemostasis. However, the angiographic method included risk of complications, the most hazardous being thromboembolic complications.

To conclude, STAN does not provide improvement in intrapartum fetal monitoring when compared to cardiotocography, but the need for fetal blood sampling is reduced. This may relate to the fact that subjective interpretation of STAN data is moderate at best. Prophylactic catheterization and embolization of pelvic arteries does not improve the surgical outcome of patients with placenta accreta. In the management of postpartum hemorrhage, pelvic artery embolization should be considered, especially in cases with uterine atony.

Keywords: arterial embolization, fetal asphyxia, interobserver agreement, placenta accreta, primary post-partum hemorrhage, STAN
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Oulu, April, 2010

Kati Ojala
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BE</td>
<td>Base excess</td>
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<tr>
<td>BD</td>
<td>Base deficit</td>
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<tr>
<td>BPM</td>
<td>Beats per minute</td>
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<td>CP</td>
<td>Cerebral palsy</td>
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<td>CS</td>
<td>Cesarean section</td>
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<td>CTG</td>
<td>Cardiotocogram</td>
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<td>ecf</td>
<td>Extracellular fluid</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>FBS</td>
<td>Fetal blood sample/sampling</td>
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<td>FECG</td>
<td>Fetal electrocardiogram</td>
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<td>FHR</td>
<td>Fetal heart rate</td>
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<tr>
<td>GA</td>
<td>Gestational age</td>
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<tr>
<td>H⁺</td>
<td>Hydrogen ion</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>Bicarbonate ion</td>
</tr>
<tr>
<td>H₂CO₃</td>
<td>Carbonic acid</td>
</tr>
<tr>
<td>HIE</td>
<td>Hypoxic-ischemic encephalopathy</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<tr>
<td>IQ</td>
<td>Intelligence quotient</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NICU</td>
<td>Neonatal intensive care unit</td>
</tr>
<tr>
<td>PPE</td>
<td>Postpartum embolization</td>
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<td>PPH</td>
<td>Primary postpartum hemorrhage</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>STAN</td>
<td>Automated ST-analysis</td>
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<td>STV</td>
<td>Short term variability/variation</td>
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List of original publications

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1 Introduction

In Finland, as in other developed countries, the incidence of maternal and neonatal mortality in labor is low. However, even in delivery units equipped with modern technology, labor carries some well-known but not totally controllable risks. For the fetus, the most threatened complication in labor is asphyxia. For the mother, the most hazardous risk in labor is a massive hemorrhage.

Intrapartum fetal asphyxia is estimated to result in neonatal brain injury in approximately 1 per 1000 deliveries (Thornberg et al. 1995). In developing countries without either fetal monitoring or emergency operative deliveries, the risk of a hypoxic injury is remarkable. In 1995, the World Health Organization estimated that perinatal asphyxia accounted for a fifth of global neonatal deaths (Hack & Stork 2009). The aim of intrapartum fetal monitoring is the timely identification of developing asphyxia, and thus rescuing the fetus. Electronic fetal monitoring was developed with the introduction of cardiotocography in the 1960s (Hon & Hess 1960). At the same time, pH analysis of fetal scalp blood sample was introduced as a diagnostic method to identify the acidotic fetus in labor (Saling 1964). Despite their well-known limitations, combination of these two methods has been regarded as the reference methodology in intrapartum fetal surveillance for decades. The most recent technology in fetal monitoring is automated ST waveform analysis (STAN) of the fetal electrocardiogram (FECG). In adults, ST waveform changes occur during myocardial hypoxemia. Extrapolation of these changes to the hypoxic fetus forms the background of fetal ST analysis. The current STAN technology was introduced at the beginning of this millennium, but its development originates in the 1970s (Rosen et al. 1976).

Globally, over a half a million women die annually from causes related to pregnancy and childbirth. Hemorrhage accounts for over one-fourth of all direct maternal deaths and remains the most common cause of maternal deaths (Ramanathan & Arulkumaran 2006). Between 1970 and 1994, there were 100 maternal deaths in Finland; in 23%, the cause of death was major obstetric hemorrhage (Erkkola 1997). A common etiology causing severe primary postpartum hemorrhage is placenta accreta. If placenta accreta is diagnosed prenatally, elective cesarean delivery may be planned ahead and, thus, maternal morbidity may be minimized (Eller et al. 2009). Endovascular embolization techniques have been used since the 1960s to control pelvic hemorrhage. Successful selective embolization of the uterine arteries in the management of postpartum hemorrhage was first described in 1979 (Brown et al. 1979). The
technique has been further developed to prevent obstetric hemorrhage. Prophylactic occlusion balloon catheterization and embolization of the internal iliac arteries have been used with success in patients with prenatally diagnosed placenta accreta (Dubois et al. 1997).

This study focused on two major complications in labor: fetal asphyxia and maternal hemorrhage. The roles of fetal electrocardiographic ST-analysis and pelvic artery embolization in the prevention and management of these complications were investigated.
2 Review of the literature

2.1 Intrapartum fetal asphyxia

Asphyxia may be defined as a condition of impaired gas exchange that, if persistent, leads to hypoxemia, hypercapnia, and accumulation of waste products, with significant metabolic acidosis. When profound and prolonged, asphyxia ultimately leads to death or permanent cellular damage. In Finland, birth asphyxia is determined according to the International Classification of Disease (ICD-10) based on the terms of Apgar scores: a 1-minute Apgar score of 4–7 for mild to moderate birth asphyxia, and a 1-minute Apgar score of 0–3 for severe birth asphyxia, together with neonatal signs of asphyxia. However, the ICD codes for diagnosing birth asphyxia have been widely criticized for inaccuracy (ACOG 1998a, Dzakpasu et al. 2009). The American College of Obstetricians and Gynecologists suggest that the term “birth asphyxia” should be reserved for neonates with all the following conditions: 1) profound metabolic or mixed acidemia (pH<7.0) in an umbilical artery sample if obtained, 2) Apgar-score of 0–3 for longer than 5 minutes, 3) neonatal neurologic manifestations such as seizures, coma, or muscle tone abnormalities, or signs of multisystem organ failure (ACOG 1998a).

2.1.1 Respiratory and metabolic acidosis

Intrapartum fetal asphyxia occurs commonly via hypoxemia under a decreased availability of oxygen. Hypoxemia means low oxygen content in the blood, whereas during hypoxia, the tissues suffer from low oxygen content. In ischemia fetal organs are restrictively perfused. During disturbed gas exchange in the placenta, fetal blood oxygen tension (pO_2) gradually falls and carbon dioxide tension (pCO_2) elevates, resulting in hypercapnia. The excess pCO_2 is removed by bicarbonate – carbonic acid buffering system:

\[
H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O
\]

Respiratory acidemia or acidosis occurs in response to excess CO_2 levels, which lead to an increase in hydrogen (H^+) ions in the blood. Respiratory acidosis may be defined as decreased blood pH with an elevated blood pCO_2 (Siggaard-Andersen & Engel 1960)
With a continuously reduced oxygen supply, hypoxemia results in a shift from aerobic to anaerobic metabolism in the fetal tissues. The end products of anaerobic metabolism are lactate and $\text{H}^+$. Even a slight deviation of $\text{H}^+$-ion concentration from normal values can cause marked changes in chemical reactions. Therefore, the maintenance of body homeostasis is effectively defended with buffering systems. The most important buffer is the bicarbonate buffer; other buffers include hemoglobin, plasma proteins, and organic/inorganic phosphate. Metabolic acidemia or acidosis may be regarded as an active metabolic response to hypoxia. It can be defined as decreased blood pH and reduced base excess below the normal range (Siggaard-Andersen & Engel 1960).

### 2.2 Intrapartum fetal surveillance

The aim of intrapartum fetal monitoring is to identify fetal hypoxia and intervene appropriately before severe asphyxia and permanent damage occur. Changes in the fetal heart rate (FHR) associated with uterine contractions are regarded as potential signs of fetal distress. FHR monitoring may be achieved with auscultation or electronic devices. Other current methods aimed at detecting intrapartum fetal asphyxia include STAN, fetal scalp pH or lactate sampling, and fetal pulse oximetry (Nordstrom et al. 1994, Peat et al. 1988, Rosen et al. 1976).

#### 2.2.1 Fetal heart rate monitoring

Auscultation of the FHR may be performed with a Pinard stethoscope or Doppler ultrasound. Intermittent FHR auscultation means counting the fetal heart beats at specific intervals. Electronic FHR monitoring is achieved with either an external Doppler transducer overlaying the fetal heart on the mother’s abdomen, or an internal spiral scalp electrode. Cardiotocography (CTG) allows for the simultaneous electronic monitoring of FHR and uterine contractions. The pressure-sensitive external contraction transducer, a tocodynamometer or tocotransducer, measures the tension of the maternal abdominal wall as an indirect measure of the myometrial activity and intrauterine pressure; intrauterine pressure can alternatively be monitored via an internal catheter. Intrapartum FHR monitoring may be performed either intermittently or continuously.

Intermittent FHR auscultation has been compared with continuous electronic FHR monitoring in several clinical trials. The Dublin randomized controlled trial (RCT) included 12964 women; the intermittent auscultation was performed either
with a Pinard stethoscope or intermittent Doppler ultrasound. The study showed no differences in the neonatal outcomes, including an Apgar score <3 at 1 or 5 minutes, umbilical cord venous pH, and the need for resuscitation or a special care unit. The cesarean section (CS) rates were also similar (MacDonald et al. 1985). A Cochrane meta-analysis concluded that a continuous CTG compared to intermittent auscultation showed no significant difference in overall perinatal death rate or in the incidence of cerebral palsy (CP), but it is associated with a halving of neonatal seizures. The rates of CS and instrumental delivery are higher with continuous CTG compared to intermittent auscultation (Alfirevic et al. 2006). By contrast, a smaller RCT, including 1428 mothers, showed that continuous electronic FHR monitoring was associated with decreased perinatal mortality when compared to intermittent auscultation (2.6 per 1000 vs. 13 per 1000, p=0.04) (Vintzileos et al. 1993). In high-risk pregnancies, continuous intrapartum CTG monitoring has been found to be useful in detecting asphyxia and preventing neonatal encephalopathy (Westgate et al. 1999). Use of continuous CTG in all parturients may restrict the existence of CP resulting from intrapartum asphyxia to only unavoidable hypoxic accidents (Gaffney et al. 1994, Sameshima et al. 2004).

Interpretation of the CTG is based on visual, subjective analysis of the FHR patterns, and thus it is subject to intra- and inter-observer variation. Since the introduction of CTG, a number of attempts have been made to formalize the interpretation and thus improve consistency in the assessment of CTG tracings. The International Federation of Gynecology and Obstetrics (FIGO) launched a clinical guideline to the interpretation of CTG tracings in 1987 (Rooth et al. 1987). The guideline recommends classifying FHR patterns as follows:

**Baseline fetal heart rate**, expressed in beats per minute (bpm), is the mean level of the FHR when this is stable. Normal baseline FHR ranges between 110 and 160 bpm. **Bradycardia** refers to a FHR ≤110 bpm for more than 10 minutes, and **tachycardia** is FHR ≥160 bpm for more than 10 minutes. **Variability** is measured by description of the amplitude around the baseline. Variability may be further classified into absent, minimal (≤5 bpm), moderate (from 6 to 25 bpm) or marked (>25 bpm) variability, according to the amplitude; marked variability is sometimes called saltatory variability. As a result of physiological conditions, fetal beat-to-beat intervals are constantly subject to small changes. This short term variability (STV) cannot be interpreted by the naked eye. Therefore, in a clinical assessment of CTG tracings, variability usually means gross or long-term variability, excluding accelerations and decelerations. **Sinusoidal pattern** has a smooth, sine wave-like pattern of regular frequency and amplitude. **Accelerations**
are transient increases in heart rate of $\geq 15$ bpm and lasting $\geq 15$ seconds; acceleration of $\geq 10$ minutes is a baseline change. Decelerations are transient episodes of slowing of FHR below the baseline of $\geq 15$ bpm, and lasting $\geq 10$ seconds. Early deceleration is a shallow, brief deceleration occurring at the same time as the peak of the contraction. Late deceleration is delayed in timing with the nadir of the deceleration occurring after the peak of the contraction. Variable decelerations are associated with uterine contractions, but their onset, depth and duration vary. (Rooth et al. 1987) The guidelines for interpretation of FHR have since been updated several times. The most recent update, including, e.g., a more detailed definition of decelerations, was launched by the American College of Obstetricians and Gynecologists in 2008 (Macones et al. 2008).

FHR variability results from a continuous balancing and interacting of the sympathetic and parasympathetic branches of the autonomic nervous system (Dalton et al. 1983). Normal FHR variability indicates that the fetus is compensating well, is capable of centralizing the oxygenated blood and thus is unlikely to have significant acidosis (Paul et al. 1975). Undetectable or minimal FHR variability is the most consistent indicator of developing acidemia, especially when combined with other FHR abnormalities, indicating central nervous system depression (Ikeda et al. 1998, Parer et al. 2006, Shields & Schifrin 1988). Decreased variability may alternatively be related to drugs depressing the central nervous system (Ingemarsson & Ingemarsson 1987).

Tachycardia is a result of an increase in the sympathetic and decrease in the parasympathetic activity (Cohen & Yeh 1986). It may be a sign of an early fetal hypoxia, especially if associated with late decelerations or decreased variability (Ingemarsson & Ingemarsson 1987). Alternatively, tachycardia may be the first sign of intrauterine infection or maternal fever. Increased FHR may also be related to fetal anemia, maternal hyperthyroidism, increased maternal sympathetic tone, use of betasympathomimetic drugs or increased fetal activity (Ingemarsson & Ingemarsson 1987).

Bradycardia is the response of the fetus to hypoxia: the myocardial activity is depressed during restricted oxygen supply (Fletcher et al. 2006). The fall in the FHR is a result from a vagal stimulus mediated by the fetal chemoreflexes, and can be prevented by parasympathetic blockade (Itskovitz et al. 1983, Jensen & Hanson 1995). If hypoxemia is severe and prolonged, the initial vagal bradycardia results in myocardial hypoxia (Harris et al. 1982). Non-asphyxial causes of fetal bradycardia include fetal head compression, the mechanism probably being increased intracranial pressure and reduced cerebral perfusion, atrio-ventricular...
heart block, and congenital heart anomalies (Crawford et al. 1985, Young & Weinstein 1976).

During labor, FHR decelerations occur mostly as a direct consequence of uterine contractions and consequent reduction in uterine and placental perfusion (Ingemarsson & Ingemarsson 1987, Westgate et al. 2007). The depth of the deceleration is grossly related to the severity of hypoxia: shallow decelerations indicate a modest fall in uteroplacental blood flow, and a deep deceleration indicates total or near-total reduction in blood flow. Brief and shallow early decelerations are not associated with fetal acidosis (Ingemarsson & Ingemarsson 1987). Prolonged, repeated deep decelerations are associated with a decrease in the availability of oxygen, and when repeated frequently, gradually lead to metabolic acidosis (Sameshima et al. 2004, Parer et al. 2006). However, the FHR patterns indicating fetal asphyxia are frequently also seen in normal, well-being fetuses, indicating that the CTG is not a specific tool in the identification of neonatal metabolic acidosis (Larma et al. 2007).

Despite attempts to formalize the interpretation of CTG tracings, several studies have demonstrated that the interobserver agreement in assessing CTG tracings is inadequate even among experienced obstetricians (Ayres-de-Campos & Bernardes 1999, Bernardes et al. 1997, Blix et al. 2003, Vayssiere et al. 2009, Westerhuis et al. 2009). For clinical purposes intrapartum CTG might be convenient for classification into categories according to the presence or absence of non-reassuring FHR features (Dellinger et al. 2000). Classification systems attempt to discriminate healthy fetuses from those proceeding to acidemia; thus, they serve as a clinical guideline for making the decision to intervene.

2.2.2 Fetal electrocardiogram

The electrocardiogram (ECG) is a record of fluctuations in the myocardial action potentials during the cardiac cycle (Fig. 1). Atrial depolarization, which equals to atrial contraction, is represented by a P wave in ECG. The PR segment reflects the conduction time to the atroventricular (AV) node, and the QRS complex reflects ventricular depolarization, i.e., ventricular contraction. The ST segment and T wave reflect ventricular repolarization (relaxation). These processes are based on the action of the sodium/potassium (Na/K) pump, which is fuelled by adenosine triphosphate (ATP) and activated by intracellular calcium (Ca). Since repolarization of the ventricles is an energy-requiring process, the morphology of the ST waveform is dependent on the substances influencing the Na/K pump.
Reduced efficiency of the Na/K pump causes K⁺ release, which in turn results in an elevation of the ST segment. These ST waveform changes occur during myocardial hypoxemia in adults, and extrapolation of these changes to the hypoxic fetus forms the background of ST waveform studies. From the ECG, STAN analyzes the T-wave, expressed as a ratio of heights of the T wave and concomitant QRS complex (T/QRS ratio), and the ST-segment waveform. The features of a normal ECG-complex are shown in Fig. 1.

Fig. 1. The normal electrocardiogram complex.

T wave and ST interval elevation

Ventricular action is dependent on the equilibrium between the available energy and energy consumed. In the hypoxic state, this equilibrium is compromised, and a negative energy balance will occur. Fetal adaptation to this situation occurs through chemoreceptor-mediated adrenaline surge, β-adrenoceptor-mediated anaerobic metabolism, and myocardial glycogenolysis. Hypoxemia stimulates catecholamine release, and associated myocardial glycogenolysis correlates with higher blood lactate levels, elevated ST waveform and a raised T/QRS ratio (Greene et al. 1982, Rosen & Kjellmer 1975, Rosen et al. 1976, Rosen et al. 1984, Rosen & Isaksson 1976). As the rate of glycogenolysis increases, the T-wave amplitude will rise (Rosen & Isaksson 1976).
Observational studies have shown increased T/QRS ratios in human newborns with low Apgar scores and low umbilical artery pH values (Hokegard et al. 1979, Jenkins et al. 1986). A progressive elevation in the ST waveform combined with abnormal CTG is shown to correlate with developing fetal metabolic acidosis (Westgate et al. 1993). Some other early observational human studies were unable to demonstrate associations between T/QRS ratio and birth asphyxia, low Apgar scores, and FHR changes (Maclachlan et al. 1992, Murphy et al. 1992, Newbold et al. 1989, Newbold et al. 1991). Moreover, a study comprising 47 chronically instrumented fetal sheep showed no correlation between T/QRS ratio and fetal metabolic status and survival; the inter-animal variation in the T/QRS complex was large during asphyxia but also during the normoxemic period (de Haan et al. 1995).

Interestingly, persistent ST elevation with a normal CTG has been associated with a higher median arterial pH at delivery (Westgate et al. 1993). In addition, a significant correlation between nulliparity and ST elevation has been found (Yli et al. 2008). These findings may indicate that, in normal labor, the increased sympathetic tone stimulates myocardial glycogenolysis causing a rise in the T wave amplitude (Yli et al. 2008).

In summary: the fetus is shown to react to acute intrapartum hypoxemia with an elevation of the ST segment and increase of the T wave. These changes indicate adaptation of the myocardium to the hypoxic stress with myocardial glycogenolysis and enhanced myocardial performance (Rosen et al. 2004).

**Negative ST interval**

Under progressive hypoxia, when the energy balance can no longer be maintained with anaerobic metabolism, ischemia occurs in the endocardium. This results in an imbalance between the endocardium and the myocardium. The imbalance causes altered repolarization in the myocardial cells and prolonged depolarization in the endocardium, reflected in the ECG complex through a depression of the ST interval below the baseline (Wohlfart 1987). In the fetus, a negative ST interval indicates that the myocardium is not fully responding to the hypoxic stress (Rosen et al. 2004). In growth-retarded guinea pigs, a negative ST waveform was shown to be associated with ineffective anaerobic metabolism under hypoxia (Widmark et al. 1991). In an animal study comprising chronically instrumented fetal sheep, the appearance of negative and biphasic ST waveforms indicated the development of severe fetal decompensation under progressive hypoxia (Westgate et al. 2001).
A negative ST interval has been observed to correlate with severe birth asphyxia in human neonates, yet a recent case-control study failed to show any association between negative ST interval and neonatal cord artery pH (Melin et al. 2008, Westgate et al. 1993).

The myocardial performance may also be affected by other factors beyond hypoxia. A negative ST interval has been observed more frequently in fetuses of mothers with diabetes mellitus compared to non-diabetic pregnancies; maternal diabetes is a predisposing factor for fetal hypertrophic cardiomyopathy (Yli et al. 2008).

**PR interval**

The relation of the FECG PR time-interval to FHR changes has been thoroughly investigated. Normally when the heart rate slows and the R-peak to R-peak interval lengthens, the PR interval lengthens consequently. During hypoxia, this is reversed in the fetus: the PR interval of the fetal ECG shortens, thus optimizing the filling of the atrium (Strachan et al. 2000, Widmark et al. 1992). An explanation of this might be a different response of the fetal sinoatrial and atrioventricular nodes to hypoxia (Murray 1986). In a RCT on 1038 women undergoing high-risk labor, the PR time-interval analysis added to CTG did not show a significant benefit in neonatal outcomes or the rate of operative delivery when compared to CTG only (Strachan et al. 2000).

### 2.2.3 Automated ST analysis (STAN)

The clinical application of the FECG ST analysis, STAN, is an automatic system providing continuous information on T wave and ST interval changes during labor (Luzietti et al. 1999). The most recent STAN technology is a combination of CTG and ST analysis. In the presence of a ST event, the decision for possible intervention is based on combined information from STAN and CTG, in the context of the clinical situation (Amer-Wahlin et al. 2001). The clinician has to interpret and classify the concurrent CTG according to the STAN clinical guideline matrix as presented in Table 1; the matrix is based on the FIGO FHR interpretation guidelines (Rooth et al. 1987). With a combination of several intermediary observations, the CTG should be classified as abnormal (Amer-Wahlin et al. 2007).
Table 1. Classification of cardiotocography (CTG) tracings according to the STAN guideline matrix (Sundström et al. 2000).

<table>
<thead>
<tr>
<th>CTG</th>
<th>Basic heart rate (bpm)*</th>
<th>Variability, reactivity</th>
<th>Decelerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>110–150</td>
<td>Normal (5-25bpm),</td>
<td>No/early decelerations, uncomplicated variable decelerations &lt;60 sec and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>accelerations</td>
<td>loss of &lt;60 beats</td>
</tr>
<tr>
<td>Intermediary</td>
<td>100–150 or 150–170</td>
<td>Decreased &gt;40 min,</td>
<td>Uncomplicated variable decelerations &lt;60 sec and loss of &gt;60 beats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no accelerations</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>&gt;170 or &lt;100</td>
<td>Decreased &gt;60 min,</td>
<td>Repeated late decelerations, variable complicated decelerations &gt;60s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sinusoidal pattern</td>
<td></td>
</tr>
<tr>
<td>Preterminal</td>
<td>Silent pattern</td>
<td>No variability, no</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>accelerations</td>
<td></td>
</tr>
</tbody>
</table>

*bpm=beats per minute

A ST event may be expressed as an episodic T/QRS rise, a baseline T/QRS rise or the appearance of repeated episodes of biphasic ST segment (Luzietti et al. 1999). An episodic T/QRS rise means a temporary increase in the median T/QRS values of >0.10 units for less than 10 minutes. A baseline T/QRS rise means consistent increase in the T/QRS ratio values of >0.05 units for more than 10 minutes. A biphasic ST segment means depression of the ST interval. The ST segment changes are quantified by a scoring system into three grades: biphasic ST grade 1 means a negative ST segment slope above the baseline of the ECG, biphasic ST grade 2 indicates a negative ST segment slope cutting the baseline, and biphasic ST grade 3 represents a negative or depressed ST segment below the baseline. In clinical practice only the biphasic ST grades 2 and 3 are significant. When these biphasic ST segments grade 2 or 3 are seen repeatedly, they form an episode, and repeated episodes of biphasic ST’s indicate a ST event (Sundström et al. 2000).

The clinical guideline matrix provides the clinician with a tool to identify possible fetal distress and thus make a timely intervention (Table 2). According to the guideline, intervention may be either operative delivery within 20 minutes with cesarean section or assisted vaginal delivery, or alleviation of fetal distress by changing maternal position, stopping oxytocin infusion or administering intravenous fluids (Amer-Wahlin et al. 2001).
**Table 2. Clinical guidelines for ST-information and concomitant cardiotocography (CTG) indicating intervention (Sundström et al. 2000).**

<table>
<thead>
<tr>
<th>ST change</th>
<th>CTG classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Episodic T/QRS rise</td>
<td>&gt;0.15</td>
</tr>
<tr>
<td>Baseline T/QRS rise</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Biphasic ST segment</td>
<td>Continuous &gt;5min</td>
</tr>
</tbody>
</table>

*Abnormal CTG persisting ≥60 minutes indicate intervention.

The first RCT comparing CTG only and CTG with STAN, the Plymouth study, was conducted using the former STAN technology, which provided on-line numeric information of alterations in T/QRS ratio to be verified by visual inspection of the paper printout (Westgate et al. 1993). Among 2434 women in high-risk labor, the combination of STAN and CTG was associated with a 46% reduction in operative deliveries for fetal distress (ODFD). In addition, a trend toward less metabolic acidosis and fewer low 5-minute Apgar scores was seen in the STAN arm; however, the difference did not reach statistical significance. The rate of fetal blood sampling (FBS) was similar in both groups. The authors concluded that ST analysis can be safely used to discriminate CTG changes in labor.

The current automated STAN monitor was used in the Swedish RCT, that compared CTG and CTG with STAN in intrapartum fetal monitoring in a non-selected population (Amer-Wahlin et al. 2001). In 4966 women, assigned into two groups according to the monitoring system, the CTG+STAN group showed significantly lower rates of metabolic acidosis (0.7% vs. 2%, p=0.02), and operative delivery for fetal distress (8% vs. 9%, p=0.047) than the CTG group. The rate for FBS was equal in the groups: 9% vs. 11%, p=0.12. No differences between the groups were found regarding Apgar scores, admissions to a neonatal intensive care unit (NICU), or neonatal encephalopathy. Controversially, a French RCT of 799 women showed no difference between CTG+STAN and CTG only in neonatal outcome or operative delivery rate; the rate of FBS was significantly lower in the STAN group (Vayssiere et al. 2007).

Several retrospective and prospective observational studies have indicated improvement in fetal surveillance with the use of STAN. The addition of STAN to
CTG monitoring is reported to improve the specificity of detecting fetal compromise and decrease the rates of operative deliveries, neonatal metabolic acidosis and neonatal encephalopathy (Amer-Wahlin et al. 2002, Kwee et al. 2004, Luzietti et al. 1999, Massoud et al. 2007, Noren et al. 2003, Noren et al. 2006, Welin et al. 2007). Contradictorily, however, some observational studies suggest that STAN has poor positive predictive value and sensitivity for metabolic acidemia at birth, and its use does not change the incidence of emergency operative delivery or neonatal encephalopathy (Dervaitis et al. 2004, Doria et al. 2007). A recent study indicated that, although the presence of ST events increases the probability of fetal acidemia, ST events are also frequent among controls with normal blood gas values. Furthermore, ST events with abnormal CTG patterns may appear late and inconsistently in the hypoxic process (Melin et al. 2008). The most recent observational study (n=12832) indicated an improvement in obstetric care with an increasing rate of STAN usage over a 7-year period (Noren & Carlsson 2010). The studies are presented in Table 3.


<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Material and method</th>
<th>Main outcome</th>
<th>Result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luzi et al. 1999</td>
<td>Retrospective multicenter</td>
<td>7 centers; 320 women monitored with STAN*</td>
<td>ST-changes; neonatal hypoxia (pH&lt;7.10, 1-min Apgar &lt;6)</td>
<td>T/QRS indicates hypoxia; 6/6 cases with asphyxia had ST changes</td>
<td>CTG+ST identify adverse events in labor.</td>
</tr>
<tr>
<td>Amer-Wahlin et al. 2002</td>
<td>Observational multicenter</td>
<td>12 centers; 573 women monitored with STAN</td>
<td>Diagnostic power of STAN for neonatal acidemia†</td>
<td>STAN identified 15/15 cases of acidemia</td>
<td>STAN clinical guidelines identify intrapartum asphyxia.</td>
</tr>
<tr>
<td>Noren et al. 2003</td>
<td>Retrospective</td>
<td>351 STAN-monitored newborns, who required special care</td>
<td>Findings related to adverse neonatal outcome</td>
<td>In 22/29 of fetuses with adverse outcome CTG+STAN indicated intervention</td>
<td>CTG+ST provide accurate information about hypoxia and may prevent asphyxia.</td>
</tr>
<tr>
<td>Dervaitis et al. 2004</td>
<td>Retrospective</td>
<td>143 STAN-monitored women</td>
<td>Sensitivity, specificity, NPV and PPV of STAN for acidemia (pH&lt;7.15, BD&gt;12)</td>
<td>STAN had sensitivity of 43%, specificity 74%, NPV 96% and PPV 8% for acidemia</td>
<td>ST guidelines have poor PPV and sensitivity for acidemia at birth.</td>
</tr>
<tr>
<td>Kwee et al. 2004</td>
<td>Prospective observational</td>
<td>449 STAN-monitored high-risk labors</td>
<td>ST-changes; neonatal acidemia</td>
<td>ST changes present in 5/5 of acidemia</td>
<td>CTG+ST is more specific in detecting acidemia than CTG.</td>
</tr>
<tr>
<td>Noren et al. 2006</td>
<td>Prospective observational</td>
<td>2 year period; 4830 STAN-monitored labors</td>
<td>Neonatal acidemia; ODFD rate</td>
<td>Acidemia 0.76 to 0.44%; rate for ODFD did not change</td>
<td>STAN improved fetal outcome without increasing ODFD.</td>
</tr>
</tbody>
</table>

*) STAN®8801 recorder; CTG= Cardiotocography; †) Neonatal acidemia = pH<7.05 and BD>12 mmol/l unless other notified; NPV= Negative predictive value, PPV= Positive predictive value; BD= Base deficit; ODFD= Operative delivery for fetal distress.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Material and method</th>
<th>Main outcome</th>
<th>Result</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massoud et al. 2007</td>
<td>Retrospective</td>
<td>Comparison of periods 2000-02 and 2002-05: 1889 STAN-monitored women</td>
<td>Use of STAN, neonatal acidemia, delivery modes</td>
<td>STAN usage increased; no change in delivery modes or neonatal acidemia</td>
<td>STAN introduced successfully into clinical practice.</td>
</tr>
<tr>
<td>Welin et al. 2007</td>
<td>Retrospective clinical audit</td>
<td>1875 labors monitored with STAN, 1322 with CTG</td>
<td>Neonatal acidemia; delivery mode</td>
<td>Overall and emergency CS rates smaller with STAN, no difference in neonatal outcomes</td>
<td>STAN was safely implemented in a medium-sized labor ward unit.</td>
</tr>
<tr>
<td>Doria et al. 2007</td>
<td>Prospective observational</td>
<td>1502 STAN-monitored high-risk pregnancies</td>
<td>Neonatal acidemia; evaluation of reasons behind adverse outcomes</td>
<td>Incidence of acidemia 2.8%, of which STAN identified 70%; 14 cases with encephalopathy</td>
<td>STAN has not changed rates of emergency operations or encephalopathy. More training on CTG and STAN is needed.</td>
</tr>
<tr>
<td>Melin et al. 2008</td>
<td>Retrospective case-control</td>
<td>Acidemic newborns (n=389), controls (n=117), monitored with STAN</td>
<td>CTG+ST changes; severe (pH&lt;7.0, lactate &gt;10) or moderate (pH=7.0-7.09, lactate ≥10) acidemia</td>
<td>Indication to intervene occurred in 96% of cases with severe, 62% of moderate acidemia, and 23% of controls</td>
<td>Presence of ST events indicates acidemia; events are also frequent among controls</td>
</tr>
<tr>
<td>Noren et al. 2010</td>
<td>Prospective observational</td>
<td>7 year period; 12832 STAN-monitored labors</td>
<td>Neonatal acidemia</td>
<td>Acidemia decreased from 0.72% to 0.06%</td>
<td>Established STAN usage improves obstetric care.</td>
</tr>
</tbody>
</table>

Neonatal acidemia = pH<7.05 and BD>12 mmol/l unless other notified; BD= Base deficit; CTG= Cardiotocography; CS= Cesarean section
It has been suggested that the addition of ST analysis to standard CTG may improve observer consistency in decision-making for intervention and thus decrease unnecessary interventions: a level of agreement in decision making of about 90% has been reported with the use of STAN (Amer-Wahlin et al. 2005, Ross et al. 2004, Vayssiere et al. 2009, Westerhuis et al. 2009). Furthermore, a multicenter study indicated agreement of 87% between American obstetricians newly trained for STAN and Swedish STAN experts (Devoe et al. 2006). A recent French study reflected the intrapartum decisions against the outcome of labor. As a result, an increased risk for inappropriate non-intervention was seen with STAN monitoring, when compared to monitoring with CTG (Vayssiere et al. 2009).

2.2.4 Fetal scalp blood sampling

FBS analysis directly examines the developing fetal acidosis (Saling 1964). From the early years of electronic fetal monitoring, FBS has been used as a diagnostic test for intrapartum fetal hypoxia in the presence of abnormal FHR patterns.

The pH values in blood samples from fetal scalp skin have been shown to correlate well with the pH values of the central arteries, even in cases with caput succedaneum (Morgan et al. 2002, Saling 1981). Saling considered a pH of 7.20 as the lower limit of adequate oxygenation; the choice of 7.20 was arbitrary and initially based on a study of 79 cases (Saling 1964). In later reports this limit was tested in extended series and confirmed by other investigators (Beard & Morris 1965). The cut-off -levels for intrapartum fetal scalp pH (Table 4), are included in most manuals on fetal monitoring:

<table>
<thead>
<tr>
<th>FBS result (pH)</th>
<th>Recommended action</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 7.20</td>
<td>Immediate delivery</td>
</tr>
<tr>
<td>7.21–7.25</td>
<td>Repeat FBS within 30 minutes or consider delivery</td>
</tr>
<tr>
<td>&gt;7.25</td>
<td>Repeat FBS if fetal heart rate abnormalities persist</td>
</tr>
</tbody>
</table>

In a prospective study with 46 infants with a scalp pH<7.20, none of the newborns had an umbilical artery pH<7.00 (Kuhnert et al. 1998). Higher rates of FBS are associated with higher mean cord arterial pH at delivery (Goodwin et al. 1994, Steer 1987, Westgate & Greene 1994). A cohort study of almost 50 000 deliveries showed that deliveries complicated by pathologic FHR and controlled
with FBS, compared to monitoring with CTG only, were associated with an improved short-term neonatal outcome. In the FBS group the ORs were 0.55 and 0.71 for an umbilical artery pH<7.00, and a 5-minute Apgar score <5, respectively (Stein et al. 2006).

The potential risks related to FBS are fetal infection and continuous bleeding from the incision. A total of five cases of persistent bleeding after FBS have been reported in the literature during the last 30 years; all reported cases were later diagnosed with fetal coagulopathy (Pachydakis et al. 2006). The occasional failures in FBS result from technical errors, such as calibration errors within the analyzer, or contamination in the sampling procedure (Kuhnert et al. 1998, Losch et al. 2003, Saling 1981). An in-vitro study indicated that contamination of fetal blood with amniotic fluid increases fetal blood pH, which may result in a masking of fetal distress (Losch et al. 2003). However, unlike pO₂ and pCO₂, pH is not easily affected by aerobic contamination, although in in-vitro studies blood pH has been shown to increase with marked capillary aeration (Morgan et al. 2002, Sherman et al. 1994). In addition, maternal hyperventilation may mask fetal acidemia (Losch et al. 2003). The error rate in FBS is estimated to be 2.4–11% (Saling 1981, Tuffnell et al. 2006, Wiberg-Itzel et al. 2008).

**Fetal scalp lactate measurement**

An alternate to a fetal scalp blood pH is a fetal scalp lactate measurement (Nordstrom et al. 1994). It has been suggested that pH does not provide information on the possible metabolic component of fetal acidosis. Respiratory acidemia, reflected by a transient decrease in scalp blood pH, does commonly occur during normal delivery, while in metabolic acidosis, lactic acid accumulates in the fetal blood and tissues (Nordstrom 2004). A randomized trial of 341 parturients with ominous CTG tracings indicated that scalp lactate is no better in detecting fetal asphyxia than scalp pH (Westgren et al. 1998). A more recent multicenter RCT including 3000 women compared pH analysis to lactate analysis; the cut-off levels for intervention were pH<7.21 and lactate >4.8 mmol/l. There was no difference between the groups in the incidence of neonatal metabolic acidemia, umbilical artery pH <7.00, 5-minute Apgar scores <7, or operative delivery for fetal distress. Since the lactate measurement requires a smaller amount of blood, it is easier to perform: the rate of failure in lactate sampling was smaller than in pH sampling (1.2 vs. 10.4%) (Wiberg-Itzel et al. 2008).
2.2.5 Fetal pulse oximetry

Pulse oximetry focuses on recording the level of hypoxemia by measuring oxyhemoglobin and deoxyhemoglobin in the arterial blood with alternating pulses of red and near-infrared light. Fetal pulse oximetry was developed from adult oximeters, and was introduced into obstetrics in the 1980s (Peat et al. 1988). During labor, the oximetry sensor is placed transvaginally between the uterine wall and the fetus, with a contact on the soft tissue of the fetal cheek.

The usefulness of fetal pulse oximetry in intrapartum fetal surveillance has been tested in RCTs. In the first RCT, with 1010 patients, no differences between CTG alone and CTG with fetal pulse oximetry were detected in overall CS rates, neonatal outcomes including 1- and 5-minute Apgar scores, umbilical artery blood gas values, or neonatal short-term morbidity, or in maternal outcome (Garite et al. 2000). Accordingly, another RCT with 5341 parturients found no difference between the groups in the CS rates or outcomes of the newborns including 5-minute Apgar score <4, umbilical artery pH value <7.0, or neonatal short-term morbidity (Bloom et al. 2006). Cochrane meta-analysis concluded that there is limited support for the use of fetal pulse oximetry in intrapartum monitoring, and its use does not reduce CS rates (East et al. 2007).

2.3 Neonatal outcome assessment

2.3.1 Umbilical blood gas analysis

The blood gas measures commonly used to diagnose intrapartum asphyxia and predict subsequent neonatal outcome are umbilical artery pH and base excess. The blood gas analyzers directly measure pH, pO₂, and pCO₂ from blood samples. The levels of bicarbonate (HCO₃⁻) and base excess (BE) or base deficit (BD) are calculated by an algorithm using pH and pCO₂ (Siggaard-Andersen & Engel 1960). Metabolic acidemia results either in a negative BE value or a positive BD value. The BE of extracellular fluid (ecf) reflects the non-respiratory component of pH disturbances, and it is considered the most relevant parameter of the metabolic disturbance in the acid-base status (Burnett et al. 1995, Kofstad 2003).

Umbilical arterial blood reflects fetal status directly, whereas umbilical venous blood also reflects maternal acid-base status and placental function (Thorp et al. 1996). The mean difference between umbilical arterial and venous pH in unselected deliveries is approximately 0.09, arterial sample being lower (Tong et al. 2002),
A comparison of umbilical artery and vein samples may provide some insight into the timing of acid-base disturbance in certain situations, but for clinical purposes, the benefit of collecting a sample from both vessels is in verifying the true source of the sample (Low 1993, Thorp et al. 1996, Tong et al. 2002, Westgate et al. 1994).

In population-based studies with 16 000–20 000 unselected newborns, mean umbilical artery pH values of 7.24–7.26 and base excess values between –5.6 and –4 mmol/l have been reported (Helwig et al. 1996, Victory et al. 2004). In these studies, the 2.5th to 5th percentile values for pH and base excess were 7.10 and –11 mmol/L (Helwig et al. 1996, Victory et al. 2004). The incidence of pH<7.10 has been reported to be 0.3–3% in non-selected newborns, and correspondingly 0.4–1.3% for pH<7.00 (Gilstrap et al. 1989, Perlman 2006, Sameshima et al. 2004, van den Berg et al. 1996, Victory et al. 2004).

The clinically significant cut-off level for defining neonatal acidemia in relation to adverse later outcome has been widely studied. One suggested cut-off level is umbilical artery pH<7.10. There is evidence that some morbidity may be seen in fetuses with an umbilical artery pH between 7.0 and 7.1 (Parer & King 2000). Incidence of adverse clinical outcome such as need for assisted ventilation or admission to NICU increases ten-fold with an umbilical artery pH < 7.10 (Parer & King 2000, Victory et al. 2004). A pH<7.10 has also been associated with CP (van de Riet et al. 1999). Among 42 newborns with seizures, the incidence of seizures was similar in newborns with pH levels of 7.0–7.05 and 7.05–7.10 (Williams & Singh 2002).

More often, a cut-off value of pH<7.00 has been proposed as a measure of significant asphyxia. An umbilical artery pH<7.00 has been associated with increased risk for permanent neurological damage in several studies (Gilstrap et al. 1989, Goldaber et al. 1991, Perlman 1997, van den Berg et al. 1996). However, 27–60% of newborns born with pH<7.00 have no neurologic sequelae (Goldaber et al. 1991, Ross & Gala 2002, van den Berg et al. 1996). Low pH as a sole pathologic marker in a clinically normal, vigorous newborn does not associate with later neurological morbidity (Ruth & Raivio 1988).

It is widely accepted that the umbilical artery base excess is more informative than pH; this is the most direct measure in assessing long-term neonatal outcome (Goldaber et al. 1991, Ross & Gala 2002, van den Berg et al. 1996). The outcome of infants with respiratory acidemia may not differ from controls, whereas severe metabolic acidemia (pH<7.0 and BE ≤12 mmol/l) may associate with neonatal complications (Herbst et al. 1997, Larma et al. 2007, Low 1993). The incidence
of BE $<-12$ mmol/l is 2% in the normal obstetric population, representing 2 SDs below the mean (Ross & Gala 2002). The risk for newborn complications increases with an increasing severity of metabolic acidosis (Low 1993, Victory et al. 2004). A BE $<-16$ mmol/l associates better than a BE $\leq -12$ mmol/l with later morbidity (Goldaber et al. 1991). However, the majority of fetuses with metabolic acidosis at birth exhibit no long-term neurological morbidity (Low 1993, Perlman 1997). A Swedish follow-up study failed to demonstrate any difference in developmental outcome measures between controls and children born with metabolic acidosis at the age of 4 years (Herbst et al. 1997). The presence of severe acidemia in central blood does not provide information on fetal adaptive capacity to maintain oxygenated cerebral perfusion (Perlman 1997).

As a conclusion, a strict threshold of umbilical blood gas analysis that could predict later morbidity is not available. Neonatal acidemia should be interpreted as a continuum of progression of risk with the worsening of acidemia (Victory et al. 2004). In clinical studies, the cord artery metabolic acidosis defined as pH$<7.00$ or 7.05 and BE $<-10$ or $<-12$ mmol/l is most often regarded as a biochemical marker diagnostic of birth asphyxia.

\subsection{2.3.2 Apgar score}

Currently, in ICD-10, the 1-minute Apgar score is used as a diagnostic criterion for birth asphyxia (Apgar 1953). However, it has been proposed, that a low 1-minute Apgar score should not be considered inevitably indicative of intrapartum asphyxia (Perlman 1997, van de Riet et al. 1999, van den Berg et al. 1996, Williams & Arulkumaran 2004). Low Apgar scores, reflecting poor neonatal outcome, may result from other etiologies apart from asphyxia, such as low birth weight, maternal analgesia, neonatal prematurity, chorioamnionitis, group B streptococcal sepsis and maternal pyrexia (Odd et al. 2008, Thorngren-Jerneck & Herbst 2001, Ugwumadu 2008). Thus the Apgar score should be interpreted as a clinical tool for the selection of infants for intensive care (Ruth & Raivio 1988, van de Riet et al. 1999, Williams & Arulkumaran 2004). The assessment of Apgar scores may also be liable to interobserver variation.

Despite the criticism related to the predictive value of Apgar scores, several studies have shown a correlation between Apgar scores and the long-term outcome of the infant. A 1-minute Apgar score of $\leq 3$ and a 5-minute Apgar score of $<7$ have shown to be associated with later neonatal morbidity (van de Riet et al. 1999, van den Berg et al. 1996). The long-term outcome is commonly abnormal.
in neonates born with 1-, 5- and 10-minute Apgar scores of 0 (Haddad et al. 2000, Harrington et al. 2007). Two large Swedish population-based cohort studies showed that infants with a 5-minute Apgar score <7 without neonatal encephalopathy have increased risk of a low intelligence quotient (IQ) score at the age of 15–16, and an overall increased risk of severe neurological morbidity and mortality (Odd et al. 2008, Thorngren-Jerneck & Herbst 2001). A high Apgar score is believed to rule out intrapartum asphyxial brain damage (Helwig et al. 1996).

2.4 Perinatal morbidity and mortality in birth asphyxia

During restricted oxygen supply, the fetal brain is protected by the preferential redistribution of the circulation. During hypoxia, a centralization of fetal blood flow is seen in favor of the brain, myocardium, and adrenal glands, at the expense of peripheral organs: muscle, skin, liver, kidneys, and intestine (Cohn et al. 1974, Jensen et al. 1999, Richardson et al. 1996). As a consequence, a multi-organ failure consisting of cardiovascular, renal, and respiratory complications may occur in association with severe perinatal asphyxia. The brain-sparing compensatory phase, subject to the severity of the hypoxia, may continue for several hours. During labor, this provides a time frame in which the diagnosis of hypoxia can be made, and, with an appropriate intervention, brain damage can be avoided. However, if the hypoxia persists, a threshold will be reached when fetal cardiovascular decompensation will occur, and circulatory centralization cannot be maintained (Low 1993). Cardiac output eventually diminishes, resulting in hypotension, and ultimately a decrease in cerebral blood flow. Deprivation of both glucose and oxygen during ischemia, and the simultaneous cascade of several metabolic events result in neuronal necrosis, unless immediate resuscitation occurs (Jensen et al. 1999).

The neuronal injury resulting from severe intrapartum asphyxia is hypoxic-ischemic encephalopathy (HIE). Diagnostic neurological symptoms for HIE are neonatal seizures, alertness, hypo- or hypertonia, hyperreflexia, and abnormal respiratory status and feeding responses (Sarnat & Sarnat 1976). The prevalence of HIE is estimated to range from 1 to 10 of 1000 live term births (Badawi et al. 1998b, Miller et al. 2005, van de Riet et al. 1999). The mortality and morbidity related to neonatal HIE is considerable: 20% of affected infants die in the perinatal period, and 25% will have permanent deficits of motor or cognitive function (Miller et al. 2005). CP is a non-progressive motor disorder resulting
from acquired brain injury, which may occur as a consequence of HIE resulting from birth asphyxia. The overall incidence of CP varies between 0.05% and 0.4%, and it is suggested to be a consequence of intrapartum asphyxia in 10–36% of the cases in term neonates (Nelson et al. 1996, Perlman 1997, van de Riet et al. 1999, Parer & King 2000, Hagberg et al. 2001, Sameshima et al. 2004).

Since protective mechanisms protect the brain from hypoxic-ischemic damage, most infants recover with minimal or no neurological sequelae, even when asphyxia is severe, while in some cases moderate or severe asphyxia causes permanent brain damage (Low 1993, Perlman 1997). What is not always known is the timing: whether the asphyxia was limited to the intrapartum period or began before the onset of the labor (Low 2004). It has been estimated that a majority, perhaps 70% of the HIE cases result from antenatal risk factors, the most important factor being restricted intrauterine growth (Badawi et al. 1998a). Intrapartum events may be the primary cause of HIE in 30% of cases (Badawi et al. 1998b). Apart from asphyxia, another significant intrapartum risk factor for HIE is chorionamnionitis (Badawi et al. 1998b, Victory et al. 2004). The presence of antepartum risk factors does not mean that intrapartum events have no contribution to the final outcome. If the reserves of the fetus are diminished in antepartum period, it has less capacity to cope with intrapartum hypoxic events (Badawi et al. 1998b).

In recent years, magnetic resonance imaging (MRI) has been used to determine the timing and etiology of the hypoxic-ischemic brain injury (Barkovich 1992, Cowan et al. 2003, Miller et al. 2005). The pattern of brain injury seen in MRI depends on the severity and duration of the asphyxial event. Controversially for epidemiologic studies, a large cohort study showed that more than 90% of term infants with neonatal HIE had evidence of intrapartum insults in MRI, and very low rate of brain injury was acquired before birth (Cowan et al. 2003).

As severe perinatal asphyxia may result in major neurological morbidity, milder events may cause subtle defects in cognitive function (Odd et al. 2009). A cohort study of 6000 children showed an association between resuscitation at birth and lower IQ at the age of 8 years. Increased risk of a low IQ score was recorded in resuscitated infants with HIE (OR 6.22, 95%CI 1.57–24.65) and without HIE (OR 1.65, 95%CI 1.13–2.43), compared to the non-resuscitated group (Odd et al. 2009). Moreover, perinatal asphyxia, resulting in neonatal HIE and a complicated perinatal course, have been related to lower verbal performance in children without motor deficits (Steinman et al. 2009).
2.5 Primary postpartum hemorrhage

Primary postpartum hemorrhage (PPH) is defined by the World Health Organization as a bleeding from the genital tract of more than 500 ml in the first 24 hours following delivery. Alternative values of 1000 ml or 1500 ml, a substantial fall in the hemoglobin or hematocrit levels, or the need for blood transfusion have also been proposed as definitions of PPH (ACOG 1998b, Shevell & Malone 2003). The blood volume expansion that occurs during pregnancy ensures that a healthy parturient at term pregnancy can tolerate up to 1000 ml of acute blood loss without significant hemodynamic disturbances (ACOG 1998b). A blood loss of more than 1000 ml is most often used as a clinical diagnosis of major PPH (Mousa & Walkinshaw 2001, Ramanathan & Arulkumaran 2006, Fiori et al. 2009). However, blood loss is frequently underestimated by as much as 30–50% with greater discrepancies occurring as blood loss increases (ACOG 1998b, Bonanno & Gaddipati 2008). The incidence of a major PPH is estimated to be 3–7 per 1000 deliveries in developed countries (Waterstone et al. 2001, Brace et al. 2007, Zwart et al. 2008).

The most common cause of PPH has been uterine atony, which is the cause in 40–50% of the cases (Clark et al. 1984, Erkkola 1997, Brace et al. 2007). However, in the most recent studies, abnormal placentation has risen to become the primary cause of PPH. A Dutch study showed that the primary diagnoses in PPH were retained placenta or placental rests in 48%, and uterine atony in 38% of cases (Zwart et al. 2008). Other possible causes of hemorrhage are uterine rupture, lower genital tract lacerations, uterine inversion or inherited coagulopathy (Zwart et al. 2008). Morbid adhesion of the placenta and placentation disorders are the most frequent indications of emergency peripartum hysterectomy (Kastner et al. 2002).

2.6 Placentation disorders

2.6.1 Placenta previa

The term placenta previa refers to a placenta that implants in the lower uterine segment, covering the internal os of the cervix. The incidence of previa varies according to gestational age: more than 90% of the low-lying placentas diagnosed in early pregnancy will migrate from the lower segment before term (Iyasu et al. 1993, Taipale et al. 1998). It is not clear whether the placenta actually moves or
only grows preferentially toward the better vascularized fundus. Placental parts lying over the less vascularized cervix would thus undergo atrophy, and the placental attachment sites would be constantly reformed and renewed (King 1973). The apparent movement of the placenta may also only be due to the development of the lower uterine segment (Oyelese & Smulian 2006). Anterior low-lying placenta may migrate toward the fundus more often and faster than posterior placenta (Cho et al. 2008). The later in pregnancy the placenta previa is diagnosed, the higher the likelihood of its persistence to delivery (Dashe et al. 2002). At term, placenta previa has been reported to complicate 0.3–5% of the pregnancies, yet in a Finnish non-selected population the incidence of placenta previa was only 0.14% (Iyasu et al. 1993, Taipale et al. 1998).

Risk factors for placenta previa include a history of prior cesarean section, uterine surgery, increasing maternal age and multiparity. The incidence is directly related to the number of previous cesarean sections: in nulliparous women the incidence is 0.3–0.4%, and with a history of three or more previous cesarean sections the incidence is 4–5% (Miller et al. 1997, Juntunen et al. 2004). The association between a placenta previa and a previous curettage has not been clearly shown (Kastner et al. 2002). In in-vitro fertilization pregnancies, there is an increased risk for placenta previa (Tan et al. 1992).

### 2.6.2 Placenta accreta, increta, and percreta

In normal implantation, the trophoblasts of the placenta invade uterine decidua in a controlled fashion (Fig. 2). In placenta accreta, trophoblasts penetrate more deeply into the myometrium, in the absence of the normal decidua basalis, and the fibrinoid layer of Nitabuch. Trophoblast invasion is regulated by the synergistic effects of angiogenic growth factors and their receptors, cell-adhesion molecules, extracellular matrix proteins, hormones, and transcription factors. Immunohistochemical analyses have shown lower levels of Tie-2 receptor and higher angiopoietin-2 receptor expression in patients with placenta accreta (Tseng et al. 2006).
Fig. 2. Histology of normal placenta shows decidual cells (D) in the implantation site (left). In placenta accreta, the chorionic villi are attached directly to the myometrium (M) (right). The slides were stained by hematoxylin eosin (HE) in the upper row and by immunohistochemistry against alpha smooth muscle actin (A-SMA) in the lower row.

The invasive placentation is divided into three variants: placenta accreta, placenta increta, and placenta percreta, based on how deeply the trophoblasts invade. Often all three variants are collectively called placenta accreta, and the lowest degree of trophoblast invasion is called placenta accreta vera. Placenta accreta (vera) means that the villi are attached directly onto the myometrium, the true diagnostic feature being the lack of decidua. In placenta increta, the villi invade into the myometrium, while in placenta percreta, the villi penetrate through uterine wall and into adjacent organs (Baergen 2005).

Clinically, the most significant feature of placenta accreta is the abundant uteroplacental neovascularization. The histological changes within myometrial spiral arteries that convert into uteroplacental arteries are different in placenta accreta (Khong & Robertson 1987). The vascularization and endometrial
decidualization may also be only focally disturbed or absent, while the rest of the placental bed is normal (Alanis et al. 2006, Teo et al. 2008).

**Predisposing factors and incidence of placenta accreta**

The most frequent predisposing condition for deficient decidua is a previous CS. This is suggested to be secondary to a failure of the reconstitution in the endometrium after a cesarean incision (Baergen 2005). The risk for an abnormal trophoblast invasion increases with a history of repeated CSs (Juntunen et al. 2004). Other predisposing factors are uterine scars, previous curettage, multiparity, maternal age >35 years, submucosal leiomyoma, cornual implantation, and, especially, placenta previa (Miller et al. 1997, Baergen 2005, Japaraj et al. 2007). In a population-based study of 155 000 mothers, placenta accreta occurred in 9.3% of women with placenta previa and in 0.004% of women without placenta previa (Miller et al. 1997). Vice versa: 80% of the histologically diagnosed accretas occur in conjunction with placenta previa (Miller et al. 1997). This may result from less developed decidua in the lower uterine segment and endocervix (Baergen 2005). It has been suggested that the frequency of accreta in the presence of placenta previa increases from 24% after one CS to 67% after four or more CSs (Clark et al. 1985a, Sumigama et al. 2007). The risk for placenta accreta is also associated with the number of previous uterine curettages (Kastner et al. 2002). It is widely accepted that the incidence of placenta accreta and its variants is increasing along with increasing CS rates (Dildy 2002, Rosen 2008).

In the United States, the incidence of placenta accreta rose from 5.4/10 000 to 11.9/10 000 deliveries over the period of 1996–2008 (Eller et al. 2009). At the same time, the CS rate increased from 20.7% in 1996 to 31.1% in 2006 (Bonanno & Gaddipati 2008).

The overall incidence of placenta accreta varies widely, since the diagnosis can be based on strictly histological analysis or on clinical suspicion only. The incidences vary from 1 in 500 to 1 in 70 000 deliveries (Miller et al. 1997, Oyelese & Smulian 2006, Sumigama et al. 2007). In a retrospective analysis of 155 000 patients, the incidence of histologically confirmed placenta accretas was 1 in 2500 deliveries (Miller et al. 1997). Remarkably, in the same population the incidence of placenta accreta based on clinical diagnosis was 1 in 1226 deliveries. The exclusion of histologically unconfirmed cases may thus underestimate the true incidence of accreta. Placenta increta and placenta percreta are more rare conditions. Approximately 80% of the placenta accreta cases are placenta accreta

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vera, 15% placenta increta, and 5% placenta percreta (Breen et al. 1977). Since placenta accreta strongly correlates to placenta previa, placenta accreta should be highly suspected in cases with placenta previa and previous CS (ACOG 1998b, Comstock 2005, Japaraj et al. 2007).

2.6.3 Prenatal diagnosis of invasive placenta

Ultrasonographic findings

In the first trimester early ultrasound screening, the gestational sac is normally in the fundus, surrounded by a thick myometrium on all sides. Patients who later prove to have placenta accreta may have low-lying gestational sacs, and the sac can be seen attached to the uterine scar (Comstock et al. 2003).

In the second and third trimesters, a diagnostic sonographic sign for placenta accreta is suggested to be the placental lacunae giving the placenta a “Swiss-cheese” or a “moth-eaten” –appearance (Finberg & Williams 1992, Twickler et al. 2000, Comstock et al. 2004, Comstock 2005, Oyelese & Smulian 2006, Japaraj et al. 2007). The lacunae, representing dilated vessels, may appear linear and irregularly shaped more often than round; they do not have an echogenic border, and they do not necessarily lie directly on the area of invasion (Twickler et al. 2000, Wong et al. 2008). The predictive value of the lacunae for placenta accreta have varied widely in clinical studies: presence of the lacunae is suggested to have a positive predictive value of 17–82%, sensitivity of 78–100% and a specificity of 39–100% for placenta accreta (Twickler et al. 2000, Comstock 2005, Japaraj et al. 2007, Sumigama et al. 2007, Wong et al. 2008). Absence of lacunae does not exclude placenta accreta, and vice versa: large, round, smoothly contoured sinuses can be seen in patients without placenta accreta (Comstock 2005, Wong et al. 2008).

The irregularity or absence of the hyperechoic interface between the uterus and the bladder, and the bulging of the border between the bladder and the myometrium, are considered to be diagnostic signs of placenta accreta (Finberg & Williams 1992, Kirkinen et al. 1998, Comstock et al. 2004, Wong et al. 2008). However, the bulging may simply result from enlarged vessels in the previous cesarean scar, and not from placental growth through the myometrium, giving a false-positive sign of invasion (Comstock 2005). Protrusion of an exophytic placental mass beyond the uterine serosa may suggest placenta percreta (Fig.3)

Other suggested diagnostic features for placenta accreta are thinning of the myometrium overlying the placenta to thinner than 1 mm and absence of the normal hypoechoic line representing decidua basalis between the placenta and myometrium (Taipale et al. 2004, Twickler et al. 2000, Wong et al. 2008). However, the dark line may be absent in many normal patients with anterior placentas, and the specificity of the sign may be limited (Comstock et al. 2004, McGahan et al. 1980, Wong et al. 2008).

Several studies have shown that adding color Doppler ultrasound to grayscale ultrasound imaging may be helpful in detecting abnormal vascular invasion into the myometrium and surrounding tissues (Fig. 3) (Japaraj et al. 2007, Lerner et al. 1995, Levine et al. 1997, Wong et al. 2008, Shih et al. 2009). However, benign bladder wall varices consequent to previous surgery may falsely present as placental invasion into the bladder wall in color-Doppler ultrasonography (Levine et al. 1997, Comstock 2005, Shih et al. 2009). It is not clear whether turbulent blood flow inside the placental lacunae is diagnostic for accreta (Chou et al. 1992, Wong et al. 2008).
The overall sensitivity and specificity of ultrasound in the prenatal diagnosis of placenta accreta are 85–95% and 71–100% respectively (Finberg & Williams 1992, Levine et al. 1997, Japaraj et al. 2007, Dwyer et al. 2008, Wong et al. 2008). The presence of multiple ultrasound findings appears to be most predictive of placenta accreta, specifically the presence of placental lacunae, disruption of the placental-uterine wall interface, and the presence of vessels bridging the sites of interface disruption (Comstock et al. 2004, Comstock 2005, Wong et al. 2008).

**Magnetic resonance imaging**

MRI may increase the accuracy of the prenatal diagnosis of placenta accreta (Levine et al. 1997), and may be useful in determining the degree of placental myometrial invasion (Fig. 4). In cases with posterior placenta, MRI may be superior to ultrasonography (Levine et al. 1997, Teo et al. 2008). The sensitivity of prenatal MRI is 80–85% in detecting accreta (Dwyer et al. 2008, Eller et al. 2009). However, a few studies comparing MRI to ultrasonography in diagnosing placenta accreta have shown no improvement in the accuracy of diagnostics (Oyelese & Smulian 2006, Dwyer et al. 2008).
The role of MRI in the diagnostics of placental pathology remains to complement rather than to replace ultrasonography (Oyelese & Smulian 2006, Japaraj et al. 2007). When MRI is performed following a suspicious ultrasound finding, the sensitivity and specificity of the diagnostics may improve (Warshak et al. 2006). No single diagnostic technique affords the clinician complete assurance of the presence or absence of placenta accreta (Sumigama et al. 2007).

### 2.7 Prevention of primary post partum hemorrhage

Prenatal diagnosis of placenta accreta allows the delivery to be planned to minimize morbidity (Oyelese & Smulian 2006). Several studies have shown that intraoperative blood loss is less abundant and the risk for postoperative morbidity is lower in women undergoing a scheduled cesarean hysterectomy compared to an emergency hysterectomy for placenta accreta (Alvarez et al. 1992, Comstock 2005, Eller et al. 2009). The preparation of a scheduled CS includes assembling a multidisciplinary team and a thorough planning of surgical techniques and anesthesia. The preparation may also include autologous blood salvage technology (Shih et al. 2009). Preoperative ureter stenting may help to reduce the risk of intraoperative ureter injury (Eller et al. 2009). A scheduled CS should be
considered before term to prevent unexpected vaginal bleeding and emergency CS in cases of suspected placenta accreta (Eller et al. 2009).

### 2.7.1 Prophylactic balloon occlusion and embolization of pelvic arteries

A cesarean hysterectomy in the presence of severe hemorrhage is an extremely challenging procedure. Slowing the blood loss improves the surgical field making the procedure technically easier and reducing the risk of surgical complications (Mok et al. 2008). Radiological interventions have been used in an effort to reduce blood loss in elective CS in patients at risk for severe hemorrhage. Devascularization of the uterus supplying arteries includes occlusion of either the uterine or internal iliac arteries by angiographic intervention before an elective CS. The aim is to reduce pulse pressure distal to the site of the occlusion, thus preventing and reducing intraoperative blood loss.

Two different prophylactic angiographic techniques have been described. The first involves placement of catheters with or without occlusive balloons and embolization of the uterine vasculature prior to a potential hysterectomy (Mitty et al. 1993). The second involves placement of intravascular catheters with occlusive balloons only into the pelvic vasculature to limit blood flow to the uterus (Levine et al. 1999, Oei et al. 2001).

**Prophylactic catheterization and embolization of pelvic arteries**

Mitty et al. (1993) described the method of prophylactic arterial catheterization before elective CS to control hemorrhage. The three patients referred for prophylactic catheterization had prenatal diagnoses of placenta accreta, placenta previa, and abdominal pregnancy, and were thus considered to have an increased risk for severe hemorrhage. A catheter was preoperatively introduced by an interventional radiologist from the left axillary artery into the descending aorta. When serious hemorrhage occurred and was not adequately controlled by local measures, the radiologist successfully advanced the catheter into the uterine arteries bilaterally and performed embolization with gelatin sponge pledgets under fluoroscopic control (Mitty et al. 1993). Next, Dubois et al. (1997) described two patients with placenta percreta who underwent balloon occlusion and embolization of internal iliac arteries. The occlusion balloons were inflated after the delivery to reduce hemorrhage, and embolization was performed prior to
proceeding with a hysterectomy (Dubois et al. 1997). In the following years, several studies reported reduced hemorrhage after the prophylactic use of occlusion balloons and embolotherapy in patients with placenta accreta (Hansch et al. 1999, O’Rourke et al. 2007, Tan et al. 2007). Furthermore, several case reports have argued that hysterectomy may be avoided with elective arterial embolization in patients with placenta accreta (Alanis et al. 2006, Mitty et al. 1993, Tan et al. 2007, Yu et al. 2008). Controversially, some other studies have failed to show any improvement with the use of arterial embolization in the surgical outcomes of patients with placenta accreta (Bodner et al. 2006, Mok et al. 2008).

**Prophylactic occlusion balloon catheterization of pelvic arteries**

In addition to the embolization of uterine and iliac arteries, pelvic arterial occlusion balloons have been used prophylactically to reduce blood loss and surgical complications. Levine et al. (1999) compared five subjects with placenta accreta, with prophylactic balloon catheterization, to four control subjects with unsuspected placenta accreta. The use of balloon occlusion catheters did not improve the outcomes of the study subjects (Levine et al. 1999). Similarly, Shrivastava et al. (2007) reported no difference in estimated blood loss or other surgical outcomes in 69 patients with placenta accreta and cesarean hysterectomy with (n=19) or without (n=50) prophylactic balloon catheterization (Shrivastava et al. 2007).

### 2.8 Management of primary post partum hemorrhage

The management of PPH is aimed at eradicating the specific cause of bleeding, while attempting to maintain intravascular volume to preserve tissue perfusion. Physical examination will suggest the diagnosis, and the etiology of hemorrhage determines the proper management. Although hysterectomy should ultimately control hemorrhage, several conservative approaches are attempted to avoid hysterectomy and preserve future fertility.

#### 2.8.1 Uterine compression

Conservative management of PPH starts with a bimanual uterine massage and compression. A vigorous uterine massage prevented PPH after vaginal delivery in
non-selected parturients (Hofmeyr et al. 2008). Uterine packing with gauze has become less frequent because of concern for concealed hemorrhage and subsequent risk for infection (Mousa & Walkinshaw 2001). Intruterine tamponade with a Rüsch urological hydrostatic balloon catheter has successfully been used to control hemorrhage in placenta accreta following vaginal delivery (Johanson et al. 2001). Bakri et al. described successful hemostasis in postpartum bleeding caused by low-lying placenta or placenta previa in five patients, using a 500-ml fluid-filled tamponade balloon (Bakri et al. 2001).

2.8.2 Medical therapy

Medical therapy includes uterotonic drugs and hemostatic agents. The most common uterotonic drugs are oxytocin and prostaglandin derivatives (Gulmezoglu et al. 2001). Misoprostol is a widely used prostaglandin E1 analogue with few side-effects; the side-effects include fever, shivering, and gastrointestinal effects (Gulmezoglu et al. 2007). Misoprostol is shown to reduce blood loss in primary PPH following vaginal delivery (Ng et al. 2001). A prostaglandin F2 analogue, sulprostone, is also shown to reduce PPH and shorten the third stage of vaginal labor (Poeschmann et al. 1991). Recombinant activated factor VII (NovoSeven®) was developed to promote hemostasis in patients with hemophilia A or B with inhibitors to factor VIII or IX. It has also been successfully used intravenously to treat primary PPH (Ahonen & Jokela 2005, Bouwmeester et al. 2003).

2.8.3 Suturing techniques

In 1997, the B-Lynch suturing technique was introduced into the management of uterine atony and subsequent hemorrhage (B-Lynch et al. 1997). Sutures are placed longitudinally over the uterine fundus to achieve compression. The sutures reduce blood flow to the uterus from the lateral margins and from the placental bed vessels. Fertility and subsequent pregnancy outcomes are unaffected in women who have had compression sutures in the management of PPH (Ramanathan & Arulkumaran 2006). Occasionally, the B-Lynch suturing technique has been successfully used in the treatment of hemorrhage resulting from placenta increta (Mechsner et al. 2008). Hemorrhage from placenta accreta may also be treated by removal of the placenta and subsequent oversewing of the
placental vascular bed, or wedge resection of the implantation site (Alanis et al. 2006).

2.8.4 Leaving the placenta in situ

In recent years, several case series have suggested that hysterectomy may be avoidable in CS for placenta accreta by leaving the placenta in situ, and additionally treating the patient with parenteral methotrexate postoperatively. However, this method has often been associated with severe maternal morbidity, such as intrauterine infection or massive secondary hemorrhage leading to an emergency hysterectomy (Tan et al. 2007, Mok et al. 2008, Teo et al. 2008, Yu et al. 2008, Eller et al. 2009). In addition, recurrent placenta accreta has been described in the subsequent pregnancy following this management (Kayem et al. 2007). A case report described a patient with placenta percreta left in situ, and later death as a result of intolerance to methotrexate (Chauleur et al. 2008). A recent French case series (n=167) presented a 78% success rate in avoiding hysterectomy with conservative treatment of placenta accreta; the rate for severe maternal morbidity was 6% (Sentilhes et al. 2010).

2.8.5 Ligation of arteries supplying uterus

Devascularization of the uterus may be achieved by ligation of the supplying blood vessels, specifically the uterine arteries or internal iliac arteries. Uterine arteries provide approximately 90% of the uterine perfusion (Ramanathan & Arulkumaran 2006). However, the actual efficacy of uterine artery ligation in avoiding hysterectomy is not known. Bilateral ligation of the internal iliac arteries requires knowledge of the vascular, ureteral, and neuronal pelvic anatomy. The technique is difficult, especially in the circumstances of a Pfannenstiel incision, an enlarged uterus and a significant amount of blood in the pelvis. Internal iliac artery ligation has been reported with 25–60% success rates in uterine atony; lower success rates have been reported in cases with placenta accreta (Clark et al. 1985b, Evans & McShane 1985). This may be due to the extensive collateral circulation in the pelvis, which maintains a significant blood flow in spite of the ligation (Gilbert et al. 1992). The usefulness of the iliac artery ligation technique is also limited due to the high risk of complications, specifically ligation of the external iliac arteries, laceration of the iliac veins, ureteral injury and retroperitoneal hematoma. While proximal vascular ligation is required,
prominent collateral vessels in the gravid pelvis may also contribute to re-bleeding and require hysterectomy (Hong et al. 2004). In a recent retrospective study of 76 cases of placenta accreta, internal iliac artery ligation did not reduce maternal blood loss when compared to those managed without ligation (Eller et al. 2009).

2.8.6 Hysterectomy

The hysterectomy is considered as the ultimate method of achieving hemostasis in an obstetric hemorrhage; Porro (1876) was the first to describe a successful cesarean subtotal hysterectomy to prevent maternal death from uterine hemorrhage. The overall incidence of peripartum hysterectomy is approximately 1 in 1000 (0.03–0.33%) deliveries, and the incidence is increasing in Western countries (Kastner et al. 2002, Daskalakis et al. 2007, Bodelon et al. 2009). In cases with placenta accreta, the rate for hysterectomy is nearly 100% (Eller et al. 2009). In fact, placenta accreta has emerged as the most common indication for peripartum hysterectomy accounting for 38–60% of all cases (Zélop et al. 1993, Dildy 2002, Kastner et al. 2002, Knight & UKOSS 2007). Placenta previa without accreta accounts for 8–30% of the causes for hysterectomy (Kastner et al. 2002, Daskalakis et al. 2007, Knight & UKOSS 2007).

Peripartum hysterectomy can be performed either as a total or a supracervical hysterectomy. Total hysterectomy would be advisable in cases of placenta accreta, given the frequency of involvement of the cervix, whereas supracervical hysterectomy may be reasonable in cases with uterine atony (Shevell & Malone 2003). The blood loss and operating time are equal for both techniques (Kastner et al. 2002, Knight & UKOSS 2007). The risk of postoperative complications may be higher with total hysterectomy; on the other hand, cyclical stump bleeding is a widely reported consequence of the subtotal operation (Knight & UKOSS 2007). The surgeon’s experience should perhaps be the factor determining the method of choice (Daskalakis et al. 2007).

In cases with placenta accreta, an attempt to remove the placenta during a CS may be correlated with a significant increase in maternal morbidity in terms of blood loss and postoperative complications, and yet the attempt may not reduce the incidence of hysterectomy (Eller et al. 2009, Oyelese & Smulian 2006). Thus, some authorities recommend a fundal incision with a closure of the uterus after the delivery of the baby, and a subsequent hysterectomy with the placenta left in situ (Dubois et al. 1997). Women who do not receive any treatment for
hemorrhage other than hysterectomy may have lower blood loss and lower rates of maternal morbidity than those who receive other treatments prior to hysterectomy. These findings suggest that earlier hysterectomy may result in better surgical outcomes (Knight & UKOSS 2007).

2.8.7 Embolization

As an alternative to a hysterectomy, postpartum embolization (PPE) of the uterus-supplying arteries has been proposed as a second-line therapeutic option when initial medical treatment fails to stop bleeding. Successful selective embolization in the management of PPH was first described by Brown et al. (1979). Since then, several case series have reported high success rates of 92–100% with PPE in the treatment of obstetric hemorrhage (Bloom et al. 2004, Chauleur et al. 2008, Chung et al. 2003, Gilbert et al. 1992, Greenwood et al. 1987, Hong et al. 2004, Mathe et al. 2007, Pelage et al. 1998, Pelage et al. 1999, Rosenthal & Colapinto 1985, Sentilhes et al. 2009, Soncini et al. 2007). Postpartum embolization of the pelvic arteries has been used successfully in the treatment of hemorrhage from placenta accreta (Alanis et al. 2006, Mitty et al. 1993). However, placenta accreta is also a frequently reported cause of failure in arterial embolization (Mathe et al. 2007, Pelage et al. 1999, Zelop et al. 1993). This may be due to uterine artery spasm, embolization of a single artery or embolization too proximal for the development of collateral networks (Deux et al. 2001).

PPE is usually performed in the angiographic suite by an interventional radiologist. The patient should be hemodynamically stable before the transfer to the suite. The procedure is performed under local anesthesia. The common femoral artery is punctured, and a guide-wire followed by a catheter is advanced into the distal aorta. An initial pelvic angiogram is obtained followed by selective bilateral internal iliac arteriograms. When the major bleeding vessel is identified, it is catheterized, and the embolic material is injected until stasis of flow is confirmed angiographically (Fig. 5A and B) (Brown et al. 1979). Ipsilateral internal iliac arteriography is repeated to exclude the possibility of additional bleeding vessels, which occasionally become apparent only after the major bleeder is occluded. The contralateral iliac artery is then examined in the same manner, and embolization is performed if needed. In some cases, the actual site of extravasation cannot be identified angiographically. However, several case reports have also shown the successful control of bleeding with bilateral embolization of
the internal iliac arteries in these cases (Greenwood et al. 1987, Pais et al. 1980, Pelage et al. 1998).

Fig. 5. A. An initial pelvic arterial angiography demonstrating extravasation of contrast agent (black arrow) from a branch of the left uterine artery in primary postpartum hemorrhage. B. After successful embolization of the bleeding artery, no more extravasation of the contrast agent is seen (black arrow).

Embolic materials available for occlusion include gelatin sponge pledgets, polyvinyl alcohol particles, steel coils, and n-butyl-2-cyanoacrylate glue. The gelatin sponge (Gelfoam) is the material of choice in the treatment of PPH, as it results in temporary distal occlusion of one to three weeks duration (Bloom et al. 2004). The vascular bed will eventually recanalize, allowing the uterine vascularity to return to normal. The other embolic materials may provide unwanted permanent occlusion of the uterine vasculature.

The overall rate for complications associated with a pelvic artery embolization in obstetric hemorrhage is approximately 6–11% (Alanis et al. 2006, Bloom et al. 2004, Vedantham et al. 1997). The complications include transient fever, transient buttock ischemia, transient foot ischemia, iliac artery perforation, pelvic abscess, bladder and rectal wall necrosis, and small bowel infarction.
(Gilbert et al. 1992, Greenwood et al. 1987, Rosenthal & Colapinto 1985, Sieber 1994). No deaths related to pelvic artery embolization have been reported.
3  **Aims of the study**

The purpose of the present study was to assess two modern methods, STAN and pelvic arterial embolization, in the prevention and management of the major complications of labor, fetal asphyxia, and maternal post partum hemorrhage. The specific aims of the study were:

1. To investigate the interobserver variability in interpreting intrapartum ST-tracings (II).
2. To examine whether intrapartum monitoring by means of ST-analysis reduces the rate of neonatal acidemia and the number of intrapartum operative interventions, compared with conventional monitoring with CTG (I).
3. To test the hypothesis that in pregnancies complicated by placenta accreta, the maternal surgical outcome is improved with prophylactic iliac artery occlusion balloon catheterization and embolization when compared to non-prophylactic management (IV).
4. To evaluate the impact of post-partum embolization in the management of primary postpartum hemorrhage (III).
4 Material and methods

4.1 Study populations

The role of STAN in the detection of fetal acidemia was investigated in 1483 consecutive parturients, recruited in 2003–04 at Oulu University Hospital (Tables 5 and 6). The inclusion criteria were: term pregnancy, a singleton fetus in a cephalic presentation, inclusion at the first phase of labor, and decision for amniotomy. The parturient was excluded if a scalp electrode was contraindicated. After giving written informed consent, the parturients were randomly assigned either to the STAN- or CTG-group using opaque numbered sealed envelopes generated by a computer program in blocks of 100. At the time of amniotomy, the next consecutively numbered envelope available was opened. The flowchart of the parturients in this RCT (I) is presented in Fig. 6.

In order to study interobserver variability in assessing STAN (II), 200 ST-tracings were selected from the STAN archives by a STAN expert who was not involved in the actual reading of the study data (Table 5).

The prevention of PPH by using prophylactic catheterization and the embolization of the pelvic arteries in cases with prenatally diagnosed placental disorders, were studied retrospectively in 28 patients (IV) (Table 5). The data were collected from the obstetrical databases of the Oulu and Helsinki University Hospitals, covering 2001–08. In addition, clinical effects and complications related to post partum embolization (III, n=15) were evaluated (Table 5). The characteristics of the study populations are presented in Table 6.
Fig. 6. Flow diagram of the recruited subjects in the randomized clinical trial comparing fetal automated ST-analysis and conventional CTG (I).
Table 5. Materials, methods and outcome measures in studies I-IV.

<table>
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<th>Study I</th>
<th>Study II</th>
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<td>Included subjects</td>
<td>Women in the first phase of labor with term pregnancy, singleton fetus in a cephalic presentation. 1) CTG (n=722) 2) STAN (n=714)</td>
<td>1) 140 reassuring ST-tracings 2) 60 non-reassuring ST-tracings</td>
<td>1) Post partum embolization for primary PPH (n=15) 2) Prophylactic catheterization for prenatally diagnosed placenta previa and/or accreta (n=7)</td>
</tr>
<tr>
<td>Study setting</td>
<td>RCT 3 observers reading the tracings</td>
<td>Observational case series 3 observers reading the tracings</td>
<td>Retrospective multi-center</td>
</tr>
<tr>
<td>Maternal outcome measures</td>
<td>CS and VO rates, FBS rate</td>
<td>Blood loss, transfusion requirements, postoperative morbidity</td>
<td>Blood loss, need for hysterectomy, postoperative morbidity</td>
</tr>
<tr>
<td>Neonatal outcome measures</td>
<td>UA pH &lt;7.10 and &lt;7.05, metabolic acidosis= pH&lt;7.05 and BE&lt;-12mmol/l; Neonatal morbidity</td>
<td>Interobserver agreement in terms of Kappa and total agreement (%)</td>
<td></td>
</tr>
</tbody>
</table>

CTG; Cardiotocography, STAN; ST-analysis of fetal electrocardiography, RCT; Randomized controlled trial, CS; Cesarean section, VO; Vacuum outlet, FBS; Fetal blood sampling, UA; Umbilical artery, BE; Base excess
Table 6. Clinical characteristics of the study populations (I, III and IV). Values given are mean (SD), median [range] or number (%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study I</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects</td>
<td>Controls</td>
<td>PPE</td>
</tr>
<tr>
<td>Number</td>
<td>714</td>
<td>722</td>
<td>15</td>
</tr>
<tr>
<td>Maternal age (y)</td>
<td>27.9 (5.4)</td>
<td>27.6 (5.6)</td>
<td>32.7 (5.4)</td>
</tr>
<tr>
<td>Parity</td>
<td>1.1 (1.7)</td>
<td>1.2 (1.9)</td>
<td>1 [0-13]</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>364 (51%)</td>
<td>378 (52%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Previous CS (n)</td>
<td>NA</td>
<td>NA</td>
<td>0 [0-4]</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>1 (7%)</td>
<td>4 (5%)</td>
<td>18 (86%)</td>
</tr>
<tr>
<td>Induced labor</td>
<td>144 (20%)</td>
<td>126 (18%)</td>
<td>NA</td>
</tr>
<tr>
<td>Elective CS</td>
<td>2 (13%)</td>
<td>7 (100%)</td>
<td>23 (100%)</td>
</tr>
<tr>
<td>GA at delivery (w)</td>
<td>39.7 (1.3)</td>
<td>39.7 (1.3)</td>
<td>37.6 (2.6)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3620 (518)</td>
<td>3592 (494)</td>
<td>3108 (622)</td>
</tr>
</tbody>
</table>

CS = cesarean section, GA = gestational age, NA = Information not available
PPE = patients with postpartum embolization
PBCE = patients with prophylactic balloon catheterization and embolization
*) p<0.05

4.2 Methods

4.2.1 Intrapartum FHR monitoring

Before the start of studies I and II, the labor ward midwives and obstetricians were educated and trained to use the STAN methodology, including being examined on their STAN knowledge. In the STAN studies, FHR monitoring was performed continuously either with STAN S21 monitors (Neoventa, Gothenburg, Sweden) with a scalp electrode, or with CTGs (Hewlett-Packard 8030A; Philips Medical Systems, Boeblingen, Germany) via either an internal scalp electrode or an external sensor. The clinical guidelines used for interpreting ST-information are shown in tables 1 and 2 in the review-section of this thesis. The appropriate intervention indicated by ST-analysis was either delivery, alleviation of the cause of fetal distress such as uterine overstimulation or maternal hypotension, or FBS. In both groups, FBS was optional according to the clinician’s judgment. If the fetal scalp blood pH was <7.20, immediate delivery was recommended.

In order to study interobserver variability in the STAN methodology, 200 ST-tracings were selected from the ST-analysis archives. A tracing was judged as
reassuring if the CTG was normal or if, in the presence of an intermediary/abnormal CTG, STAN information did not suggest intervention. A tracing was considered non-reassuring if the CTG was intermediary or abnormal, and an intervention was indicated by STAN information. This schema is in line with the clinical guidelines provided by the manufacturer (Tables 1 and 2) (Sundström et al. 2000). A 60-minute sample was chosen from the end of each recording, excluding the last 30 minutes before delivery. The recording speed was 1 cm/min. The tracings were reviewed independently by three consultants; all reviewers had undergone STAN training and had at least four years’ experience of using STAN in daily clinical work. The CTG tracings and ST information were available for the reviewers, but they were blinded to all clinical data, including the outcome of the labor. The reviewers were asked to classify the CTG tracings (Table 1), and to decide whether to make an intervention, according to STAN guidelines (Table 2). Intervention was defined as either a fetal blood sample or an immediate delivery.

4.2.2 Umbilical cord blood analysis and neonatal outcome

After the delivery, the umbilical cord was double clamped and arterial and venous cord blood was sampled. Blood samples were drawn in pre-heparinized 2-ml plastic syringes and a complete cord blood gas analysis was performed immediately at 37°C (Chiron Diagnostics 348; Chiron Diagnostics Ltd, Halstead, England).

The neonatal outcome measures were umbilical arterial pH and BEecf, Apgar scores, need for intubation, admission to neonatal intensive care unit (NICU) or incidence of neonatal seizures or encephalopathy. The BEecf was calculated using the Siggaard-Andersen algorithm (Siggaard-Andersen & Engel 1960).

4.2.3 Prevention and management of PPH

The prenatal diagnosis of placenta accreta was based on grayscale and color-Doppler ultrasound examinations and/or magnetic resonance imaging (MRI). The ultrasonographic features indicating placenta accreta were lack of a hypoechochogenic zone between the placenta and myometrium, presence of irregularly shaped placental lacunae with or without turbulent blood flow, presence of increased vascularity between the placenta and myometrium in power Doppler imaging, abnormal vascular invasion through uterine serosa, or
protrusion of placental mass beyond the bladder wall (Finberg & Williams 1992, Twickler et al. 2000, Wong et al. 2008). MRI was performed to specify the prenatal diagnosis if ultrasonographic findings indicated bladder invasion (Warshak et al. 2006). The diagnosis of placental disorder was confirmed by a histological analysis of the biopsied pathologic placental site, or placenta accreta was diagnosed through the clinical judgment of the obstetrician performing the operation. The clinical criteria for the diagnosis of placenta accreta were an evidence of placental growth through the uterine wall, or a failure to remove the placenta partially or totally.

The main outcome measures in studies III and IV were blood loss, need for hysterectomy, and postoperative morbidity. Blood loss was evaluated from the surgical databases, and it was originally based on a visual estimation and actual weighing of the surgical towels. The patients were later examined by an obstetrician in a two-month follow-up visit.

**Technique for prophylactic occlusion balloon catheterization and embolization**

At the time of an elective cesarean delivery, pelvic arterial catheterization was performed either in the angiographic suite of the Department of Interventional Radiology, transferring the patient subsequently to an obstetric operating theater, or in an operating theater equipped with facilities for interventional radiology. A bilateral transfemoral puncture was performed by an interventional radiologist, and 45 cm, 7 French introducer sheaths (Destination, Terumo, MD, USA) were advanced into both internal iliac arteries. The anatomies of both internal iliac arteries and especially the locations of the ostiums of the uterine arteries, were confirmed with manual injections of contrast medium. Then, occlusion catheters, with up to 8.5 mm expandable, compliant latex balloons (Standard Occlusion Balloon, Boston Scientific, Cork, Ireland), were advanced at the very proximal part of the anterior trunk of the internal iliac artery. The cesarean delivery was performed through an isthmic incision in all cases. Immediately after the delivery, the occlusion balloons were inflated with saline and contrast agent under fluoroscopic control. In cases with severe hemorrhage, the operation continued either with embolization or hysterectomy; hysterectomy was performed without a delay if the bleeding was life-threatening. In the bilateral iliac artery embolization, gelatin sponge pledgets (Gelitaspon, Gelita Medical, Amsterdam, Netherlands) were injected until the flow in the treated arteries ceased. In all cases the balloons
were deflated before skin closure. The catheters were left in place for 24 hours with a view for emergency embolization for restarted bleeding.

**Technique for postpartum embolization**

The postpartum embolization for severe PPH was performed by an interventional radiologist in the angiographic suite of the Department of Interventional Radiology. After an angiography with contrast injections, a selective catheterization of the uterine artery or the anterior trunk of the internal iliac artery was performed via a transfemoral route as described above. Embolization was started from the most evident site of bleeding. The material was injected until the flow in the treated arteries ceased. Embolization was always performed bilaterally.

### 4.3 Statistical analysis

#### 4.3.1 Power analysis

For the RCT evaluating STAN in clinical practice (I), calculation of the required sample size was based on the 6.4% incidence of neonatal acidemia (umbilical artery pH <7.10) among all parturients at Oulu University Hospital in 2002. Power analysis was calculated using Stata 7.0 software (Stata Corp LP, Bryan/College Station, TX, USA). A hypothesized reduction of 50% in the incidence of neonatal acidemia indicated a sample size of 761 per arm ($\alpha = 0.05$, $\beta = 0.20$).

The study evaluating interobserver variability in assessing STAN tracings (II) was powered on a Kappa value of 0.4, meaning moderate interobserver agreement, which was considered clinically relevant. Thus, with three observers, 140 reassuring and 60 non-reassuring tracings were reviewed (two-tailed test null value =0.40; n=200 cases at 80% power) (Sim & Wright 2005).

#### 4.3.2 Interobserver variability

**Kappa coefficient**

Kappa is a measure of agreement between observers in nominal scale measurements (Khan & Chien 2001). Kappa-coefficient corrects for the
agreement expected by chance. It indicates the achieved beyond-chance agreement as a proportion of the possible beyond-chance agreement. It is defined as follows:

$$ K = \frac{\text{observed agreement} - \text{chance agreement}}{\text{perfect agreement} - \text{chance agreement}} $$

Kappa values range from 0 to 1, with 0 representing no agreement beyond chance and 1 representing perfect agreement. Landis and Koch have proposed the following strengths of agreement for Kappa: 0= none, ≤0.20= poor, 0.21–0.40= fair, 0.41–0.60= moderate, 0.61–0.80= good and 0.81–1.00= very good (Landis & Koch 1977). Kappa allows an estimation of its statistical significance with a standard error and 95% confidence intervals; yet, the magnitude of the Kappa value is considered a clinically more important measure than its statistical significance (Khan & Chien 2001).

Weighted Kappa is used in ordinal scale measurements. It corrects for chance agreement and allows credit for partial agreement. It is obtained by giving different weights to the judgments according to their distance from the diagonal that indicates agreement. Disagreement near to the diagonal is considered less serious than disagreement where the discrepancy is two or three categories. Weighted Kappa can be statistically estimated with a standard error and 95% confidence intervals. Again, the quantitative significance of weighted Kappa is more important than its statistical significance (Khan & Chien 2001).

### 4.3.3 Statistical comparison of groups

The software used for statistical analyses was SPSS version 12.0.1 (I) or 16.0 (IV) for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was considered at a $p < 0.05$.

In the RCT comparing STAN to CTG (I), the variance between the groups was expressed in terms of difference (%) or relative risk (RR), with 95% CI. The analyses were performed with the intention-to-treat principle, despite 83 cases of inadequate monitoring: 5 in the CTG group and 78 in the STAN group.

The interobserver agreement (II) was evaluated using Kappa and weighted Kappa coefficients, as well as percentage of agreement (%). The null hypothesis that Kappa was $=0.40$ was tested using the CIs. If 0.40 lay within the CI, the null hypothesis was retained.
In studies on PPH, the normality of the distribution was tested using the Shapiro-Wilk test. Fisher’s exact test was employed for categorical variables. Comparisons between the groups were performed by using the Mann-Whitney U test for parameters with skewed distribution and the t-test for normally distributed parameters.
5 Results

5.1 STAN in intrapartum fetal monitoring

5.1.1 Interobserver agreement in assessing ST-tracings

Agreements between the three observers in terms of classifying CTG recordings and in deciding whether to make an intervention on the basis of combined information from ST-analysis and CTG according to the STAN clinical guidelines are shown in Table 7. The weighted Kappa values varied from 0.47 to 0.48 and were judged as moderate in classifying CTG. The interobserver agreement in deciding whether to manage the labor conservatively or to make an intervention, based on ST-information, varied from 0.47 to 0.60, and the agreement was judged as moderate. However, only the agreement in the decision making between observers 1 and 3 was considered clinically acceptable in the light of CI’s.

Table 7. Interobserver agreement in classifying the intrapartum CTG tracings according to STAN guidelines and deciding whether to make an intervention based on ST-information (Sundström et al. 2000).

<table>
<thead>
<tr>
<th>Classifying CTG</th>
<th>Total agreement (%)</th>
<th>Kappa (95% CI)</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1 vs. Observer 2</td>
<td>59</td>
<td>0.47 (0.38-0.56)</td>
<td>moderate</td>
</tr>
<tr>
<td>Observer 1 vs. Observer 3</td>
<td>56</td>
<td>0.47 (0.37-0.56)</td>
<td>moderate</td>
</tr>
<tr>
<td>Observer 2 vs. Observer 3</td>
<td>57</td>
<td>0.48 (0.40-0.56)</td>
<td>moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decision for intervention</th>
<th>Total agreement (%)</th>
<th>Kappa (95% CI)</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1 vs. Observer 2</td>
<td>85</td>
<td>0.53 (0.38-0.68)</td>
<td>moderate</td>
</tr>
<tr>
<td>Observer 1 vs. Observer 3</td>
<td>86</td>
<td>0.60 (0.47-0.73)</td>
<td>moderate</td>
</tr>
<tr>
<td>Observer 2 vs. Observer 3</td>
<td>80</td>
<td>0.47 (0.33-0.61)</td>
<td>moderate</td>
</tr>
</tbody>
</table>

5.1.2 STAN in the management of labor

FBS was performed in 166 cases (11%) in the total population monitored either with STAN or CTG. The rate of FBS was significantly lower in the STAN group than in the CTG group, with a RR (95% CI) of 0.45 (0.33–0.61). The overall cesarean section rate in the total study population of 1483 parturients was 5.6%, and cesarean delivery due to fetal distress was performed in 2.0% of the cases. The cesarean section and vacuum outlet rates were similar in the groups (Table 8).

There were no complications related to the use of FBS, CTG or STAN.
Table 8. Operative deliveries and fetal blood sampling (FBS) in the groups monitored by ST-analysis or CTG (I). Values given are n (%).

<table>
<thead>
<tr>
<th></th>
<th>STAN (n=733)</th>
<th>CTG (n=739)</th>
<th>RR (95 % CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean section</td>
<td>47 (6.4)</td>
<td>35 (4.7)</td>
<td>1.35 (0.86–2.07)</td>
<td>0.124</td>
</tr>
<tr>
<td>Fetal indication</td>
<td>15 (2.0)</td>
<td>15 (2.0)</td>
<td>1.01 (0.50–2.05)</td>
<td>0.262</td>
</tr>
<tr>
<td>Vacuum outlet</td>
<td>70 (9.5)</td>
<td>79 (10.7)</td>
<td>0.89 (0.66–1.21)</td>
<td>0.530</td>
</tr>
<tr>
<td>Fetal indication</td>
<td>36 (4.9)</td>
<td>48 (6.5)</td>
<td>0.76 (0.50–1.15)</td>
<td>0.206</td>
</tr>
<tr>
<td>FBS*</td>
<td>51 (7.0)</td>
<td>115 (15.6)</td>
<td>0.45 (0.33–0.61)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*FBS = fetal blood sample

5.1.3 STAN and neonatal outcome

The neonatal outcomes in the STAN and CTG groups are summarized in Table 9. When neonatal acidemia was defined as umbilical artery pH<7.10, the incidence of acidemia did not differ between the groups. If pH<7.05 was used as a cut-off value, the RR (95% CI) for acidemia was 2.53 (1.12–5.70) in the STAN group. The incidence of metabolic acidosis was 0.7% (n= 722) in the CTG group and 1.7% (n= 714) in the STAN group; the difference was not statistically significant. There was no difference between the groups in other neonatal short-term outcome measures. There was no neonatal or maternal mortality in the study population.

Table 9. Outcomes of the neonates monitored by either ST-analysis or CTG (I). The results are presented as n (%).

<table>
<thead>
<tr>
<th></th>
<th>STAN (n=714)</th>
<th>CTG (n=722)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord artery blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH&lt;7.10</td>
<td>41 (5.8)</td>
<td>34 (4.7)</td>
<td>1.22 (0.78–1.90)</td>
<td>0.407</td>
</tr>
<tr>
<td>pH&lt;7.05</td>
<td>20 (2.8)</td>
<td>8 (1.1)</td>
<td>2.53 (1.12–5.70)</td>
<td>0.022</td>
</tr>
<tr>
<td>pH&lt;7.05, BE&lt;-12</td>
<td>12 (1.7)</td>
<td>5 (0.7)</td>
<td>2.43 (0.86–6.85)</td>
<td>0.093</td>
</tr>
<tr>
<td>5-min Apgar &lt;7</td>
<td>9 (1.3)</td>
<td>8 (1.1)</td>
<td>1.14 (0.44–2.93)</td>
<td>0.776</td>
</tr>
<tr>
<td>Intubation</td>
<td>7 (1.0)</td>
<td>9 (1.2)</td>
<td>0.79 (0.29–2.10)</td>
<td>0.710</td>
</tr>
<tr>
<td>Admission to NICU*</td>
<td>26 (3.6)</td>
<td>26 (3.6)</td>
<td>1.01 (0.59–1.72)</td>
<td>0.967</td>
</tr>
<tr>
<td>Seizures</td>
<td>0</td>
<td>2 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NICU = neonatal intensive care unit
5.2 Prevention and management of primary postpartum hemorrhage

5.2.1 Prevention of PPH in placental abnormalities

There was no statistically significant difference in the total blood loss between patients treated either with prophylactic catheterization (n=21) or conventionally (n=13) (Table 10). The median (range) blood loss in patients with placental disorder was 6000 ml (1000 ml-17000 ml). Among parturients (n=21) with prenatally diagnosed placental disorder and prophylactic iliac artery balloon catheterization and embolization, hysterectomy was avoided in 24% (16/21) of the cases. Compared to non-catheterized control patients, there was no statistical difference in the hysterectomy rates (76 vs. 92%, p=0.370). During the follow-up period, none of the patients who avoided hysterectomy became pregnant again.

The overall postoperative complication rate in the patients with PPH was 38%. No difference in the complication rate was observed between catheterized and non-catheterized PPH patients. The rate of complications related directly to the angiographic method was 14%. Two serious complications occurred in patients treated with catheterization and embolization: a pulmonary embolism and a bilateral femoral vein embolization. Both patients recovered with low molecular heparin treatment. The postoperative complications in both groups are presented in Table 10. There was no difference between the groups in the number of postoperative hospitalization days or days in the intensive care unit.
Table 10. Outcomes of patients with prenatally diagnosed placental disorder and elective cesarean delivery with (Catheterization) or without (Control) prophylactic balloon catheterization of bilateral internal iliac arteries (IV). The values given are n (%), mean (SD) or median [range].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Catheterization (n=21)</th>
<th>Control (n=13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy</td>
<td>16 (76%)</td>
<td>12 (92%)</td>
<td>0.370</td>
</tr>
<tr>
<td>Variant of accreta present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accreta</td>
<td>10 (48%)</td>
<td>9 (69%)</td>
<td></td>
</tr>
<tr>
<td>Increta</td>
<td>3 (14%)</td>
<td>3 (23%)</td>
<td></td>
</tr>
<tr>
<td>Percreta</td>
<td>8 (38%)</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>5000 [2000-15000]</td>
<td>6500 [1000-17000]</td>
<td>0.436</td>
</tr>
<tr>
<td>Days in intensive care unit</td>
<td>1.0 (±1.1)</td>
<td>0.9 (±0.8)</td>
<td>0.553</td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>7.9 (±4.5)</td>
<td>7.9 (±4.6)</td>
<td>0.989</td>
</tr>
<tr>
<td>Post-op. complications</td>
<td>9 (43%)</td>
<td>4 (33%)</td>
<td>0.719</td>
</tr>
<tr>
<td>Bladder lesion</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Relaparotomy</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Groin hematoma</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal hematoma</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bilateral femoral vein thrombosis</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

5.2.2 Management of PPH

In our case series (n=15) during 2001-03, etiologies of PPH were uterine atony (n=7), disseminated intravascular coagulopathy (n=1), placenta previa (n=1), placenta accreta (n=3), and retroperitoneal hematoma following vaginal laceration (n=3) (III). Patients were first treated conservatively by means of bimanual uterine massage and medication: oxytocin, sulprostone, or misoprostol, before proceeding to embolization. Oxytocin was given first as a 10 IU intravenous or intramuscular bolus, and it was further infused intravenously in a dilution of 50 IU oxytocin in 500 mL of sodium chloride. Misoprostol tablets were administered rectally, with a maximum dose of 1200 µg. Sulprostone was administered either via an intravenous infusion or intrauterine injection, diluted in sodium chloride. The mean blood loss in the studied patients was 9600 ml [range 4000–15 000].

The overall success rate for postpartum embolization in achieving hemostasis was 73% (11/15). In 8/15 patients, embolization was performed prior to hysterectomy to achieve hemostasis, and it was successful in controlling hemorrhage and avoiding hysterectomy in six cases. In 7/15 patients,
embolization was performed after a cesarean hysterectomy for persistent hemorrhage, and it was successful in five patients. In avoiding hysterectomy, the success rate was highest (5/7) among patients with uterine atony. In patients with abnormal placentation hysterectomy was avoided in only one out of four patients.

5.2.3 Complications related to catheterization and embolization

In the management of PPH, there were seven (n=7/15) cases with complications presumably directly related to the angiographic technique. The complications and their outcomes are listed in Table 11. There was neither maternal nor neonatal mortality.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrosis of cervix and proximal vaginal epithelium</td>
<td>Conservative</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Thrombosis of left popliteal artery</td>
<td>Surgical</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Ischemia of sciatic nerve</td>
<td>Conservative</td>
<td>Gradual recovery</td>
</tr>
<tr>
<td>Large groin hematoma (n=4)</td>
<td>Conservative</td>
<td>Complete recovery</td>
</tr>
</tbody>
</table>
6 Discussion

6.1 Neonatal and maternal outcomes with STAN in intrapartum fetal monitoring

The present RCT (I) indicates that in intrapartum fetal monitoring STAN does not improve neonatal or maternal outcomes when compared to CTG. No difference in the incidence of neonatal acidemia, low Apgar scores, admission to NICU, incidence of HIE or rate for operative deliveries were detected between the groups. Only the use of FBS was reduced in the STAN group. In accordance with our results (I), a French RCT of 799 women showed no difference in the neonatal outcomes and the rate of operative deliveries between STAN and CTG. The rate of FBS was lower with the use of STAN (Table 12), as in our RCT (Vayssiere et al. 2007) Contradictory to our results, a Swedish RCT (n=4966) showed a lower incidence of neonatal metabolic acidosis with the use of STAN, while no differences between the groups were detected regarding Apgar scores, admission to NICU or incidence of HIE. Lower rates of operative delivery for fetal distress in the STAN group were detected in this RCT, yet there were no differences in the overall CS rate or CS for fetal distress rate (Table 12) (Amer-Wåhlín et al. 2001). Due to current investigations into the reliability of the Swedish trial, it is recommended that the results be interpreted with caution (Neilson 2006).

An earlier RCT, the Plymouth study (n=2434), comparing intrapartum CTG to ST analysis, reported a 46% reduction in operative deliveries because of fetal indication (Westgate et al. 1993). In addition, a trend toward less metabolic acidosis and fewer low 5-minute Apgar scores was seen in the ST arm; yet, the difference did not reach statistical significance. However, the non-automated device (STAN® 8801) used in the Plymouth study was different from the current, automated ST-analyzer (STAN® S21). In addition, the clinical guidelines for interpretation and recommended interventions were different in the Plymouth study, and thus the results should not be compared with more recent STAN RCTs.
Table 12. Randomized controlled trials comparing automated STAN and CTG in intrapartum fetal monitoring.

<table>
<thead>
<tr>
<th>n</th>
<th>Neonatal metabolic acidosis*</th>
<th>Operative delivery for fetal distress rate</th>
<th>Cesarean section</th>
<th>Cesarean section for fetal distress</th>
<th>Fetal blood sampling rate</th>
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<tbody>
<tr>
<td></td>
<td>STAN vs. CTG (%)</td>
<td></td>
<td></td>
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<tr>
<td>Amer-Wåhlin et al. 2001</td>
<td>4966</td>
<td>0.7 vs. 2</td>
<td>8 vs. 9</td>
<td>8.3 vs. 9.1</td>
<td>4 vs. 4</td>
</tr>
<tr>
<td>Ojala et al. 2006</td>
<td>1483</td>
<td>RR 2.43 [0.86–6.85]</td>
<td>p=0.261</td>
<td>RR 1.35 [0.86–2.07]</td>
<td>RR 1.01 [0.50–2.05]</td>
</tr>
<tr>
<td>Vayssiere et al. 2007</td>
<td>799</td>
<td>NS**</td>
<td>54.1 vs. 55.3</td>
<td>NS**</td>
<td>13.5 vs. 16.3, NS**</td>
</tr>
</tbody>
</table>

* pH< 7.05 and BD> 12 mmol/l1 or BE< -12 mmol/l2, † calculated with chi-square test
**NS = non significant
A recent Cochrane Database Systematic Review incorporated three RCTs, including the present study (I), in a meta-analysis comparing STAN to continuous electronic FHR monitoring (n=9671) (Amer-Wahlin et al. 2001, Westgate et al. 1993). In this meta-analysis STAN was associated with fewer babies with neonatal encephalopathy (RR 0.37, 95%CI 0.14–1.00), fewer FBS during labor (0.65, 0.59–0.72), and fewer operative vaginal deliveries (0.89, 0.81–0.98). There were no statistically significant differences in the incidence of metabolic acidosis (0.73, 0.49–1.09), CS rate (0.93, 0.83–1.03), low 5-minute Apgar scores (0.82, 0.58–1.14), or admissions to NICU (0.90, 0.75–1.07). The findings provide some support for the use of STAN in intrapartum fetal monitoring (Neilson 2006).

Several observational studies have indicated improvement in fetal surveillance with the use of STAN (Amer-Wahlin et al. 2002, Kwee et al. 2004, Luzietti et al. 1999, Massoud et al. 2007, Noren et al. 2003, Noren et al. 2006, Welin et al. 2007) A recent Swedish study on a low-risk population, including over 12000 STAN-monitored women, showed a decrease in the incidence of neonatal metabolic acidosis over a 7-year period without an increase in the cesarean deliveries for fetal distress; at the same time, STAN usage increased from 26% to 69% (Noren & Carlsson 2010). The authors speculate that this might be due to improved expertise through continuous staff education (Noren & Carlsson 2010a). Intensive training and assessment of the users may help to improve outcomes.

In the present RCT, the only improvement with the use of STAN was a decreased FBS rate. Observations from retrospective clinical audits have suggested that use of STAN could replace FBS entirely in labor (Kwee et al. 2004, Noren et al. 2007); the reliability of the two methods has not yet been compared in a RCT. On the other hand, FBS is easy to perform, the potential risks related to FBS are sporadic and the error rate is relatively low (Pachydakis et al. 2006, Saling 1981, Tuffnell et al. 2006, Wiberg-Itzel et al. 2008). Furthermore, as the present study indicated, a liberal use of FBS combined with CTG results in a very low incidence of neonatal metabolic acidosis. Therefore, FBS should not be abandoned when it comes to intrapartum fetal monitoring.

### 6.2 Clinical usefulness of STAN

The present study (I) showed a higher incidence of umbilical artery pH<7.05 in the STAN group compared to the CTG group. This may imply that, at least in some cases, STAN did not alert the clinician early enough, pushed non-
interventional surveillance to the edge, and resulted in low neonatal umbilical artery pH values. A recent study by Melin et al. (2008) also reported that ST events together with abnormal CTG patterns may appear late and inconsistently in the hypoxic process. False-negative tests resulting in severely acidotic neonates have been reported with the use of STAN (Doria et al. 2007, Westerhuis et al. 2007). In addition, false-positive test results among healthy controls with normal cord blood gas values have also been detected (Melin et al. 2008, Westgate et al. 1993). These findings indicate that the sensitivity and specificity of STAN may be limited, although Amer-Wåhlin et al. (2002) reported 100% sensitivity and 95% specificity in detecting fetal metabolic acidosis with STAN. In a more recent Canadian retrospective study, the sensitivity of STAN was 43% and the specificity was 74% in detecting metabolic acidemia (Dervatis et al. 2004), and in a Swedish retrospective study, STAN clinical guidelines indicated intervention in only 62% of cases with metabolic acidemia (Melin et al. 2008).

The eventually limited diagnostic power of STAN may result from several factors. The most likely confounding factor is that the clinical significance of the ST changes depends on the visual, subjective analysis of the concurrent CTG. Problems inherent in subjective interpretation of CTGs have been well recognized and were forecasted in the late 1970s. The first interobserver study on CTG interpretation, published in 1978, concluded that “the interpretation of the CTG is not as easy nor as reproducible as one may wish” (Trimbos & Keirse 1978). Previous studies on CTG interpretation have shown poor to moderate agreement between observers in terms of Kappa coefficient (Ayres-de-Campos & Bernardes 1999, Bernardes et al. 2003). To facilitate CTG analysis, the STAN manufacturer has provided a classification matrix according to which the CTG should be interpreted. Our findings on interobserver variability in the interpretation of CTG (II) were similar to those of previous studies: the percentage of agreement in classification of CTG did not exceed 60%. Both the percentage of agreement and weighted Kappa values showed that even experienced obstetricians could reach only a moderate agreement in the classification of CTG. Interobserver agreement may be better for classification for a normal or a preterminal CTG, but the consistency decreases when CTG traces are intermediate or abnormal (Westerhuis et al. 2009). However, in the present study (II), obstetricians categorized even preterminal CTG tracings to adjacent classes.

The agreement in clinical decision-making (whether or not to perform an intervention) according to the STAN clinical guidelines varied from 80 to 86%, which is expressed in terms of Kappa as a moderate level of agreement. This is
slightly poorer agreement than in previous studies, which have reported 87–89% agreement (Amer-Wahlin et al. 2005, Devoe et al. 2006). At any rate, the addition of STAN to CTG improves observer consistency in the decision-making and timing of an intervention, and concurrently reduces the number of unnecessary interventions, indicating increased specificity when compared to CTG alone (Ross et al. 2004, Vayssiere et al. 2009, Westerhuis et al. 2009). However, with the use of STAN the risk of inappropriate non-intervention may also be increased, indicating limited sensitivity in the monitoring method (Vayssiere et al. 2009).

Apart from difficulties in interpretation, poor signal quality may limit the use of STAN, while the accuracy of the monitoring is dependent on continuous recording of changes in fECG (Amer-Wahlin et al. 2001, Dervaitis et al. 2004, Kwee et al. 2004, Westerhuis et al. 2007). Poor signal quality limited the use of STAN in 3% in our RCT (I). Because of the reported difficulties in the correct interpretation of CTG and subsequent difficulties in following STAN clinical guidelines, the guidelines were modified by European experts meeting to overcome errors and to simplify decision making (Amer-Wahlin et al. 2007). To further simplify the interpretation, it has been suggested that the two CTG categories representing non-reassuring fetal status (intermediate and abnormal) should be merged (Ayres-de-Campos et al. 2009). However, with a smaller number of CTG categories the cut-off points for intervention would decrease, probably resulting in either an increased number of unnecessary interventions or an increased rate of false-negative results.

A future possibility for improving STAN assessment and its accuracy might be adding automatic analysis of CTG or FHR variability into the methodology. Computerized analysis of CTG, based on continuous measurement of FHR beat-to-beat variance, has been successfully introduced into antepartum fetal assessment; the method has not yet proved useful in intrapartum fetal monitoring (Dawes et al. 1992). However, there is experimental evidence indicating that changes in the intrapartum FHR variability, detected by power spectral analysis, do correlate with ST-events and thus may be predictive of neonatal metabolic acidosis (Siira et al. 2005, Siira et al. 2007).

6.3 Prevention of PPH with prophylactic catheterization and embolization

The aim of prophylactic pelvic artery occlusion balloon catheterization, with or without embolization, is to reduce hemorrhage in elective cesarean deliveries in
patients with prenatally diagnosed placenta accreta. In some cases, under perfect control of hemorrhage, hysterectomy might be avoided. However, the results of the present study (IV) indicate that prophylactic pelvic arterial catheterization and embolization does not reduce blood loss and the need to perform a hysterectomy in patients with placental disorder, compared to conventionally managed patients.

Several case reports have shown that hysterectomy may be avoided in patients with invasive placenta with the use of prophylactic catheterization and embolization (Alanis et al. 2006, Bodner et al. 2006, Mitty et al. 1993, Tan et al. 2007). In a retrospective case-control study, reduced blood loss was reported with internal iliac artery occlusion and embolization in CS for placenta accreta (n=11) when compared to patients without endovascular intervention (n=14) (Tan et al. 2007). Controversially, Bodner et al. (2006) found no improvement in the patients’ surgical outcomes with the use of prophylactic balloon occlusion and embolization in their retrospective case-control study (n=28). In our study (IV) the success rate for avoiding hysterectomy by means of prophylactic catheterization was 24%, with no statistical difference when compared to the patients treated conventionally. Neither did Mok et al. (2008) detect a reduction in the need for cesarean hysterectomy in their non-controlled series (n=13) of placenta accreta. A recent cohort series including 26 cases with placenta accreta indicated decreased maternal morbidity with the successful use of staged embolization (n=8) in cesarean hysterectomy for placenta accreta (Angstmann et al. 2010).

Failure of the pelvic catheterization and embolization to reduce blood loss and avoid hysterectomy in placenta accreta may be explained by the extensive vascular anastomoses in the gravid uterus. Collateral circulation from cervical, ovarian, rectal, femoral, lumbar and sacral arteries contributes to the vasculature of the uterus. The success of the prophylactic embolization may be dependent on the site and degree of the placental invasion: in cases where the abnormal placental site is supplied mainly by the uterine artery, the embolization might be a sufficient intervention to stop bleeding. Although blood loss in our study did not differ statistically significantly between the groups, it can be speculated whether a 1.5 L lower blood loss in the embolization group has any clinical significance. Hemorrhagic complications like acidosis and coagulopathy and blood transfusions with hemolytic reactions and immunological consequences carry significant clinical risks. Unfortunately, we were unable to compare blood transfusion requirements between the groups, since cell-saver technology was utilized with several patients.
The sole use of prophylactic occlusion balloons in pregnancies complicated by placenta accreta has not shown improvement in the surgical outcomes of the patients. Levine *et al.* (1999) compared five subjects with placenta accreta and prophylactic balloon catheterization to four control subjects with unsuspected placenta accreta. The use of balloon occlusion catheters did not improve the outcome of the study subjects. Accordingly, Shrivastava *et al.* (2007) reported no difference in estimated blood loss or other surgical outcomes in patients with placenta accreta and cesarean hysterectomy with (n=19) or without (n=50) prophylactic balloon catheterization. It is suggested that inflation of the arterial occlusion balloons may even exacerbate the collateral blood flow (Shrivastava *et al.* 2007). It is possible that embolization could be more useful in controlling hemorrhage, since the arterioles are reached more distally (Vedantham *et al.* 1997). In our study population (IV) ten women were treated with balloon occlusion only, and eight with occlusion and embolization. However, our material does not allow a comparison between these two methods, since the decision as to whether to perform an embolization or to continue the operation with hysterectomy was made after a clinical judgment of the situation.

In the present study on placenta accreta, the success rate was 24% in avoiding hysterectomy with prophylactic catheterization. This is far from the 78% success rate reported with a conservative management (i.e., leaving the placenta in situ) (Sentilhes *et al.* 2010). However, Sentilhes *et al.* (2010) reported severe complications (sepsis, secondary postpartum hemorrhage and maternal death) in their conservatively treated patients. Internal iliac artery ligations have shown 25–60% success rates in uterine atony; the success rate has been estimated to be lower in cases with placenta accreta (Clark *et al.* 1985b, Evans & McShane 1985).

### 6.4 Management of PPH with post partum embolization

Selective embolization may be performed if bleeding continues after cesarean hysterectomy, or it may serve as an alternative to a hysterectomy when conservative treatment fails to stop bleeding. In the present case series (III) the management of massive PPH by means of pelvic arterial embolization was successful in 11 out of 15 patients (73%), which is lower than in previous studies (93–100%) (Bloom *et al.* 2004, Chung *et al.* 2003, Gilbert *et al.* 1992, Greenwood *et al.* 1987, Hong *et al.* 2004, Mathe *et al.* 2007, Pelage *et al.* 1998, Pelage *et al.* 1999, Rosenthal & Colapinto 1985, Soncini *et al.* 2007). The difference may be due to the indications for the procedure; the technique is also
widely used in moderate postpartum hemorrhage (Mathe et al. 2007). In our series (III), the mean blood loss was 9600 ml (range 4000–15000 ml), indicating severe bleeding in complicated cases. The patients included in the present study were among the first angiographically treated PPH cases in Finland. Thus, the established technique and clinical expertise gained may have since improved the outcome.

Emergency peripartum hysterectomy is a procedure associated with high morbidity. Complications associated with peripartum hysterectomy include infections, urologic injuries, pelvic hematoma, and bowel injuries (Ramanathan & Arulkumaran 2006, Zelop et al. 1993). Furthermore, an emergency hysterectomy includes a 20% risk of damage to adjacent organs or an unintended removal of the ovaries, and a 20% risk of return to an operating theater (Knight & UKOSS 2007). If hysterectomy could be avoided, the risk of complications for the patient might be decreased. For our patients (III), the success rate in avoiding hysterectomy by means of post partum embolization was 6 out of 8 (75%). This is in line with a retrospective analysis by Brace et al. (2007), which showed a success rate of 71% in avoiding hysterectomy. PPH caused by abnormal placentation is more difficult to control and leads more often to a hysterectomy than bleeding caused by uterine atony (Brace et al. 2007, Pelage et al. 1998). In our patients with uterine atony, embolization was also more often successful than in patients with abnormal placentation.

When hysterectomy is avoided by means of embolization, fertility is preserved. Embolization of the uterus-supplying arteries with absorbable material like gelatin does not affect adversely in menstruation, fertility, or subsequent pregnancies (Chauleur et al. 2008, Descargues et al. 2004, Fiori et al. 2009, Ornan et al. 2003, Salomon et al. 2003, Stancato-Pasik et al. 1997). The recovery of normal menstruation indicates that the radiation exposure affects neither the endometrium nor the ovarian function (Fiori et al. 2009, Salomon et al. 2003). Occasional case reports have described recurrence of severe postpartum hemorrhage in subsequent labor with adherent placenta requiring manual removal or placenta accreta, increta or percreta (Kayem et al. 2007, Kitao et al. 2009, Salomon et al. 2003). Controversially, larger case series have failed to show recurrence of placenta accreta (Descargues et al. 2004, Fiori et al. 2009, Ornan et al. 2003). Not surprisingly, the risk for a CS in the subsequent delivery is very high (50–60%) (Chauleur et al. 2008, Goldberg et al. 2002). We did not perform a long-term follow-up to assess the outcome of possible future pregnancies, but the
two-month follow-up ultrasonography indicated normal endometrium in all patients.

A remarkable advantage of arterial embolization over arterial ligation or hysterectomy in managing PPH is that it does not require general anesthesia and laparotomy. Moreover, the bleeding vessel may be identified more easily with an angiography, and the risk for rebleeding from collaterals may be decreased as a result of more distal occlusion with the embolization (Badawy et al. 2001, Ko et al. 2002, Vedantham et al. 1997). In our case-series (III, IV), iliac or uterine arterial ligation was not used and thus comparison to embolization is impossible.

6.5 Complications related to pelvic arterial catheterization and embolization

In all of our PPH patients (II, IV) treated with catheterization and embolization, the complication rate was 11%. In the literature, an overall complication rate of 6−9% in the postpartum embolization has been reported (Badawy et al. 2001, Chung et al. 2003, Hansch et al. 1999, Mitty et al. 1993, Pelage et al. 1999, Vedantham et al. 1997). Frequently described complications include postoperative fever, pelvic abscess and groin hematoma (Gilbert et al. 1992, Greenwood et al. 1987). Patients with single ischemic complications, such as uterine necrosis, bladder gangrene, femoral artery subtotal occlusion, buttock ischemia, and transient sciatic nerve ischemia, have also been reported (Corr 2001, Cottier et al. 2002, Greenwood et al. 1987, Lingam et al. 2000, Pirard et al. 2002, Salomon et al. 2003). Occasional case reports have described internal iliac artery perforation and permanent ovarian failure (Chou et al. 2004, Ornan et al. 2003). The complications in our series were similar to those reported previously.

The use of prophylactic occlusion balloon catheters may present a risk factor per se. Cases with a massive arterial thromboembolism of the lower limb have been reported after occlusion balloon catheterization in cesarean section (Sewell et al. 2006, Greenberg et al. 2007, Shrivastava et al. 2007). It is estimated that the use of occlusion balloons equals to a 40-minute aortic clamping in terms of the risk of thromboembolism, since the patients are in a hypercoagulative condition (Greenberg et al. 2007). Accordingly, in our study population, one patient was diagnosed with thrombosis of the left popliteal artery, and two patients with severe venous thromboembolism. To minimize vascular complications, it is advised that the balloon catheters be removed as early as possible after the therapy (Greenberg et al. 2007). Meanwhile some clinicians prefer leaving the catheters in situ for
one postoperative day with a view for emergency embolization, in case of
restarted hemorrhage (Tan et al. 2007). In our study, two subjects underwent
embolization within 24 hours after primary cesarean operation via catheters left in
situ, and hemostasis was thereby achieved.
7 Limitations of the study

In the RCT comparing STAN and CTG (I) the calculation of the required sample size was based on the previous years’ incidence of neonatal acidemia in all deliveries in our hospital. In the analysis it became apparent that the incidence of acidemia in the study population was lower than expected. The probable explanation is that the study was conducted recruiting unselected, low-risk, term parturients, with whom the risk for adverse neonatal outcome is low. However, the most adequate surveillance method in low-risk parturients needed to be determined, since 25% of cases of intrapartum fetal asphyxia occurs among these patients (Low 1999). It is of note that the incidence of acidemia was also similarly lower than expected among women who would have been eligible for the study but were not included. Moreover, the power analysis was calculated with a hypothesized reduction of 50% in the incidence of neonatal acidemia, which may have been too optimistic. The ultimate purpose of the intrapartum fetal monitoring is the prevention of neonatal death and long-term neurological morbidity resulting from birth asphyxia. Indisputably, this study lacks the power to assess the potential of ST-analysis within these measures. Considering the low incidence of permanent, measurable injury resulting from intrapartum asphyxia, the number of parturients needed for a clinical trial to show reduction in true long-term outcome measures will probably remain unobtainable.

In the evaluation of interobserver variability in the interpretation of STAN tracings according to STAN guidelines, the observers interpreted 60-minute STAN recordings and were blinded to all clinical data. The interobserver agreement was moderate at best. Access to all clinical information might have made the interpretations more consistent.

The observational case series (III) on PPH were conducted as a clinical audit evaluating new tools in the management of PPH. The lack of a control group limits the findings of this study, as in any clinical audit. In study IV, comparing prophylactic pelvic artery catheterization and embolization to conventional management of placenta accreta in a cesarean delivery, the study setting was retrospective and the control group was historical. This may have introduced a selection bias. The patients treated with the prophylactic catheterization may have been more complicated than subjects in the control group. The significantly higher number of previous pregnancies and cesarean deliveries in the study group may reflect the selection bias. A prospective, randomized study with a power analysis would offer an ideal and comprehensive setting to test these methods.
8 Conclusions

The following conclusions can be drawn from the results of the present thesis:

1. In non-selected term pregnancies, the interobserver agreement among experienced obstetricians in the classification of CTG as well as in clinical decision-making according to STAN guidelines is moderate at best (II).

2. Intrapartum fetal ST monitoring does not reduce the incidence of neonatal acidemia or improve the neonatal short-term outcome, nor does it decrease the rate for instrumental deliveries due to fetal distress when compared to monitoring with conventional CTG. However, the use of automated ST analysis reduces the need for FBS during labor (I).

3. Prophylactic catheterization and embolization of pelvic arteries does not improve the surgical outcomes of patients with placenta accreta when compared to conventional management of patients with prenatally diagnosed placenta accreta (IV).

4. Post-partum embolization in the management of PPH shows an overall success rate of 73%, with best results in patients with uterine atony as the primary cause of PPH (III).
References


Original articles


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