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# Zeitpunkte von Interventionen und Ereignissen und ihre Assoziationen mit der Geburtsdauer und dem Geburtsmodus bei Frauen mit geplanter vaginaler Geburt nach vorangegangenem Kaiserschnitt

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Zum Erlangen des Doktorgrades der Epidemiologie (PhD)
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vorgelegt von

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MSc Midwifery

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# Timing of interventions and events associated with labour duration and mode of birth in women with planned vaginal births after caesarean section

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by

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| | |
|---|---|
| ACOG | American College of Obstetricians and Gynecologists |
| ARM | Artificial rupture of membranes |
| CI | Confidence interval |
| c-section | Caesarean section |
| ERSC | Elective repeat caesarean section |
| HR | Hazard ratio |
| IQR | Interquartile range |
| NICE | National Institute for Health and Care Excellence |
| OR | Odds ratio |
| pVBAC | Planned vaginal birth after caesarean section |
| ROM | Rupture of the membranes |
| SROM | Spontaneous rupture of the membranes |
| VBAC | Vaginal birth after caesarean section |

# Abstracts

Susanne Grylka-Bäschlin

**Zeitpunkte von Interventionen und Ereignissen und ihre Assoziationen mit der Geburtsdauer und dem Geburtsmodus bei Frauen mit geplanter vaginaler Geburt nach vorangegangenem Kaiserschnitt**

**Einleitung:** Kenntnisse über Geburtsprozesse von Frauen mit geplanter vaginaler Geburt nach Kaiserschnitt sind wichtig, damit das Geburtsmanagement verbessert und die Raten an vaginalen Geburten gesteigert werden können. Die Risiken einer vaginalen Geburt nach Kaiserschnitt sind für Mutter und Kind gering. Für einen Großteil der Frauen mit vorangegangenem Kaiserschnitt ohne zusätzliche Risikofaktoren ist die vaginale Geburt der Geburtsmodus der Wahl. Bisher gibt es nur wenig Forschung zu den Charakteristika der Geburtsprozesse von Frauen mit geplanter vaginaler Geburt nach Kaiserschnitt. Zudem ist die Forschung zur Geburtsdauer als abhängiger Prozess mit den bekannten Herausforderungen von Beobachtungsstudien konfrontiert, kausale Zusammenhänge interpretieren zu können. Das Ziel dieser Arbeit war, neue Erkenntnisse über das Gebären von Frauen mit geplanter vaginaler Geburt nach Kaiserschnitt zu gewinnen und daher Geburtsprozesse zu vergleichen von a) Zweitgebärenden mit vorangegangenem Kaiserschnitt versus Erstgebärende und Zweitgebärende mit zweiter vaginaler Geburt und b) Gebärenden mit erfolgreicher vaginaler Geburt nach Kaiserschnitt versus Gebärende mit sekundärem Kaiserschnitt während des Gebärens in der heutigen klinischen Praxis.

**Methode:** Diese PhD-Thesis beinhaltet die Analysen von Beobachtungsdaten zweier Multicenterstudien a) Sekundäranalyse der ProGeb-Studie, einer existierenden Kohortenstudie in 47 Geburtskliniken in Niedersachsen, Deutschland. Die analysierte Stichprobe schloss n=3.239 Teilnehmerinnen mit geplanter vaginaler Geburt ein und b) Analysen von Daten des deutschen Arms der OptiBIRTH-Studie, einer Europäischen cluster-randomisierten Multicenterstudie mit insgesamt 15 Studienzentren. Die analysierte Stichprobe beinhaltete n=387 Teilnehmerinnen mit vorangegangenem Kaiserschnitt und Geburtsbeginn für eine geplante vaginale Geburt. Kaplan-Meier Schätzer, Log-Rank-Test, Wilcoxon Test, Random-Effects logistisches Regressionsmodell und Shared Frailty Cox Regressionsmodelle mit zeitabhängigen Kovariablen wurden mit Stata 13 analysiert.

**Ergebnisse:** Die Sekundäranalyse der ProGeb-Studie verglich Daten von n=211 Zweitgebärenden mit vorangegangenem Kaiserschnitt mit n=1.897 Erstgebärenden und n=1.149 Zweitgebärende mit vorangegangener vaginaler Geburt und zeigte, dass Zweitgebärende mit vorangegangenem Kaiserschnitt älter waren (31.6 vs 28.0 Jahre, $p<0.001$), weniger oft Oxytocin erhielten (48.8 vs 57.0%, $p=0.024$), eine niedrigere Rate an

Spontangeburten (69.2 vs 83.4%, p<0.001) und eine kürzere Austreibungsphasen (0.55 vs 0.77 Std., HR=1.341, 95% KI [1.049,1.714], p=0.019) hatten als Erstgebärende. Die gesamte Geburtsdauer, die Dauer der Eröffnungsphase und die Zeitintervalle zwischen Geburtsbeginn und Interventionen sowie Ereignissen waren vergleichbar mit denjenigen von Erstgebärenden, jedoch signifikant länger als diejenigen von Zweitgebärenden mit zweiter vaginaler Geburt. Die Analyse von Daten des deutschen Arm der OptiBIRTH-Studie verglich n=291 Gebärende mit erfolgreichen vaginalen Geburten mit n=96 Gebärenden mit sekundären Kaiserschnitten und zeigte, dass Opioide bei Frauen mit erfolgreicher vaginaler Geburt früher verabreicht wurden als bei Frauen mit sekundärem Kaiserschnitt (2.30 vs 3.83 Std., p=0.019). Eine vorhergegangene vaginale Geburt erhöhte die Chance einer erfolgreichen vaginalen Geburt nach Kaiserschnitt (OR=4.98, 95% KI [1.78, 13.93], p=0.002). Negative Prädiktoren für den Erfolg der geplanten vaginalen Geburt nach Kaiserschnitt waren ein höheres kindliches Geburtsgewicht (OR per kg=0.39, 95% KI [0.21, 0.71], p=0.002, eine Amniotomie (OR=0.31, 95% KI [0.17, 0.56], p<0.001, Referenzkategorie intrapartaler spontaner Blasensprung) und eine längere Geburtsdauer (OR pro Stunde=0.93, 95% KI [0.88, 0.97], p=0.001). Bei den erfolgreichen vaginalen Geburten nach Kaiserschnitt wurde das interventionsfreie Intervall durch eine Einleitung verkürzt (HR pro Stunde=2.85, 95% KI [2.00, 4.08], p<0.001) und ein höheres Gestationsalter verlängert (HR=0.84, 95% KI [0.76, 0.94], p=0.002).

**Diskussion:** Diese Thesis führte zu neuen und wichtigen Erkenntnissen für die Betreuung rund um die Geburt. Sie deckte auf, dass Zweitgebärende mit vorangegangenem Kaiserschnitt eine eigene Gruppe von gebärenden Frauen bilden. Die Erkenntnis einer erhöhten Chance auf eine kürzere Austreibungsphase kann diese Frauen motivieren, eine vaginale Geburt anzustreben und sollte für die präpartale Beratung genutzt werden. Zudem zeigten Frauen mit erfolgreicher vaginaler Geburt nach Kaiserschnitt eine effektivere Wehentätigkeit und erhielten seltener intrapartale Interventionen als Frauen mit sekundärem Kaiserschnitt. Das Geburtsmanagement sollte deshalb darauf ausgerichtet sein, körpereigene Kontraktionen zu fördern, damit die Erfolgsraten für eine vaginale Geburt gesteigert werden können. Diese Forschung zeigte spezifische Herausforderungen von Studien, welche den Erfolg der geplanten vaginalen Geburt oder Geburtsprozesse untersuchten: Frauen mit Geburtsbeginn, welche keine Absicht hatten vaginal zu gebären, mussten aus der Studie ausgeschlossen werden und der Geburtsbeginn musste definiert werden. Die Interpretation von kausalen Zusammenhängen in Beobachtungsstudien ist eine bekannte Herausforderung. So wurden zeitabhängige Kovariablen in dieser Thesis für die Adjustierung von Modellen verwendet, aber ihre Auswirkungen auf das untersuchte Zeitintervall wurden nicht interpretiert. Diese Thesis zeigte die Notwendigkeit für weitere Forschung auf, um zusätzliches Wissen über den optimalen Zeitpunkt von Interventionen und Ereignissen zu gewinnen und damit das intrapartale Management zu verbessern. Zusätzliche methodologische Ansätze wie das Erforschen von latenten Variablen sind notwendig. Insgesamt leisten die Ergebnisse dieser Doktorarbeit einen wichtigen Beitrag zur aktuellen wissenschaftlichen Diskussion über Geburtsdauern und intrapartale Interventionen und geben einen Einblick, wie Frauen mit vorangegangenem Kaiserschnitt gebären.

Susanne Grylka-Baeschlin

**Timing of interventions and events associated with labour duration and mode of birth in women with planned vaginal births after caesarean section**

**Introduction:** Knowledge about labour processes of women with planned vaginal birth after caesarean section (VBAC) is relevant for improving the labour management and increasing VBAC rates. The overall risks of VBAC for mother and child are low. For an important proportion of women with a previous c-section and without additional risk factors, VBAC is the first choice for the mode of birth in a subsequent pregnancy. However, limited research has been done about labour and birth characteristics for planned VBAC. Additionally, research on labour duration as a dependent process faces known challenges of observational studies when trying to interpret causal relationship. The aim of this PhD-thesis was to gain knowledge about the way women with planned VBAC give birth and therefore to compare labour processes of a) secundiparae planning a VBAC versus primiparae and secundiparae planning a second vaginal birth and b) parturients with successful VBAC versus those undergoing unplanned c-section in modern clinical practice.

**Method:** This PhD-thesis consists in the analyses of observational data provided by two multicentre studies: a) secondary analysis of data of the ProGeb-study, an existing cohort study in 47 maternity units in Lower Saxony, Germany (the analysed sample included 3,239 participants planning a vaginal birth) and b) analysis of data collected within the German part of the OptiBIRTH-study, a European cluster randomised trial with a total of 15 study sites (the analysed sample included 387 participants with one previous c-section who intended to give birth vaginally and started labour for VBAC). Kaplan-Meier estimates, log rank test, Wilcoxon test, random-effects logistic regression and shared frailty Cox regression models including time-dependent covariables were analysed with Stata 13.

**Results:** The secondary analysis of the ProGeb-study compared data from n=211 secundiparae with a previous c-section with n=1,897 primiparae and n=1,149 secundiparae with a previous vaginal birth and showed that secundiparae with planned VBAC were older (31.6 vs 28.0 years, $p<0.001$), received oxytocin less often (48.8 vs 57.0%, $p=0.024$), had lower spontaneous birth rates (69.2 vs 83.4%, $p<0.001$) and shorter second stage of labour (0.55 vs 0.77 hrs, HR=1.341, 95% CI=1.049-1.714, $p=0.019$) compared to primiparae. Overall labour duration, the duration of first stage of labour and the time intervals between onset of labour and interventions were similar to primiparae but significantly longer compared to secundiparae with second vaginal birth. The analysis of German data OptiBIRTH compared n=291 parturients with successful VBAC with n=96 parturients with unplanned c-sections and revealed that opioids were administered earlier in women with successful

VBAC compared to women with unplanned c-section (2.30 vs 3.83 hrs, p=0.019). A previous vaginal birth increased the odds for a successful VBAC (OR=4.98, 95% CI [1.78, 13.93], p=0.002). Negative predictors for the success of planned VBAC were a higher infant´s birthweight (OR per kg=0.39, 95% CI [0.21, 0.71], p=0.002), amniotomy (OR=0.31, 95% CI [0.17, 0.56], p<0.001, reference intrapartal SROM) and longer labour duration (OR per hour=0.93, 95% CI [0.88, 0.97], p=0.001). In successful VBAC, induction shortened (HR per hour=2.85, 95% CI [2.00, 4.08], p<0.001) and a higher gestational age prolonged (HR=0.84, 95% CI [0.76, 0.94], p=0.002) the intervention-free time interval.

**Discussion:** This thesis contributes new and important evidence for maternity care. It shows that secundiparae with planned VBAC should be considered as a distinct category of birthing mothers. The evidence for an increased chance of having a shorter second stage of labour might motivate secundiparae with a previous c-section to plan a VBAC and should be used for antenatal counselling. Furthermore, women with successful VBAC had more effective labour but less frequent intrapartal interventions and, therefore, labour management for planned VBAC should aim to foster endogenous uterine contractions to increase success rates. The research has also highlighted specific challenges for studies investigating the success of planned vaginal birth or labour as a process, such as the need to exclude parturients with onset of labour but no intention to give birth vaginally and to define of onset of labour. The interpretation of causal-relationships in observational studies is a known challenge and time-dependent covariables were included in this thesis to adjust the models, but their accelerating or slowing effect was not interpreted. Rather, the thesis has succeeded in defining the need for future research to determine the optimal timing of interventions and events to improve intrapartum management and identified how further research and additional methodological approaches, such as the investigation of latent variables, are needed. In summary, the findings of this thesis make an important contribution to the current scientific discussion about labour duration and intrapartal interventions and add new insight into how women with a previous c-section give birth.

# 1. Introduction

Knowledge about labour and birth related characteristics of women with planned vaginal birth after caesarean section (VBAC) is relevant for improving intrapartal management and enhancing success rates. For decades, interventions to support or facilitate labour for childbirth were researched mostly using randomised controlled trials to investigate cause-effect relationships (Enkin et al. 1995, Gross 2001, Jones et al. 2012, Wei et al. 2013). In evidence based health care, randomised controlled trials are often not ethically justifiable or practicable (Baiocchi et al. 2014). Moreover, labour is a dynamic process and not suitable for static statistical analysis methods; therefore other methodical approaches such as survival analysis have been proposed (Gross 2001, Vahratian et al. 2006). A paradigm shift concerning obstetrical research could be observed during the last decades of the 20th century (Gross 2001). The consequence of this shift was an increased interest in observational studies, in particular longitudinal study designs such as cohort studies. Birth cohort studies for example investigated the associations between perinatal factors such as mode of birth, prematurity or birthweight with childhood, adolescent, adult medical and social outcomes (Richards et al. 2001, Moster et al. 2008, Tollanes et al. 2008, Stokholm et al. 2016). Observational studies were also used to research labour and birth and provided insights into its dynamic nature especially when using survival analysis (Gross et al. 2001, Vahratian et al. 2006). Longitudinal studies investigating labour as a dependent process have the potential to identify gaps in maternity care and unfavourable intrapartum management (Gross 2001). Nevertheless, causal relationships might be difficult to validate in observational studies (Baiocchi et al. 2014). It is therefore of special interest to research the dynamic of labour and birth using survival analysis and critically reflect on the methodologies used.

### 1.1. Mode of birth in a pregnancy following a c-section

In most developed countries, caesarean section (c-section) have increased in recent decades and now exceed rates of 10-16 per cent, above which there does not appear to be any reduction in maternal or neonatal mortality (ACOG et al. 2014, Ye et al. 2015, Betran et al. 2015). Rising c-section rates all over the world are of international concern (EURO-PERISTAT 2013, ACOG et al. 2014). Noteable variations have been observed between countries, regions and sites, which can only partially be explained by socio-demographic factors such as age and parity (EURO-PERISTAT 2013, Mikolajczyk et al. 2013, ACOG et al. 2014, Gross et al. 2014, Macfarlane et al. 2016). These differences indicated a lack of consensus about clinical practices (Gross et al. 2014, Macfarlane et al. 2016). Soft indications, legal issues and differing care models were also found to be the origin of rising c-section rates (Kolip et al. 2012, Gross et al. 2014). The leading indication for a c-section was found to be elective repeat c-section because of the uterine scar (Timofeev et al. 2013). Increasing VBAC-rates in women with a high chance of success is an effective strategy to decrease overall c-section rates (Cheng et al. 2011, Sabol et al. 2015) and save costs (Rogers et al. 2017).

Rising c- section rates lead to an increasing proportion of pregnant women who have had a previous c-section (Kyvernitakis et al. 2014). The dictum from Cragin (1916) “once a caesarean section, always a caesarean section” was a reasonable recommendation at its time in the United States, where c-sections for primiparous women were mostly performed because of pelvic contractions and the uterine incision was vertical (which was associated with an increased risk of uterine rupture) (Enkin 1989, Ugwumadu 2005). The change of surgery techniques from vertical into lower segment incision decreased the risk for uterine rupture considerably (Enkin 1989). In the United States, VBAC rates increased during the 1980s and early 1990ss before a considerable decrease from 28.3% in 1996 to 9.2% in 2004 was noted (Menacker et al. 2006). In Europe in contrast, VBAC has been the common practice throughout the last century (Flamm 2001) but VBAC rates have also decreased distinctively since the 1990s; for example in Hesse, Germany from 41.3% in 1996 to 23.3% in 2012 (Kyvernitakis et al. 2014). The decision about the mode of birth in a pregnancy following a c-section is characterised by weighing potential harms and benefits for mother and child and by estimating the success chances for the planned VBAC (Ugwumadu 2005, Grobman et al. 2007, Guise et al. 2010a, Clark et al. 2012). With conscientious intrapartum management, a planned VBAC has a high probability of resulting in a safe and successful vaginal birth (Guise et al. 2010a, Scott 2014). VBAC is therefore the first choice for the mode of birth after c-section for a high percentage of women without additional risk factors (Guise et al. 2010a).

#### 1.1.1. Risk and benefits of VBAC and repeat c-sections

Serious maternal and neonatal adverse outcomes associated with planned VBAC are generally rare (Landon et al. 2004, Guise et al. 2010a, Guise et al. 2010b, Nair et al. 2015). Although some recent studies found slightly higher risks for maternal life threatening outcomes and morbidities with planned VBAC compared to elective repeat c-section (ERCS) (Bickford & Jansen 2015, Kok et al. 2015), other studies found the opposite (Curtin et al. 2015) or found no difference beside the increased risk for uterine rupture for women with planned VBAC (Nair et al. 2015). Guise et al. (2010a) summarised in a literature review that maternal mortality was higher with ERCS but perinatal mortality was higher for planned VBAC. Smith et al. (2002) however stated that infant mortality for planned VBAC was comparable to women giving birth to their first child. Uterine rupture was the most feared complication in a pregnancy following a c-section and was more frequent with planned VBAC compared to ERCS (Guise et al. 2010a). Two large studies including over 29,000 and nearly 58,000 participants respectively found a lower risk of uterine rupture with spontaneous labour compared to induced or augmented labour (Dekker at al. 2010, Al-Zirqi et al. 2017). The risk of uterine rupture was highest if prostaglandin and oxytocin were used sequentially for labour induction (Al-Zirqi et al. 2017). Hospital stays were shorter, recovery after birth better, persistent pain and stress symptoms less frequent and health related quality of life higher after VBAC compared to ERSC (Guise et al. 2010a, Kealy et al. 2010, Kainu et al. 2016, Petrou et al. 2016, Chen et al. 2017). After a planned VBAC new mothers also initiated breastfeeding more often, had less breastfeeding complications and were more satisfied with the mode of birth compared to ERCS (Shorten & Shorten 2012, Karlström et al. 2013, Regan et al. 2013). Additionally, women who underwent a c-section had a lower subsequent fertility and were less likely to have more children compared to women who gave birth vaginally (Gurol-Urganci et al. 2013, Masinter et al. 2014, Radin et al. 2016). The risks for increased adverse maternal outcomes were even higher with multiple c-sections (Marshall et al. 2011, Kaplanoglu et al. 2015). The systematic review of Marshall et al. (2011) included 2,282,922 births and found increasing rates of hysterectomy, blood transfusion, adhesion and surgical injury associated with the increasing numbers of c-sections. The incidence of placenta praevia increased from 10 per 1,000 births with one previous c-section to 28 per 1,000 births with three of more c-sections (Marshall et al. 2011).

It also should be considered that c-sections in general have a long term impact on the health of mother and child. Birth by c-section changed the neonatal gut colonisation and was hypothesised to be a possible cause of immune-mediated diseases (Rutayisire et al. 2016, Stokholm et al. 2016). Tollanes et al. (2013) and Sevelsted et al. (2016) found an increased risk for childhood asthma after c-section compared to vaginal birth. The risk was higher if the c-section was performed before the rupture of the membranes (Sevelsted et al. (2016). Being born by c-section was also associated with a higher risk of adiposity in young adulthood (Mesquita et al. 2013). It was supposed that c-sections were associated with DNA-methylation alterations by affecting the epigenetic state of neonatal hematopoietic stem cells, due to more immediate stress for the new born with c-section rather than gradually increasing stress as during labour and birth (Schlinzig et al. 2009, Almgren et al. 2014, Dahlen et al. 2014). However, Virani et al. (2012) did not find any association of the mode of birth with global methylation in a larger sample after adjusting for maternal age, maternal smoking, and infant gender. The method used to investigate methylation might have been less sensitive and further research in this topic is needed to fully understand the impact of mode of birth on later health (Almgren et al. 2014).

While VBAC is the preferred mode of birth for women with no additional risk factors, unplanned c-section during labour for planned VBAC should be avoided because of increased risks for mother and child (El-Sayed et al. 2007). Unplanned c-section was observed to be associated with higher incidences of chorioamnionitis, postpartum haemorrhage, hysterectomy, neonatal jaundice and neonatal morbidities as compared to successful VBAC (El-Sayed et al. 2007). In order to prevent women from unplanned c-section, knowledge about the process of labour for planned VBAC is needed to optimise the labour management and enhance the chance of success.

#### 1.1.2. Predictors for the success of planned VBAC

Success rates of planned VBAC have been found to be between 60-85% in several studies (Balachandran et al. 2014, Knight et al. 2014, Tessmer-Tuck et al. 2014). Sociodemo-graphic factors such as younger age, Caucasian race, being married, longer education, smoking, a BMI less than 30 and private insurance were found to be associated with a higher chance of successful VBAC (Landon et al. 2005). Regarding obstetric history, a previous vaginal birth was a significant positive predictor in most studies investigating the success of planned VBAC (Grobman et al. 2007, Abildgaard et al. 2013, Birara & Gebrehiwot 2013, Landon et al. 2005, Obeidat et al. 2013, Studsgaard et al. 2013, Knight et al. 2014, Tessmer-Tuck et al. 2014, Bhide et al. 2016). VBAC success increased if the previous c-section was because of multiple birth, breach presentation or placenta praevia (Fagerberg et al. 2013). In contrast, the VBAC success was lower with a history of complications during labour and birth before the first c-section, macrosomia and maternal diabetes (Fagerberg et al. 2013). Planned vaginal birth after a previous c-section for dystocia was found to be more successful if the c-section was performed late during the labour process at nine to ten centimetres of dilatation or during second stage of labour (Abildgaard et al. 2013, Lewkowitz et al. 2015). A longer interval since vaginal birth for women with history of c-section and vaginal birth decreased the chance of successful VBAC (Miller & Grobman 2016). In contrast, cervical length and myometrial thickness of the caesarean scar were positively associated with successful VBAC (Naji et al. 2013, Beloosesky et al. 2017). A decreased ultrasonographic lower segment myometrial thickness was associated with an increased risk for uterine rupture (Kok et al. 2013), but a clear cut-off value could not be defined and therefore the current clinical applicability of this finding is uncertain (Kok et al. 2013, ROCG 2015). Factors associated with the obstetrician's cognitive traits were also found to be associated with the success chance of planned VBAC (Yee et al. 2015). The authors found that a more proactive coping attitude and lower anxiety of the professionals increased the likelihood of both planned and successful VBAC.

Several factors related to the onset of labour and the events occurring during labour are associated with a more or less successful VBAC. Spontaneous labour, greater cervical dilatation at admission, deeper vertex station, rupture of the membranes, epidural anaesthesia, lower mean birthweight and lower gestational age were positive predictors for the success of VBAC (Macones et al. 2001, Al-Shaikh & Al-Mandeel 2013, Bangal et al. 2013, Birara & Gebrehiwot 2013, Landon et al. 2005, Metz et al. 2013b, Obeidat et al. 2013, Shatz et al. 2013, Siddiqui 2013). Studies researching associations between labour induction and the success of planned VBAC provided contradicting results (Smith et al. 2005, Paptnik & Grobman 2015). Although Smith et al. (2005) found that prostaglandin induction decreased the chance of a successful VBAC, Palatnik and Grobman (2015) observed that induction at 39 gestational weeks increased the chance compared to expectant management (73.8% vs 61.3%, $p < 0.001$).

Prediction models for the success of planned VBAC used during pregnancy have been widely researched in recent years (Smith et al. 2005, Grobman et al. 2007, Fagerberg et al. 2015, Abdel Aziz et al. 2016, Annessi et al. 2016, Baranov et al. 2017). The aim of these prediction models was to identify women with low chance of VBAC success during pregnancy, for example because of increased maternal and neonatal morbidities for women with unplanned c-section during labour for planned VBAC (El-Syed et al. 2007, Curtin et al. 2015). Grobman et al. (2007) developed a model to predict the likely success of VBAC based on factors which were available at the first antenatal visit. Maternal age, body mass index, ethnicity, prior vaginal delivery, prior VBAC, and a potentially recurrent indication for the c-section were included in Grobman’s model. Fagerberg et al. (2015) confirmed these factors in a Swedish cohort study and increased the prediction - accuracy adding maternal height and the c-section rate of the maternity unit where the planned VBAC took place. In Italy, the accuracy of Grobman´s model was lower but the inclusion of the level of maternal education increased the prediction value (Annessi et al. 2016). Abdel Aziz et al. (2016) tested and confirmed the model in Middle- Eastern women who were admitted to the maternity unit close to birth. However, other studies found that the predictive value for women without a previous vaginal birth remained poor if the predicted chance of VBAC success was low (Ashwal et al. 2016, Maykin et al. 2017).

Even when selecting women for planned VBAC by taking into consideration their hypothetical success chance, some women will start labour and be confronted with the risk of unplanned c-section (Grobman et al 2007). Moreover, starting labour has advantages for subsequent pregnancies because women with a history of elective c-section have a higher risk of uterine rupture and severe complications compared to women with a history of emergency c-section (Kok et al. 2014, Colmorn et al. 2017). Multiple c-sections were associated with increased maternal risks (Marshall et al. 2011), which could be reduced if women pursue the chance to give birth vaginally in pregnancies following a c-section (Cheng et al. 2011, Sabol et al. 2015). Starting labour for VBAC should therefore be promoted. For women going into labour for a planned VBAC and having a potential risk of an unplanned c-section it is important to have knowledge about intrapartal predictors for the success of VBAC for optimizing intrapartal management. It would be meaningful to identify intrapartal predictors for unplanned c-section with progressing labour and to be able to intervene when maternal and neonatal risks are still low. The inclusion of factors such as cervical dilatation on admission or the need for labour augmentation in a prediction model was proposed by Macones et al. (2001). However, no studies have been found comparing further labour process related factors such as labour duration, the duration of labour phases, the timing of interventions or the interval free time interval for successful VBAC versus unplanned c-section.

### 1.2. The dynamic nature of labour and birth

Historically, a paradigm shift concerning obstetrical research could be observed during the last decades of the 20th century (Gross 2001). Whereas in the 1950s the uterus was considered as a dynamic organ and labour duration and rupture of the membranes as dynamic processes, active management of labour was propagated in the 1960s (Gross 2001, Friedman 1954, Friedman 1955, Friedman & Sachtleben 1963, O'Driscoll et al. 1970). This development was followed by the conduct of clinical trials to examine whether interventions were effective, e.g. for shortening or facilitating labour (Gross 2001), and evidence-based care in the late 1980s investigated the cause-effect relationship in randomised controlled trials. These studies were done to provide the most reliable evidence about the effects of care (Enkin et al. 1995), but the static approach of this experimental design, which does not take into consideration the timing of care related aspects, means that the dynamic nature of pregnancy and labour was mostly ignored in research until a good decade ago (Albers et al. 1996, Smith 2001, Gross 2001, Zhang et al. 2002, Vahratian et al. 2006). Gross investigated labour as a dependent process in observational studies using survival analysis and including time-dependent predictors (Gross 2001, Gross et al. 2014, Figure 1). Events occurring during labour and their timing showed a greater association with the duration of first stage of labour than factors that pre-existed at the time of onset of labour (Gross et al. 2005). Vahratian (2006) highlighted the methodological challenges of investigating labour duration and proposed the use of survival analysis. Interval censored regression modelling was proposed and showed labour progression from one centimetre to the next (Zhang et al. 2002, Zhang et al. 2010, Vahratian et al. 2006). Labour progression accelerated with larger cervical dilatation (Zhang et al. 2010). There are significant methodological differences between Gross et al. (2014) using Cox regression modelling and Zhang et al. (2002) using interval censored

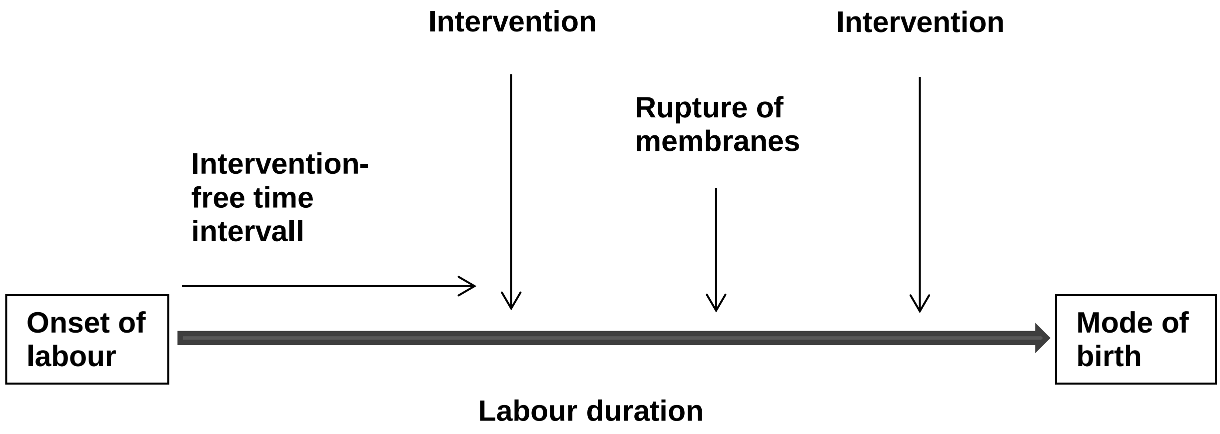


**Figure 1:** The dynamic nature of the process of labour

regression. Whereas Gross et al. (2014) focused on labour as a dependent process, Zhang et al. (2002) researched the progression of cervical dilatation at different stages of advancement.

### 1.2.1. <u>The current discussion about labour curves</u>

Friedman (1954, 1955) is well known for investigating the graphical appraisal of the relationship between cervical dilatation and time. Albers et al. (1996) however, suggested that labour might last longer than commonly expected. A few years later, Zhang et al. (2002) showed that labour curves differed from Friedman’s findings. The active phase of labour started later and there was no deceleration phase which raised doubts about Friedman’s S-shape of the cervical dilatation curve (Friedman 1954, Friedman 1955, Zhang et al. 2002, Zhang et al. 2010). Zhang’s labour curves, however, were assessed in a historical dataset with births from the years 1959-1965, when intervention rates were low, because the eighth-degree polynomial model used to construct average labor curves did not allow the inclusion of confounders (Zhang et al. 2010). Maternal characteristics at that time (such as age and BMI) were much lower compared to those of contemporary parturients, c-sections were excluded from the analysis and mean instead of median labour duration was used to compute the labour curves (Zhang et al. 2010, BPB online, Statista – das Statistik-Portal online). It can be supposed that median labour duration is even longer than Zhang’s curves showed but modern-day labour curves, taking into consideration the characteristics of today´s parturients and obstetrical practices, are still lacking.

### 1.2.2. Research on labour duration

Factors preexisting to onset of labour such as age, bodyweight, ethnicity, parity and infant´s birthweight have been found to be associated with labour duration (Albers et al. 1996, Albers 1999, Zhang et al. 2002, Vahratian et al. 2004). Older and heavier women, primiparae and women with a heavier baby had longer labour duration and American Indian first-time mothers had shorter second stage of labour than non-Hispanic white primiparae (Albers et al. 1996, Albers 1999, Zhang et al. 2002, Vahratian et al. 2004). Moreover, factors occurring during labour such as electronic fetal monitoring, being ambulatory during labour or narcotic analgesia were also associated with longer labour (Albers 1999). Randomised controlled trials and meta-analyses using static statistical methods investigated the impact of intrapartal interventions on labour duration (Bugg et al. 2013, Smyth et al. 2013, Wei et al. 2013, Wang et al. 2017). Epidural analgesia did not prolong first and second stage of labour in different studies (Singh et al. 2016, Wang et al. 2017) but Dogu et al. (2016) found shortened first stage and prolonged second stage of labour when epidural analgesia was applied. Smyth et al. (2013) observed no significant shortening of first stage of labour for routine amniotomy in normally progressing labour. Other studies included a time-related aspect comparing early amniotomy and oxytocin to prevent labour dystocia with delayed application (Wei et al. 2013). Early amniotomy was found to shorten the duration of spontaneous, augmented and induced labour in different studies (Ajadi et al. 2006, Gagnon-Gervais et al. 2012, Ghafarzadeh et al. 2015, Macones et al., 2012, Wei et al. 2013). The early administration of oxytocin also shortened labour in women with slow progress (Bugg et al. 2013). The dynamic nature of labour and birth however was not taken into account in these randomised controlled trials. In addition to these static methods to investigate labour duration, survival analyses taking the dynamic nature of labour and birth into consideration have been used in recent years (Petersen et al. 2011, Gross et al. 2014). The start of oxytocin was associated with an acceleration of labour progression (Gross et al. 2014). For primiparae, epidural analgesia administered during the first seven hours after onset of labour was associated with prolonged first stage of labour but accelerated labour when given after seven hours. For multiparae, a later timing of epidural analgesia was associated with prolonged duration of first stage of labour (Gross et al. 2014). Additionally, women’s perception of the onset of labour was associated with the frequency of epidural analgesia as well as with the timing of its administration and with cervical dilatation at the time of administration (Petersen et al. 2013a). Amniotomy accelerated labour but in multiparae the effect was greater during the first five hours after onset of labour (Gross et al. 2014). It was supposed that time-varying predictors for the duration of first stage of labour had a greater impact than time-constant ones (Gross et al. 2005), which makes survival analyses of special value for studying the dynamic nature of labour and birth.

### 1.2.3. Parity and its association with labour duration and mode of birth

Little research has been done on labour duration for secundiparae with planned VBAC compared with primiparae and secundiparae with second vaginal birth, or on labour duration of successful VBAC compared to women with unplanned c-section during labour. It could be expected that labour patterns of secundiparae with a previous c-section are similar to primiparae but different to secundiparae with previous vaginal birth. Differences in labour characteristics between primiparae and multiparae were observed in different studies (Albers et al. 1996, Zhang et al. 2010, Petersen et al. 2011, Petersen et al. 2013b, Gross et al. 2014). Overall labour duration and the durations of first and second stage of labour were shorter for multiparae compared to primiparae (Zhang et al. 2010, Petersen et al. 2011) and the median time interval between onset of labour and the beginning of care was slightly longer for multiparae compared to primiparae (Petersen et al. 2011). The sequence of interventions differed also between primiparae and multiparae (Petersen et al. 2013b). The differences between primiparae and multiparae might be due to differences in uterine activity with respect to parity (Arulkumaran et al. 1984) but might also be a consequence of the softened tissue resulting from the weight of the foetus during pregnancies and from the stretching during the first birth. Only a few studies investigated labour patterns of women with a previous c-section. Graseck et al. (2012) found similar cervical dilatations between women with planned VBAC and women without a previous c-section. Other studies suggested that labour progression of secundiparous women with VBAC differed from secundiparous women with repeated vaginal birth (Faranesh & Salim 2011) and that labour duration was similar or even longer compared to primiparous women if the previous c-section was performed because of dystocia (Harlass & Duff 1990). Women with successful VBACs were found to have a higher cervical dilatation rate than women with planned VBAC who had in an unplanned repeat c-section (Holland et al. 1992, Omole-Ohonsi et al. 2007). Sondgeroth et al. (2015) found that women who undergo labour induction for planned VBAC had a longer latent phase but similar active phase of labour compared to women with spontaneous onset of labour. There does not appear to be any published research into the timing of interventions and events in women starting labour for VBAC and there is a lack of knowledge about labour processes of planned VBAC.

### 1.2.4. The intervention-free time interval

Midwives experienced that not disturbing the physiological birth process was a key aspect to promote normal birth (Aune et al. 2017). The NICE guideline for intrapartum care (NICE 2014) recommends avoiding clinical interventions if labour is progressing normally and the parturient and the foetus are well. Nevertheless, there have been decades of debate about the timing and success of intrapartal interventions (such as amniotomy and oxytocin used to prevent or treat labour dystocia or epidural anaesthesia and opioids used for pain relief) and their positive association with shorter labour duration and higher spontaneous birth rates (Wei et al. 2013, Jones et al. 2012, O'Driscoll et al. 1970). Early amniotomy and early oxytocin administration as the main components of active labour initially appeared to show positive associations with lower caesarean rates and shorter labour duration (Wei et al. 2013). However, more recent studies have found that reduced and delayed oxytocin administration and amniotomy were associated with a higher vaginal birth rate (Rossen et al. 2016). One reason for this difference might be variations in definitions of physiological labour progression and other research has shown that the active phase of labour starts later than previously assumed and that dystocia is the leading indication for unplanned c-section during labour in primiparae (see Chapter 1.2.1; Zhang et al. 2002, ACOG 2014). Women admitted to hospital during the early labour phase were especially subjected to intrapartal interventions such as labour augmentation, epidural analgesia or c-section (Davey et al. 2013, Neal et al. 2014). This indicates that an early beginning of care is subject to an earlier start of intrapartal interventions. The start of labour augmentation is of particular interest in relation to planned VBAC because oxytocin administration requires careful consideration due to an increased risk of uterine rupture in women with a previous c-section (Dekker et al. 2010, Al-Zirqi et al. 2016). The time interval between the onset of labour and the first intervention is therefore crucial, especially as initiating of one intervention often leads to a cascade of other interventions (Petersen et al. 2013b). The intervention-free time interval ends most commonly with epidural analgesia in primiparae and with amniotomy in multiparae (Petersen et al. 2013b). Predictors and endpoints of the intervention-free time interval in relation to the success of planned VBAC have not been investigated in previous studies.

## 1.3. The ProGeb- and the OptiBIRTH-study

### 1.3.1. The ProGeb-study

Data from the ProGeb-study, a cohort study that included primiparae, multiparae and women with a previous c-section enables comparative analyses between secundiparae with planned VBAC, primiparae and secundiparae with second vaginal birth. The ProGeb-study is a longitudinal cohort study which took place in 2005 in 47 of the 96 maternity units in Lower Saxony (Gross et al. 2007, Gross et al. 2009, Petersen et al. 2011, Petersen et al. 2013a, Petersen et al. 2013b, Gross et al. 2014). The study sites had annual birth rates varying between 500 and 2000 births per year. Pregnant women with a singleton in vertex presentation, who were over 34 weeks of gestation and expected to give birth vaginally after onset of labour assessed by the midwife were included. Prospective and retrospective data were collected with a total of 3,963 participants (Petersen et al. 2011). The subsample of secundiparous women with one previous c-section comprised 211 participants and the study presented in this thesis is the first that analysed this data.

The ProGeb-study received ethical approval from the Ethics Committee of Hannover Medical School (Nr. 3429) and from the Ethics Committee of the Chamber of Physicians for all public hospitals in Lower Saxony.

#### 1.3.2. The OptiBIRTH-study

The main research project of the PhD-candidate consisted of the management of the German part of the OptiBIRTH-study. OptiBIRTH is a cluster randomised controlled trial in Ireland, Italy and Germany assessing the effectiveness of a complex intervention to enhance VBAC rates (Clarke et al. 2015). The study was developed and led by Professor Cecily Begley from Ireland. The project and data management of the German part was situated at the Midwifery Research and Education Unit at Hannover Medical School, led by Professor Dr. Mechthild Gross. The study took place in 15 centres, five in each country. Within each country, three sites were randomly allocated to the intervention and the other two were allocated to be control centres. The unit of randomisation was the site and sites were randomised before women were recruited (Clarke et al. 2015). The sites were matched within each country based on the the annual birth rates and the VBAC rates. The five German study-centres were situated in four federal states, had between 1,859 and 3,227 births in 2015 and all provided neonatal intensive care.

The pilot phase of OptiBIRTH started in January 2014 and the recruitment for the main trial took place from May 2014 to October 2015. Women with one previous c-section were eligible if they were over 18 years old, had not more than one previous c-section, no high uterus incision for the c-section, no multiple gestation and sufficient knowledge of English, German or Italian (Clarke et al. 2015). During the main study phase, a total of 2,002 participants in all three countries were recruited, of whom 755 were in Germany. The German OptiBIRTH-participants of the main phase of the trial gave birth between May 2014 and December 2015.

The complex OptiBIRTH-intervention was developed based on two systematic reviews and focus group interviews and comprised special antenatal classes, a training session for clinicians, midwife and obstetrician opinion leaders in the study sites, community of practice and online resources (Clarke et al. 2015, Lundgren et al. 2015a, Nilsson et al. 2015b Nilsson et al. 2015a, Lundgren et al. 2016, Lundgren et al. 2015b, Nilsson et al. 2017, Healy et al. submitted). The systematic reviews investigated interventions for women and clinicians to enhance VBAC rates (Lundgren et al. 2015a, Nilsson et al. 2015a). The focus group interviews with clinicians as well as women and their partners took pace in countries with high and with low VBAC rates and researched factors which foster or inhibit VBAC (Lundgren et al. 2016, Lundgren et al. 2015b, Nilsson et al. 2015b, Nilsson et al. 2017).

Data-collection for the OptiBIRTH-trial used four questionnaires: an antenatal, a labour and birth, a labour and birth supplement and a postnatal survey (Clarke et al. 2015). The main outcome of the trial was the change in the percentages of women with successful VBAC between intervention and control sites from the VBAC-baseline-data in each site in 2012 (before the study) compared to the same data for 2016 (the year after the end of the trial). OptiBIRTH received ethical approval from the Faculty of Health Sciences Ethics Committee, Trinity College Dublin, Ireland and the Ethics Committee of Hannover Medical School, Germany (Nr. 1541-2012).

Preliminary analyses of the OptiBIRTH trial, comparing the data for 2012 versus 2015 (the last year of the trial, during which the intervention was ongoing in the intervention sites), show no significant differences in the change in the proportion of parturients with VBAC between intervention and control sites in the trial overall and in the German subsample when routine data for all women at each site are analysed (Clarke et al. in preparation). The picture was similar for the subsample of women at each site who agreed to join the study and provide additional data. The outcomes for mothers and babies were comparable between the intervention and the control groups and the authors concluded that the intervention should be promoted because it was found to be feasible and safe and showed a potential to decrease ERSC rates in settings with very low VBAC rates (Clarke et al. in preparation).

### 1.4. Aims of the PhD-thesis

Since there is limited knowledge about labour and birth characteristics of women planning a VBAC, the overall aims of this thesis were to gain insight into labour processes of parturient going into labour for VBAC in order to improve labour management. The specific objectives were to use data from the ProGeb-study and the German part of the OptiBIRTH-study to:

1. Compare labour processes of secundiparae who were planning a VBAC with those of primiparae and secundiparae planning a second vaginal birth with regard to: a) sociodemographic and perinatal characteristics, b) the timing of intrapartal spontaneous rupture of membranes (SROM) and of interventions, and c) overall labour duration and the duration of first and second stage.
2. Compare labour processes of successful VBAC with those of unplanned c-section with respect to: a) sociodemographic, perinatal and labour-process-related characteristics; b) predictors for the success of planned VBAC and c) predictors and endpoints for the intervention-free time interval (interval from onset of labour until the first intervention or birth).

# 2. Methods

This PhD thesis consisted of the analyses of observational data of two multicentre studies, the ProGeb-study and the German part of the OptiBIRTH-study (see Chapter 1.3).

## 2.1. Secondary analysis of the ProGeb-study

This study consisted of a secondary analysis of data from the ProGeb-study, an existing cohort study which was conducted in 2005 in Lower Saxony, Germany (Gross et al. 2007, 2009, Petersen et al. 2011, 2013a, 2013b, Gross et al. 2014, see Chapter 1.3.1.). Results of this secondary analysis were published in the peer reviewed journal “Midwifery” in 2016 (Grylka-Baeschlin et al. 2016, see Annexe 8.3.).

### 2.1.1. Sample frame for the secondary analysis of the ProGeb-study

The ProGeb-dataset comprised 3,963 participants who gave birth in 2005 in one of 47 participating hospitals in Lower Saxony, Germany (Petersen et al. 2011, Gross et al. 2014). A total of 724 multiparous women, some with a previous c-section (n=91) and others without a c-section in history (n=633), who gave birth to their third or later child, were excluded from the current analysis, because their data was not useful for the comparison of secundiparae planning a VBAC versus primiparae and secundiparae planning a second vaginal birth.

Due to the challenge of recruiting participating hospitals in the ProGeb-study (Gross et al. 2007), prospective (n=1,169) and retrospective (n=2,794) data were included in the dataset to enhance the sample size (Petersen et al. 2011, see Chapter 1.3.1.). Petersen et al. (2011) found differences between prospective and retrospective data in the original dataset. The comparison between prospective and retrospective data of selected key variables was therefore done for the study groups of the current analysis to investigate the relevance of the variable ‘type of documentation’ to be included in the multivariable analysis.

The Ethics Committee of Hannover Medical School and the Ethics Committee of the Chamber of Physicians for all public hospitals in Lower Saxony approved the ProGeb-study.

### 2.1.2. Definitions and data preparation for the secondary analysis of the ProGeb-study

The definition of onset of labour was crucial for the calculation of time intervals and was defined by regular or irregular contractions associated with cervical dilatation but was not tied to an exact centimetre of cervical dilatation (Gross et al. 2009).

The variable ‘no medical intervention’ was defined as no performance of amniotomy and no administration of oxytocin, epidural analgesia or opioids. The intervention-free time interval was defined as the shortest duration between onset of labour and one of the four medical interventions mentioned above, or birth. Previous analysis of the ProGeb-dataset did not take into consideration opioid administration and computed the intervention-free time interval from onset of labour until the first performance of either amniotomy, oxytocin or epidural analgesia (Petersen et al. 2013b). Three different types of opioids were used in the ProGeb-study sites: pethidine, meptazinol and pentazocine. All three types of opioids were combined in one variable ‘opioids’ meaning that this variable was coded 1 if any of these three types of opioids were used. The timing of the first opioid administration was calculated as the time interval between onset of labour and the first of any of these three types of opioids.

Units of measurement were minutes for time-related variables in the ProGeb-dataset. The simultaneous timing of onset of labour and birth with interventions or events but also between interventions respectively events seemed unlikely and were assumed to be due to documentation matters. When computing Kaplan-Meier estimates, the statistics programme Stata excludes durations of zero minutes, so it was assumed that these simultaneously recorded events and interventions occurred one minute after onset of labour or one minute before birth. If two interventions or events were recorded to have occurred simultaneously during labour, it had to be decided which intervention or event was most likely to have been first. In an expert discussion with ten professionals conducted for a previous study, it was determined that amniotomy was performed most likely before oxytocin administration (Petersen et al. 2013b). In a further expert discussion with five professionals during the preparation of the current secondary analysis of the ProGeb-data, it was agreed that the simultaneous occurrence of SROM and oxytocin seemed random and was probably also due to documentation matters. Oxytocin administration most likely occurred just before SROM, because in case of SROM, one would observe first the development of the uterine contractions before oxytocin administration would be decided. The addition or subtraction of one minute did not affect the medians of the durations of time intervals but enabled the analyses of the whole sample without excluding cases that had time intervals of zero minutes.

#### 2.1.3. Data analysis for the secondary analysis of the ProGeb-study

Descriptive statistics were used to present socio-demographic and perinatal characteristics of the subsamples “primiparae”, “secundiparae with planned VBAC” and “secundiparae with second vaginal birth”. The comparison of the subgroups was done with Chi squared tests, one-way ANOVA with Tukey post-hoc tests and Kruskal-Wallis-tests as appropriate according to the type of variables.

Descriptive analyses of labour duration, the duration of labour phases and the timing of interventions and events (time intervals between onset of labour and interventions or events) were done with Kaplan-Meier estimates. Kaplan-Meier analyses are often used to investigate survival time after treatments but the endpoint does not have to be death or an adverse outcome (Sedgewick 2014) and have been used to investigate labour as a process in previous studies (Gross 2001, Petersen et al. 2011). This method computes the survival probability at any particular point in time and successive probabilities are cumulated to get the final estimate (Blossfeld et al. 2007, Goel et al. 2010, Sedgwick 2014). For the calculations for labour duration, the probability $S_t$ at any time point of not yet having given birth at that point is computed with the following formulas (Goel et al. 2010):

$$S_t = \frac{\text{number of subjects living at the start} - \text{number of subjects died}}{\text{number of subjects living at the start}}$$

or with the example of labour duration:

$$S_t = \frac{\text{number of women not having given birth at onset of birth} - \text{number of women who already gave birth}}{\text{number of women not having given birth at onset of birth}}$$

Special attention is given to the median survival time, the time point at which the Kaplan Meier probability is 0.5 and 50 percent of the cases have had the event (Sedgwick 2014). Median durations of time intervals were calculated in the secondary analysis of the ProGeb-study for labour duration, the duration of labour phases, time intervals between onset of labour and SROM and interventions as well as time intervals between SROM respectively interventions and birth.

Log rank tests and Wilcoxon tests were used to compare subgroups with respect to the shapes of the Kaplan-Meier curves and the sensitivity region of the test. Data of time-intervals were treated as right-censored if the endpoints full-cervical dilatation or spontaneous birth did not occur, because for example of c-section or instrumental birth. Time-intervals between onset of labour and SROM respective interventions were computed for women only who had this event or intervention and no censoring was applied.

Multivariable analyses with the outcome variables overall labour duration and the duration of first and second stage were computed using shared frailty Cox regression models and including time-dependent covariables. The Cox regression model is a semiparametric proportional hazard model and is based on a computed transition rate at a certain time for the transition from a given original state to the destination state (Blossfeld et al. 2007). Cox regression models are based on the assumption that the hazard of a group being investigated is always proportional to the hazard of the reference group (Stata service online). Each transition is explained by a set of covariables which has to be defined for all cases included in the model (Blossfeld et al. 2007). The estimate of the Cox regression is the Hazard ratio comparing the hazard rate of a certain characteristic with the one of the reference category (Stata service online). A Hazard ratio below 1 indicates that the characteristic of interest has a lower hazard in the group being investigates than in the reference category, indicating that the characteristic of interest is associated with a prolonging effect on the dependent time interval. In contrast, a Hazard ratio above 1 indicates an increasing effect of the covariable on the dependent duration.

The shared frailty Cox regression models, which were used in the secondary analysis in this PhD-thesis, take into consideration the variability between the 47 study sites of the ProGeb-study (Gutierrez 2002, Blossfeld et al. 2007). The shared frailty Cox regression takes into account heterogeneity or random effects (Gutierrez 2002) or in other words for the frailty which is shared in a cluster (Wienke 2003). It assumes that observations with equal values share the same frailty (Stata online). The variability between the study sites was not taken into consideration in previous publications of the ProGeb-study (Petersen et al. 2011, Petersen et al. 2013a, Petersen et al. 2013b, Gross et al. 2014).

The inclusion of variables which change over time is a huge advantage of Cox regression modelling (Therneau et al. 2017). It was an explicit aim of the analyses for this PhD-thesis to use Cox regression modelling including time-dependent covariables to avoid so called immortal time bias. Immortal bias occur when time-constant covariables are included in Cox regression models because the time interval before interventions and events is not considered as “being at risk” but considered as having had the intervention or event (Shintani et al. 2009, Daniel et al. 2015, Jones & Fowler 2016). The methodological approach to include time-dependent covariables in Cox regression models is episode splitting (Blossfeld et al. 2007). The original episode or time interval is split into sub episodes and for each sub episode a new record is created, meaning that for the same study-id several rows may exist in the dataset (Blossfeld et al. 2007). In the current secondary analysis of the ProGeb-study, overall labour duration and the duration of first and second stage were used as dependent variables. Women who had had an intervention before the time interval used as the dependent variable were not considered as being at further risk of the same intervention during this interval. Technically, this was done by recoding the time-dependent variable from zero to one if the intervention already had occurred before the beginning of the time interval of interest. Regression modelling was also done explanatorily to gain insights into the accuracy and usefulness of the inclusion of time-dependent variables. Preliminary models then revealed that two time-dependent predictors excluding each other for an event that occurs in all cases of a dataset (in this case rupture of the membranes (ROM), either spontaneous or artificial) cannot be included in the same multivariable models. ROM was then included in the models as a time-constant variable with the categories ‘prelabour

SROM', 'prelabour amniotomy', 'intrapartal SROM' and 'intrapartal amniotomy' for the different events and interventions (see Table 14 in Appendix 8.1).

In a first step of the multivariable analysis, the crude associations between potential predictors and the dependent variables were assessed using log rank tests for categorical variables and univariable Cox regression for metric variables. Potential predictors in the ProGeb-dataset were: maternal age, health insurance, no risk factor in medical history, obesity, diabetes, gestational diabetes, induction, cervical dilatation at admission, meconium-stained liquor, rupture of the membranes, sex of the baby, birthweight, episiotomy (only for overall labour duration and second stage of labour), duration of the first stage of labour (only for second stage of labour) and the type of documentation. According to the model building strategy of Hosmer and Lemeshow (2000), variables were included in the main effect model if the p-value was <0.25. Episode splitting was used to include time-dependent covariables for oxytocin, epidural analgesia and opioid administration. Based on Likelihood Ratio test p<0.05, stepwise backward elimination was done per hand in the multivariable models for variables which were not significantly associated with the dependent variable (p>0.05). Maternal age and birthweight were retained in the models, because they were found to be valid predictors in previous studies (Albers 1999, Zhang et al. 2002). The type of documentation was also retained, because differences between prospective and retrospective data were found in previous analyses of the dataset (Petersen et al. 2011) and were investigated again in the current secondary analysis. Interactions between the variable defining the study groups and time-dependent variables were tested and the interaction-terms were included in the full effect model if p<0.10. The interaction-terms were backward eliminated again if p>0.05.

The significance level for statistical tests was 0.05 and analyses were done with the statistics programme Stata 13 (StataCorp, USA).

## 2.2. Analysis of observational data from the German part of OptiBIRTH

The second part of this PhD-thesis consisted of the analysis of observational data collected within the German part of the OptiBIRTH-study. The OptiBIRTH-study was a European cluster randomised controlled trial to assess the effectiveness of a complex intervention to enhance VBAC rates (Clarke et al. 2015, see Chapter 1.3.2.). The German part of the OptiBIRTH-trial provided the opportunity for the main research project for this PhD-thesis.

### 2.2.1. Project management of the German part of OptiBIRTH at Hannover Medical School

The Midwifery Research and Education Unit at Hannover Medical School under the lead of Prof. Dr. Mechthild Gross managed the study process and the data collection in the five German study-sites for the OptiBIRTH-study. These tasks included general project management, personnel management of the study midwives and research assistants and their support with the recruitment of the participants, the implementation of the intervention, fidelity checks and data management.

After a four months pilot phase from January to April 2014, recruitment to the OptiBIRTH-study lasted one and a half years until October 2015. Originally, six German study sites joined the trial, whereby the two Hannover sites were planned to be together as one centre. During the pilot phase of the study, one study-site withdrew because of staff problems and insufficient commitment. This loss was compensated by considering the two Hannover sites as separate ones, and the potential loss of one site had been built into the sample size calculation for the trial. The study midwives and research assistants in the study sites completed relevant tasks such as recruitment of participants, data collection for antenatal, labour and birth as well as gathering postnatal data, data entry and in the intervention sites, the implementation of the complex intervention.

In all study sites of the German part of the OptiBIRTH-study, significant efforts to enhance recruitment and response rates were made to minimise loss of follow-up and missing values. Individual recruitment strategies, adapted to the situation in each hospital, were implemented. Women were contacted and reminded several times to participate in the study and return questionnaires. Additionally, stamped return envelopes were provided for sending back consent forms and questionnaires to enhance response rates (CDC 2010).

### 2.2.2. Sampling frame for the analysis of German OptiBIRTH-data

The analysis of the German part of the OptiBIRTH-study for this PhD-thesis was based on observational labour and birth data from the German study sites. A total of 755 women were recruited in Germany during the main phase of the trial. Women with successful vaginal birth or unplanned c-section after starting labour for VBAC were potential candidates for the current analysis but further inclusion and exclusion criteria were needed. The analysis for this PhD-thesis included only those participants at the German study sites who had reported the onset of labour after at least 34 gestational weeks and who intended to give birth vaginally. OptiBIRTH-participants who did not intend to give birth vaginally but who had an unexpected onset of labour and consequently an unplanned c-section during labour were excluded from the analysis. The main variable to distinguish this intention was ‘mode of birth’ which consisted of following categories: a) spontaneous vaginal, b) ventouse, c) forceps, d) elective repeat caesarean section, e) not in labour, emergency caesarean section and f) unplanned c-section during labour. Whereas the exclusion of the categories d) and e) were clear, the inclusion of women coded in category f) needed further specification because some parturients had unexpected onset of labour with correct data entry for mode of birth indicating the category ‘unplanned c-section during labour’. Most if these women experienced contractions with cervical dilatation before the c-section date. A variable for ‘intention to give birth vaginally’ was therefore created. The indications for the unplanned c-sections (string variable) was coded independently by two coders for the intention to give birth vaginally. One coder was a midwife with an MSc degree and the other was the PhD-student herself. Conflicts were resolved by consensus.

Potential study participants received oral and written information and gave written consent before participation. Participants were informed about their right to withdraw at any moment during the study process without disadvantage and data were treated confidentially. The OptiBIRTH-study received ethical approval from the Faculty of Health Sciences Ethics Committee, Trinity College Dublin, Ireland and the Ethics Committee of Hannover Medical School, Germany (Nr. 1541-2012).

#### 2.2.3. Definitions, data cleaning and data preparation

Onset of labour was defined by the OptiBIRTH-consortium and the trial group as “regular or irregular contractions associated with progressive cervical dilatation, assessed by the midwife”.

During preliminary data cleaning of the German data, plausibility of calculated labour intervals (overall labour duration, the duration of first and second stage of labour, durations between onset of labour and events/interventions and durations between events/interventions and birth) was extensively checked by the PhD student in the May 2015 data download. First of all, it was checked for any negative values for the intervals between onset of labour and intrapartal interventions and events, as well as between interventions, events and birth. Warnings and data entry blocks in the Microsoft Access database prevented potential implausible values. Additionally, outliers and implausible values for the computed variables ‘overall labour duration’ (subtraction of date and time of onset of labour from date and time of birth), first stage of labour (subtraction of date and time of onset of labour from date and time of full cervical dilatation) and second stage of labour (subtraction of date and time of full cervical dilatation from date and time of birth) were identified and potential errors for unrealistic data were investigated according to the recommendations of Van den Broeck et al. (2005). The reasons for unrealistic values for overall labour duration and the duration of first and second stage of labour were checked by reading “birth stories” of 101 birth processes. As a consequence, date and time variables of onset of labour were checked in the medical records according to the OptiBIRTH-definition for the women with the 5% longest and 5% shortest labour durations, for all simultaneous onsets of labour with the time point of SROM and for a random sample of 10% of all participants. If necessary, date and time for onset of labour were redefined and corrected. This checking was in addition to general plausibility and data checks, which were a regular part of the OptiBIRTH-trial.

As in the secondary analysis of the ProGeb-study, simultaneous records of events or interventions with onset of labour or birth were considered to have taken place one minute after onset of labour or one minute before birth respectively (see Chapter 2.1.3.). This was congruent with the procedure of previous studies because simultaneous events are unlikely during labour (Petersen et al. 2013b). Membranes that were not ruptured before c-section were considered to have undergone amniotomy one minute before birth. ‘No medical intervention’ was defined again as not having received either of amniotomy, oxytocin, epidural analgesia or opioids. The intervention-free time interval was also defined as the shortest duration between onset of labour and one of the four medical interventions mentioned above, or birth.

### 2.2.4. Data analysis of the OptiBIRTH-study

In addition to variables related to sociodemographic and obstetric history, labour and birth characteristics were of special interest for analysis in this PhD-research, as they had also been in previous studies investigating labour as a process (Petersen et al. 2011, Gross et al. 2014, Grylka-Baeschlin et al. 2016). Factors pre-existing to the onset of labour such as previous vaginal birth and birthweight, factors occurring during labour such as rupture of the membranes, the frequency and timing of events and interventions (the time interval between onset of labour and the event or the intervention), and the duration of labour and of labour phases were therefore the main variables of interest for the analyses.

Categorical variables were compared between groups with Chi-squared tests and metric variables with Wilcoxon rank sum tests. Timings of events and interventions (intervals between onset of labour and events or interventions) were calculated precisely to the minute, described using Kaplan-Meier estimates and compared using log rank tests (Sedgwick 2014). Labour duration was considered as censored for c-sections and vaginal instrumental births, meaning that all participants in the unplanned c-section subsample had censored labour durations. Description and comparison of labour duration were performed using standard descriptive statistics and Mann-Whitney U tests. This was necessary, because the censoring of a whole group made the use of Kaplan-Meier estimates and log rank test impossible, because censored cases are not included in the numerator of the calculations at any point (Prinja et al. 2010). This leads to results of zero for all calculations of a group containing exclusively censored subjects.

A random-effects logistic regression model with the dependent variable 'success of planned VBAC' was applied for multivariable analyses. Variations between study sites were taken into account for modelling by applying random effects, as differences in labour and birth management relating to VBAC had been observed at the sites before the trial (Gross et al. 2015). Multiple imputation (Stata "mi set" with fivefold imputation) was used for variables with missing data ('health insurance', 'BMI', 'cervical dilatation on admission' and 'rupture of membranes'). Missing data was mainly due to the response rate of the antenatal questionnaire and to incomplete labour and birth documentation (see Chapter 2.2.1). According to Hosmer and Lemeshow's model-building strategy (Hosmer, Lemeshow 2000), potential predictors were entered in the main effect model if the crude associations with the outcome variable had a significance level of $p<0.25$ in the univariable analyses and the predictors were considered relevant. Stepwise backward elimination based on Wald tests was then performed. Maternal age and birthweight were retained in the model as a priori confounders (Annessi et al. 2016, Grobman et al. 2007). Sensitivity analyses using the same model-building strategy were performed excluding the variable 'previous vaginal birth', as this variable was found to be a predominant predictor.

Shared-frailty Cox regression modelling with the outcome variable 'intervention-free time interval' was computed separately for successful VBAC, unplanned c-section and the entire study population. Multiple imputation (Stata "mi set" with fivefold imputation) was used for missing data, namely for the variables 'health insurance', 'full-time or part-time employment', 'BMI' and 'cervical dilatation on admission'. The timing of spontaneous rupture of membranes (SROM) was included as a time-varying covariable using episode splitting (Shintani et al. 2009). If pre-labour SROM occurred, this was taken into account in the models. Variables with a $p<0.25$ for the crude associations in the whole study group were included in the main effect models. Backward elimination based on Wald tests was performed. Censoring was applied in respect of women with no medical intervention at the time of spontaneous vaginal birth. Women with uncertain rupture of the membranes (n=13) were excluded from the analyses relating to the intervention-free time interval. Timing of SROM remained in the model because of the relevance found in the current study. Maternal age was maintained in the model as an a priori confounder (Albers 1999).

Statistical analyses were performed with Stata 13 (StataCorp, USA).

# 3. Results

## 3.1. Results of the secondary analysis of the ProGeb-study

The results of the secondary analysis of the ProGeb-study were published in the journal Midwifery (Grylka-Baeschlin et al. 2016, doi: 10.1016/j.midw.2015.11.004, see Appendix 8.3.).

The analysed study sample included 3,239 participants, who were subdivided into three subsamples: primiparae (n=1,897), secundiparae planning a VBAC (n=211) and secundiparae planning a second vaginal birth (n=1,149). The original total ProGeb-study population comprised 3,963 parturients but multiparous women who gave birth to their third or later child (n=724) were excluded for the current secondary analysis.

### 3.1.1. Sociodemographic, medical history related and perinatal characteristics

Secundiparae with planned VBAC were older than primiparae (31.6 years versus 28.0 years, p<0.001) but were as old as other secundiparae (31.6 years versus 30.7 years, p=0.104, Table 1). The percentage of women with private health insurance or complementary private insurance did not differ significantly between the subgroups (p=0.244). The highest percentage of women without risk factors was found among secundiparae with planned VBAC, with a difference being significant compared to secundiparae with second vaginal birth (67.8% versus 58.9%, p=0.016) but not compared to primiparae (62.2% versus 58.9%, p=0.113). There was no significant difference in obesity (p=0.459), diabetes (p=0.407) and gestational diabetes (p=0.282) between the subsamples.

A difference in women with induced labour (either with oxytocin, prostaglandin amniotomy misoprostol or castor oil) was observed: between secundiparae with planned VBAC and primiparae the difference was not significant (31.3% versus 29.1%, p=0.501), but it was significant between secundiparae with planned VBAC and other secundiparae (31.3% versus 24.2%, p=0.030, Table 1 continued). The median cervical dilatation at admission to the hospital did not differ between the subgroups (p=0.513) and the occurrence of meconium-stained liquor was similar (p=0.332). The proportion of secundiparae with planned VBAC having prelabour spontaneous rupture of the membranes (SROM) was similar to primiparae (23.9% versus 25.7%, p=0.578) but was significantly higher compared to secundiparae with second vaginal birth (23.9% versus 16.6%, p=0.011). Amniotomy before onset of labour was not performed in any of the secundiparae with planned VBAC and the intervention was rare in primiparae and other secundiparae, without significant difference (p=0.274). Intrapartal SROM was more frequent in secundiparae with planned VBAC (43.1%) compared to primiparae (38.4%) or other secundiparae (40.4%), but the differences were not significant (p=0.300). Secundiparae with planned VBAC had similar frequencies of intrapartal amniotomy to primiparae (33.0% versus 34.7%, p=0.633) but significantly lower than secundiparae with second vaginal birth (33.0% versus 41.8%, p=0.018).

Oxytocin administration was less common in secundiparae with planned VBAC compared to primiparae (in total: 48.8% versus 57.0%, p=0.024 and during labour: 42.7% versus 53.4%, p=0.003). Compared to secundiparae with second vaginal birth, secundiparae with planned VBAC received oxytocin significantly less often (in total: 48.8% versus 31.9%, p<0.001 and during labour: 42.7% versus 27.2%, p<0.001). Epidural analgesia was administered most often in secundiparae with planned VBAC (36.0% in total and 35.1% during labour). Compared to primiparae (34.7% in total and 33.9% during labour), the difference was not significant (p=0.691) but it was significant when compared to other secundiparae (14.3% in total and 13.8% during labour, p<0.001). A slightly lower proportion of secundiparae with planned VBAC compared to primiparae received opioid (either pethidine, meptazinol or pentazocine) but the difference was not significant (in total: 43.1% versus 48.9%, p=0.111 and during labour: 41.2% versus 47.1%, p=0.105). As compared to other secundiparae, the administration of opioids was significantly more frequent in secundiparae with planned VBAC (in total: 43.1% versus 29.0%, p=<0.001 and during labour: 41.2% versus 28.1%, p<0.001).

**Table 1:** Baseline and perinatal characteristics (Grylka-Baeschlin et al. 2016)

| Variable | Primiparae (n=1,879) | Secundiparae with pVBAC (n=211) | Secundiparae with 2nd vaginal birth (n=1,149) | p-value[1] |
|---|---|---|---|---|
| **General information** | | | | |
| No. of locations/47 (range n of births) | 45 (1-309) | 24 (1-40) | 42 (1-178) | p=0.047[c] |
| Retrospective documentation, n (%)[2] | 1317 (70.09) | 163 (77.25) | 807 (70.23) | p=0.090[a,b] |
| **Socio-demographic and medical history related characteristics** | | | | |
| Age in years; mean (min-max) | 27.97 (14-46) | 31.55 (18-45) | 30.74 (18-45) | p<0.001[a,c] |
| Private insurance; n (%)[3] | 144 (7.66) | 18 (8.53) | 108 (9.40) | p=0.244 |
| No risk factor in history; n (%) | 1169 (62.21) | 143 (67.77) | 677 (58.92) | p=0.028[b] |
| Obesity; n (%) | 73 (3.89) | 10 (4.74) | 55 (4.79) | p=0.459 |
| Diabetes; n (%) | 12 (0.64) | 1 (0.47) | 12 (1.05) | p=0.407 |
| Gestational diabetes; n (%) | 59 (3.14) | 11 (5.21) | 38 (3.31) | p=0.282 |

**Table 1** continued

| Variable | Primiparae (n=1,879) | Secundiparae with pVBAC (n=211) | Secundiparae with 2nd vaginal birth (n=1,149) | p-value[1] |
|---|---|---|---|---|
| **Perinatal characteristics** | | | | |
| Induction of labour; n (%) | 546 (29.06) | 66 (31.28) | 278 (24.19) | p<0.006[b,c] |
| Cervical dilation at admission in cm; median (IQR) | 2.00 (1.00-4.00) | 2.00 (1.00-3.00) | 3.00 (2.00-5.00) | p=0.513 |
| Meconium-stained liquor; n (%) | 217 (11.55) | 31 (14.69) | 128 (11.14) | p=0.332 |
| Rupture of the membranes: | | | | p<0.001[b,c] |
| Prelabour SROM; n (%) | 481 (25.69) | 50 (23.92) | 191 (16.62) | |
| Prelabour ARM; n (%) | 23 (1.23) | 0 (0.00) | 14 (1.22) | |
| Intrapartal SROM; n (%) | 719 (38.41) | 90 (43.06) | 464 (40.38) | |
| Intrapartal ARM; n (%) | 649 (34.41) | 69 (33.01) | 480 (41.78) | |
| Oxytocin; n (%) | 1070 (56.95) | 103 (48.82) | 367 (31.94) | p<0.001[a,b,c] |
| Epidural analgesia, n (%) | 651 (34.65) | 76 (36.02) | 164 (14.27) | p<0.001[b,c] |
| Opioids; n (%) | 919 (48.91) | 91 (43.13) | 333 (28.98) | p<0.001[b,c] |
| Episiotomy; n (%)[4] | 799 (50.99) | 71 (48.63) | 220 (19.98) | p<0.001[b,c] |
| No intrapartal interventions; n (%) | 255 (13.57) | 35 (16.59) | 328 (28.55) | p<0.001[b,c] |
| Birthweight in g; mean (min-max) | 3407.71 (1720-5370) | 3466.29 (2060-4900) | 3532.10 (1760-5240) | p<0.001[c] |
| Female sex; n (%) | 918 (48.88) | 105 (49.76) | 557 (48.48) | p=0.936 |
| Mode of birth: | | | | p<0.001[a,b,c] |
| Spontaneous; n (%) | 1366 (72.70) | 131 (62.09) | 1078 (93.82) | |
| Vacuum; n (%) | 151 (8.04) | 12 (5.69) | 19 (1.65) | |
| Forceps; n (%) | 50 (2.66) | 3 (1.42) | 4 (0.35) | |
| C-section; n (%) | 312 (16.60) | 65 (30.81) | 48 (4.18) | |

pVBAC=planned VBAC; IQR=interquartile range; SROM=spontaneous rupture of the membranes; ARM=amniotomy
[1] Tukey post-hoc tests after ANOVA, Kruskal Wallis tests or chi squared tests
[2] Retrospective as opposed to prospective documentation
[3] Private insurance or complementary insurance with senior medical consultant in contrast to statutory insurance
[4] For vaginal births
[a] Significant difference between secundiparae with pVBAC and primiparae
[b] Significant difference between secundiparae with pVBAC and secundiparae with second vaginal birth
[c] Significant difference between primiparae and secundiparae with second vaginal birth

A similar percentage of secundiparae with planned VBAC and of primiparae did not receive any intervention (either amniotomy, oxytocin, epidural or opioids) during labour (16.6% versus13.6%, p=0.229, Table 1 continued), but the proportion among secundiparae with planned VBAC was significantly lower compared to other secundiparae (16.6% versus 28.6%, p<0.001).

The frequency with which secundiparae with successful VBAC received an episiotomy was similar to primiparae (48.6% versus 51.0%, p=0.586) but was significantly higher compared to other secundiparae (48.6% versus 20.0%, p<0.001). The neonates of secundiparae with planned VBAC had similar birthweights compared to primiparae (3466g versus 3408g, p=0.206) and to other secundiparae (3466g versus 3532g, p=0.154). The sex of the infant did not differ significantly between the subsamples (p=0.936). Secundiparae with planned VBAC had the lowest rate of successful vaginal births (comparison with primiparae: 69.2% versus 83.4%, p<0.001 and with other secundiparae: 69.2% versus 98.8%, p<0.001). Consequently, the rates of unplanned c-section during labour was highest in secundiparae with planned VBAC (comparison with primiparae: 30.8% versus 16.6%, <0.001 and with other secundiparae: 30.8% versus 4.2%, p<0.001).

#### 3.1.2. Comparison of prospective and retrospective baseline data in the study groups

The comparison of prospective and retrospective data for selected baseline characteristics in all three study subsamples (primiparae, secundiparae with planned VBAC and secundiparae with second vaginal birth) showed significant differences for certain characteristics in the study groups (Table 2). Primiparae in the retrospective dataset were older compared to the prospective dataset (28.3 versus 27.1 years, p<0.001). The proportion of primiparae (6.9% versus 2.5%, p<0.001) and secundiparae with planned VBAC (12.5% versus 2.5%, p=0.004) being obese was higher in the prospective than in the retrospective data. In primiparae, prelabour SROM was less frequent (21.0% versus 27.7%, p=0.006) but intrapartal SROM was more frequent (42.5% versus 36.6%, p=0.016) in the prospective compared to the retrospective dataset. The frequency of oxytocin administration in secundiparae with planned VBAC was higher in the prospective compared to the retrospective dataset (64.6% versus 44.2%, p=0.013). Furthermore, the proportion of primiparae (52.9% versus 47.2%, p=0.026) and secundiparae with second vaginal birth (34.2% versus 26.8%, p=0.011) receiving opioids was higher in the prospective compared to the retrospective dataset. Mode of birth in prospective and retrospective data of primiparae differed significantly (p=0.001): forceps was significantly more frequent in the retrospective compared to the prospective data (3.6 versus 0.4%, p<0.001).

**Table 2:** Comparison between prospective and retrospective data in the study groups

| Variables | Prospective data | | | Retrospective data | | |
|---|---|---|---|---|---|---|
| | **Primiparae n=562** | **Secundi-parae VBAC n=48** | **Other secundi-parae n=342** | **Primiparae n=1,317** | **Secundi-parae VBAC n=163** | **Other secundi-parae n=807** |
| **Age,** mean years[a] | 27.1** | 30.7 | 30.3 | 28.3** | 31.8 | 30.9 |
| **Private and supplementary health insurance,** n (%)[b] | 35 (6.2) | 2 (4.2) | 37 (10.8) | 109 (8.3) | 16 (9.8) | 71 (8.8) |
| **No risk factors,** n (%)[b] | 345 (61.4) | 29 (60.4) | 212 (62.0) | 824 (62.6) | 114 (69.9) | 465 (57.6) |
| **Obesity,** n (%)[b] | 39 (6.9)** | 6 (12.5)* | 19 (5.6) | 34 (2.6)** | 4 (2.5)* | 36 (4.5) |
| **Diabetes,** n (%)[b] | 5 (0.9) | 0 (0.0) | 1 (0.3) | 7 (0.5) | 1 (0.6) | 11 (1.4) |
| **Gestational diabetes,** n (%)[b] | 12 (2.1) | 2 (4.2) | 7 (2.1) | 47 (3.6) | 9 (5.5) | 31 (3.9) |
| **Induction,** n (%)[b] | 146 (26.0) | 17 (35.4) | 92 (26.9) | 400 (30.4) | 49 (30.1) | 186 (23.1) |
| **Rupture of membranes,** n (%)[b] | | | | | | |
| Prelabour SROM | 118 (21.0)* | 8 (16.7) | 53 (15.5) | 363 (27.7)* | 42 (26.1) | 138 (17.1) |
| Prelabour ARM | 4 (0.7) | 0 (0.0) | 4 (1.2) | 19 (1.5) | 0 (0.0) | 10 (1.2) |
| Intrapartal SROM | 239 (42.5)* | 24 (50.0) | 136 (39.8) | 480 (36.6)* | 66 (41.0) | 328 (40.6) |
| Intrapartal ARM | 201 (35.8) | 16 (33.3) | 149 (43.6) | 448 (34.2) | 53 (32.9) | 331 (41.0) |
| **Oxytocin,** n (%)[b] | 331 (58.9) | 31 (64.6)* | 121 (35.4) | 739 (56.1) | 72 (44.2)* | 246 (30.5) |
| **Epidural[b],** n (%)[b] | 184 (32.7) | 16 (33.3) | 41 (12.0) | 467 (35.5) | 60 (36.8) | 123 (15.2) |
| **Opioids[b],** n (%)[b] | 297 (52.9)* | 26 (54.2) | 117 (34.2)* | 622 (47.2)* | 65 (39.9) | 216 (26.8)* |
| **Mode of birth,** n (%)[b] | | | | | | |
| Spontaneous | 409 (72.8) | 32 (66.7) | 325 (95.0) | 957 (72.7)* | 99 (60.7) | 753 (93.31) |
| Vacuum | 49 (8.7) | 4 (8.3) | 5 (1.46) | 102 (7.7) | 8 (4.9) | 14 (1.73) |
| Forceps | 2 (0.4)** | 0 (0.0) | 1 (0.3) | 48 (3.6)** | 3 (1.84) | 3 (0.4) |
| C-section | 102 (18.2) | 12 (25.0) | 11 (3.2) | 210 (16.0) | 53 (32.5) | 37 (4.6) |
| **Birthweight,** mean kg[a] | 3.41 | 3.68 | 3.58 | 3.40 | 3.66 | 3.51 |
| **Sex of the baby female,** n (%)[b] | 290 (51.69) | 25 (52.1) | 171 (50.0) | 628 (47.68) | 80 (49.1) | 386 (47.3) |

ARM=Amniotomy; SROM=spontaneous rupture of the membranes
* p<0.05; ** p<0.001
[a] Independent sample t-test; [b] Chi squared test

3.1.3. Timing of intrapartal spontaneous rupture of membranes and interventions

Secundiparae with planned VBAC experienced a median duration between onset of labour and spontaneous rupture of membranes (SROM) of 2.67 hours (Table 3). This time interval was comparable to primiparae (3.42 hours, p=0.112) and secundiparae with second vaginal birth (2.67 hours, p=0.481). The time interval between SROM and birth of secundiparae with planned VBAC was similar to primiparae (3.17 hours versus 3.53 hours, p=0.762) but

**Table 3:** Duration of labour and labour phases and the timing of intrapartal SROM and interventions (Grylka-Baeschlin et al. 2016)

| **Variable** Duration, frequency and timing | **Primiparae** (n=1,879) | **Secundiparae pVBAC** (n=211) | **Secundiparae with 2nd vaginal birth** (n=1,149) | **p-value** |
|---|---|---|---|---|
| Onset of labour – birth, hrs; median (IQR) | 8.57 (5.60-13.42) | 8.83 (5.35-16.55) | 4.63 (2.85-7.05) | p<0.001[b,c] |
| First stage of labour, hrs; median (IQR) | 7.00 (4.50-10.50) | 7.42 (4.42-12.50) | 4.25 (2.60-6.50) | p<0.001[b,c] |
| Second stage of labour, hrs; median (IQR) | 0.77 (0.38-1.47) | 0.55 (0.27-1.28) | 0.22 (0.12-0.42) | p<0.001[a,b,c] |
| Onset of labour– SROM, hrs; median (IQR) | 3.42 (1.00-6.63) | 2.67 (0.48-5.83) | 2.67 (0.83-5.08) | p<0.001[c] |
| SROM – birth, hrs; median (IQR) | 3.53 (1.18-7.80) | 3.17 (1.15-8.98) | 0.88 (0.25-2.45) | p<0.001[b,c] |
| Onset of labour – ARM, hrs; median (IQR) | 5.83 (3.67-9.08) | 5.50 (3.83-7.22) | 3.93 (2.33-6.08) | p<0.001[b,c] |
| ARM – birth, hrs; median (IQR) | 2.25 (1.00-4.45) | 3.25 (1.03-5.55) | 0.60 (0.25-1.43) | p<0.001[b,b] |
| Onset of labour – oxytocin, hrs; median (IQR) | 6.00 (3.92-9.20) | 5.75 (3.98-10.25) | 4.25 (2.50-6.55) | p<0.001[b,c] |
| Oxytocin – birth hrs; median (IQR) | 3.18 (1.20-6.42) | 2.85 (1.27-8.32) | 1.37 (0.67-2.92) | p<0.001[b,c] |
| Onset of labour – epidural, hrs; median (IQR) | 4.67 (2.75-7.42) | 4.00 (2.42-7.25) | 3.50 (2.00-5.08) | p<0.001[b,c] |
| Epidural – birth, hrs; median (IQR) | 5.17 (3.45-8.42) | 5.38 (3.90-14.22) | 3.05 (1.75-4.53) | p<0.001[b,c] |
| Onset of labour – opioids, hrs; median (IQR) | 3.78 (2.00-6.67) | 3.83 (1.75-6.00) | 2.75 (1.62-5.33) | p<0.001[b,c] |
| Opioids – birth, hrs; median (IQR) | 3.87 (2.05-7.62) | 4.55 (1.82-7.75) | 1.43 (0.83-2.63) | p<0.001[b,c] |
| Onset of labour – first intervention, hrs; median (IQR) | 3.80 (2.08-6.42) | 3.67 (2.00-5.75) | 3.08 (1.67-5.17) | p<0.001[b,c] |
| First intervention – birth, hrs; median (IQR) | 4.12 (1.98-7.62) | 4.52 (1.75-7.75) | 1.37 (0.58-2.70) | p<0.001[b,c] |

pVBAC=planned VBAC; SROM=spontaneous rupture of the membranes, ARM=amniotomy
[a] Significant difference between secundiparae with pVBAC and primiparae
[b] Significant difference between secundiparae with pVBAC and secundiparae with second vaginal birth
[c] Significant difference between primiparae and secundiparae with second vaginal birth

significantly longer compared to other secundiparae (3.17 hours versus 0.88 hours, p<0.001).

The timing of amniotomy was slightly but not significantly earlier in secundiparous women with planned VBAC than in primiparous women (5.50 hours versus 5.83 hours, p=0.198) but significantly longer than in secundiparous women with second vaginal birth (5.50 hours versus 3.93 hours, p<0.001). There was also a significant difference in the median time interval between amniotomy and birth between the subsamples (p<0.001). The difference was not significant between secundiparae with planned VBAC and primiparae (3.25 hours versus 2.25 hours, p=0.162) but was significant between secundiparae with planned VBAC and secundiparae with second vaginal birth (3.25 hours versus 0.60 hours, p<0.001).

The median duration between onset of labour and oxytocin administration for secundiparae with planned VBAC was 5.75 hours. This was similar to primiparae (5.75 hours versus 6.00 hours, p=0.596). In contrast, the timing of oxytocin of secundiparae with planned VBAC was significantly later than in secundiparae with planned VBAC (5.75 hours versus 4.25 hours, p<0.001). The median time interval between oxytocin administration and birth of secondiparae with planned VBAC and primiparae was similar (2.85 hours versus 3.18 hours, p=0.645) but was significantly longer compared to other secundiparae (2.85 hours versus 1.37 hours, p<0.001).

The timing of epidural analgesia for secundiparae with planned VBAC was a median 4.00 hours after onset of labour, with no significant difference compared to primiparae (4.00 hours versus 4.67 hours, p=0.416), however it was significantly later than secundiparae with second vaginal birth (4.00 hours versus 3.50 hours, p=0.009). The median time interval between epidural analgesia and birth of secundiparae planning a VBAC was comparable to primiparae (5.38 hours versus 5.17 hours, p=0.315), but was significantly longer than for other secundiparae (5.38 hours versus 3.05 hours, p<0.001).

Opioids were administered to secundiparous women with planned VBAC in a median of 3.83 hours after onset of labour. This was similar to primiparous women (3.83 hours versus 3.78 hours, p=0.851) but significantly longer than secundiparous women with second vaginal birth (3.83 hours versus 2.75 hours, p=0.026). The duration between opioid administration and birth was comparable between secundiparae with planned VBAC and primiparae (4.55 hours versus 3.67 hours, p=0.811) but was significantly longer in secundiparae with planned VBAC than in other secundiparae (4.55 hours versus 1.43 hours, p<0.001).

The intervention-free time interval, meaning the duration between onset of labour and the first intrapartal intervention of amniotomy, oxytocin administration, epidural analgesia or opioid administration was similar between secundiparae with planned VBAC and primiparae

(3.67 hours versus 3.80 hours, p=0.375) but was significantly longer in secundiparae with planned VBAC than in other secundiparae (3.67 hours versus 3.08 hours, p=0.015). There was no significant difference in the median duration between the first intervention and birth between secundiparous women with planned VBAC and primiparous women (4.52 hours versus 4.12 hours, p=0.550). The difference between secundiparae with planned VBAC and secundiparae with second vaginal birth was significant (4.52 hours versus 1.37 hours, p<0.001).

3.1.4. <u>Labour duration and the duration of first and second stage of labour</u>

The adjusted shared frailty Cox regression model confirmed no statistically significant difference in the overall labour duration (duration between onset of labour and birth) which was already observed in the bivariable association between secundiparae with planned VBAC and primiparae (8.83 hours versus 8.57 hours, HR=1.00, 95% CI [0.83, 1.20], p=0.987, Figure 2, summary in Table 4, full model in Table 5). In contrast, compared to secundiparae with second vaginal birth, secundiparous women with planned VBAC had significantly longer overall labour duration (8.33 hours versus 4.63 hours, HR=0.32, 95% CI [0.27, 0.39], p<0.001). The evidence for heterogeneity between the study sites was strong (theta=0.30, p<0.001).

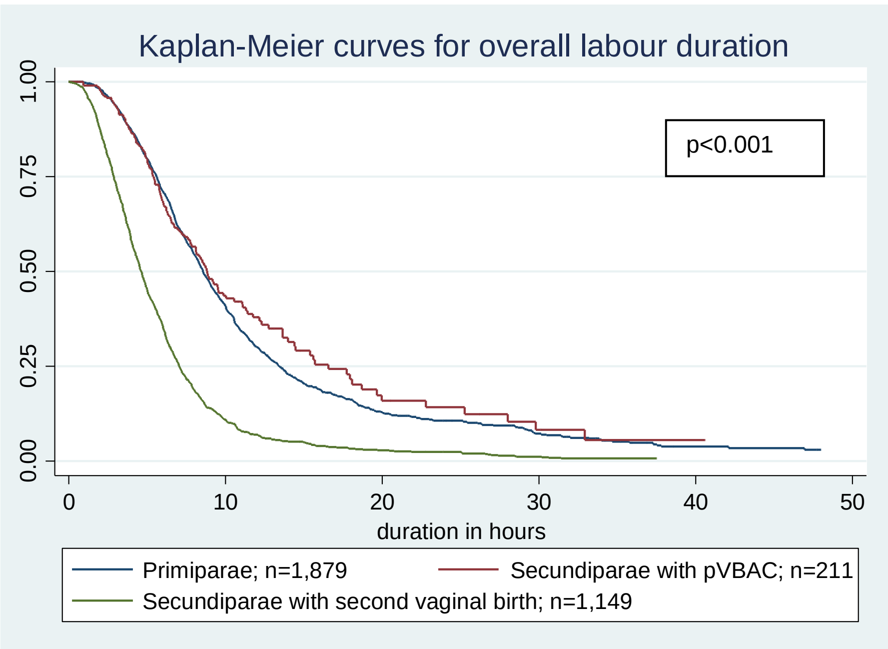


**Figure 2:** Kaplan-Meier curves for overall labour duration

The multivariable model revealed no statistically significant difference in the duration of first stage of labour between secundiparae with planned VBAC and primiparae (7.42 hours versus 7.00 hours, HR=0.92, 95% CI [0.77, 1.083], p=0.30, Figure 3, summary in Table 4, full model in Table 6). In contrast, the first stage of labour in secundiparae with planned VBAC was significantly longer compared to other secundiparae (7.42 hours versus 4.25 hours, HR=0.40, 95% CI [0.34, 0.48], p<0.001). There was also strong evidence for heterogeneity between the study sites (theta=0.23, p<0.001).

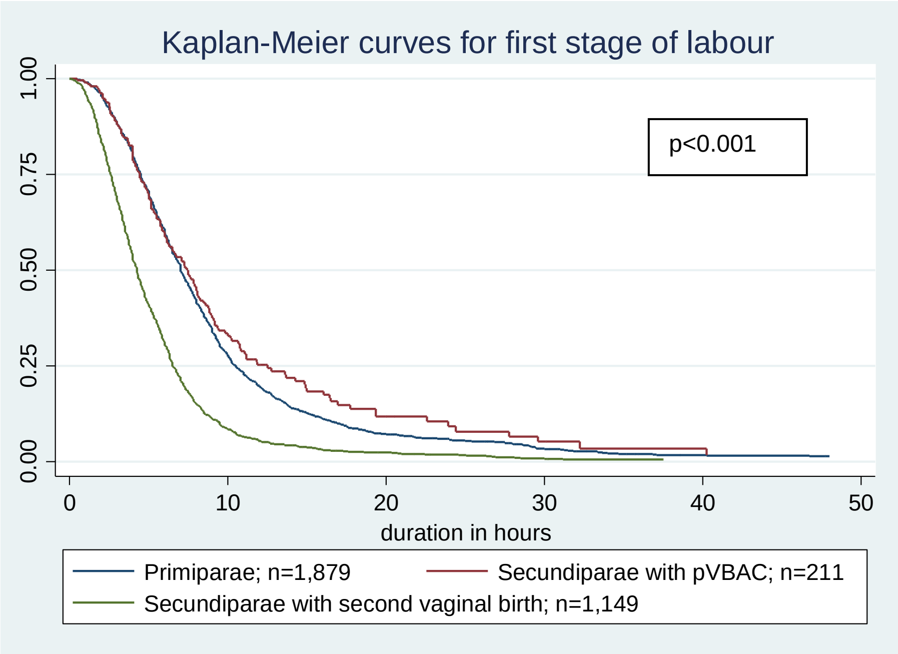


**Figure 3:** Kaplan-Meier curves for first stage duration

The multivariable shared frailty Cox regression model however showed that the duration of second stage of labour of secundiparae with planned VBAC was significantly shorter than for

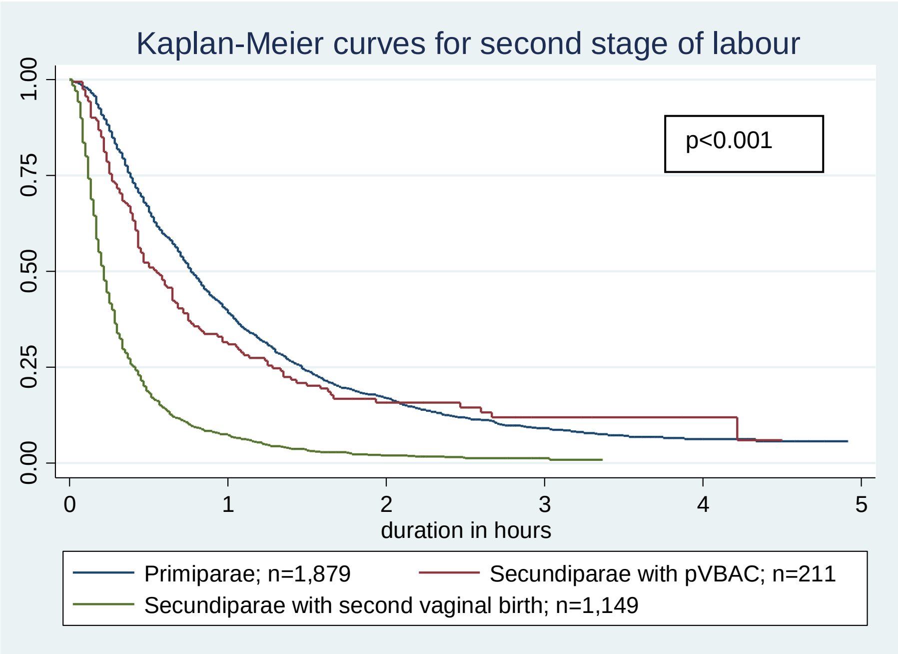


**Figure 4:** Kaplan-Meier curves for second stage duration

primiparae (0.55 hours versus 0.77 hours, HR=1.34, 95% CI [1.05, 1.71], p=0.019, Figure 4, summary in Table 4, full model in Table 6). Compared to secundiparae with second vaginal birth, the duration of second stage of labour of secundiparae with planned VBAC was significantly longer (0.55 hours versus 0.22 hours, HR=0.33, 95% CI [0.26, 0.43], p<0.001). Again, there was strong evidence for heterogeneity between the study sites (theta=0.04, p<0.001).

The adjusted shared frailty Cox regression models with the outcome variables 'overall labour duration', 'duration of first stage of labour' and 'duration of second stage labour' were built independently and were adjusted for variables which remained significantly associated with the respective outcome variable after backward elimination (see Chapter 2.1.3). All three models were additionally adjusted for maternal age, birthweight and type of documentation irrespective of the significance of the association. An overview of the main results of the adjusted frailty Cox regression models with the reference categories primiparae and secundiparae with second vaginal birth is provided in Table 4.

**Table 4**: Adjusted shared frailty Cox regression models for overall labour duration and the durations of the first and second stages (Grylka-Baeschlin et al. 2016)

| Time interval/comparison | Hazard ratio | 95% CI | p-value |
|---|---|---|---|
| **Overall labour duration[1]:** | | | |
| Secundiparae with pVBAC with reference primiparae | 0.998 | [0.830, 1.201] | 0.987 |
| Secundiparae with pVBAC with reference secundiparae with second vaginal birth | 0.319 | [0.265, 0.385] | <0.001 |
| **First stage of labour[2]:** | | | |
| Secundiparae with pVBAC with reference primiparae | 0.916 | [0.774, 1.083] | 0.303 |
| Secundiparae with pVBAC with reference secundiparae with second vaginal birth | 0.402 | [0.339, 0.478] | <0.001 |
| **Second stage of labour[3]:** | | | |
| Secundiparae with pVBAC with reference primiparae | 1.341 | [1.049, 1.714] | 0.019 |
| Secundiparae with pVBAC with reference secundiparae with second vaginal birth | 0.334 | [0.262, 0.426] | <0.001 |

[1] Adjusted for: maternal age, health insurance, no risk factor in history, induction, meconium-stained liquor, cervical dilatation at admission, birthweight, rupture of the membranes, timing of epidural, timing of opioid, interaction between the timing of epidural and the timing of opioids, type of documentation

[2] Adjusted for: maternal age, health insurance, no risk factor in history, induction, meconium-stained liquor, cervical dilatation at admission, birthweight, rupture of the membranes, type of documentation

[3] Adjusted for: maternal age, cervical dilatation at admission, birthweight, episiotomy, rupture of the membranes, timing of oxytocin, timing of epidural, interaction between parity and timing of oxytocin, interaction between timing of oxytocin and timing of epidural, type of documentation

The complete final shared frailty Cox regression models with the outcome variable 'overall labour duration' showed that higher maternal age (HR=0.99, 95% CI [0.98, 1.00], p=0.007), meconium stained liquor (HR=0.78, 95% CI [0.69, 0.89], p<0.001), higher birthweight (HR=0.97, 95% CI [0.96, 0.98], p<0.001), the performance of intrapartal amniotomy (reference intrapartal SROM, HR 0.85, 95% CI [0.78, 0.94], p=0.001), the later timing of epidural (HR=0.87, 95% CI [0.76, 0.97], p=0.044) and the interaction between the later timing of epidural analgesia and the later timing of opioid administration (HR=0.58, 95% CI [0.47,0.71], p<0.001) were found to be significantly associated with longer overall labour duration (Table 5). In contrast, secundiparae with second vaginal birth (reference primiparae, HR=3.13, 95% CI [2.87, 3.41], p<0.001), private insurance or complementary insurance with senior obstetrician (HR=1.31, 95% CI [1.13, 1.51], p<0.001), no risk factors in medical

**Table 5:** Complete shared frailty Cox regression model for overall labour duration

| Variable | Hazard ratio | 95% CI | p-value |
|---|---|---|---|
| Secundiparae with pVBAC with reference primiparae | 1.00 | [0.83, 1.20] | 0.987 |
| Secundiparae with second vaginal birth with reference primiparae | 3.13 | [2.87, 3.41] | <0.001 |
| Maternal age in years | 0.99 | [0.98, 1.00] | 0.007 |
| Private insurance or complementary insurance with senior obstetrician | 1.31 | [1.13, 1.51] | <0.001 |
| No risk factors in medical history except c-section | 1.18 | [1.08, 1.28] | <0.001 |
| Labour induction | 1.47 | [1.33, 1.62] | <0.001 |
| Meconium stained liquor | 0.78 | [0.69, 0.89] | <0.001 |
| Cervical dilation at admission | 1.23 | [1.21, 1.25] | <0.001 |
| Birthweight in 100g | 0.97 | [0.96, 0.98] | <0.001 |
| Prelabour SROM, reference intrapartal SROM | 1.30 | [1.16, 1.45] | <0.001 |
| Intrapartal ARM, reference intrapartal SROM | 0.85 | [0.78, 0.93] | 0.001 |
| Prelabour ARM, reference intrapartal SROM | 3.96 | [2.74, 5.73] | <0.001 |
| Timing epidural analgesia | 0.87 | [0.76, 1.00] | 0.044 |
| Timing opioids | 1.55 | [1.40, 1.70] | <0.001 |
| Interaction timings epidural analgesia and opioids | 0.58 | [0.47, 0.71] | <0.001 |
| Retrospective documentation, reference prospective documentation | 1.06 | [0.91, 1.24] | 0.434 |

pVBAC=planned VBAC; SROM=spontaneous rupture of the membranes, ARM=amniotomy

history except c-section (HR=1.18, 95% CI [1.08, 1.28], p<0.001), labour induction (HR=1.47, 95% CI [1.33, 1.62], p<0.001), higher cervical dilatation at admission (HR=1.23, 95% CI [1.21, 1.25], p<0.001), prelabour SROM (reference intrapartal SROM (HR=1.30, 95% CI [1.16, 1.45], p<0.001, prelabour amniotomy (reference intrapartal SROM, HR=3.96, 95% CI [2.74, 5.73], p<0.001) and a longer interval between onset of labour and opioid administration (HR=1.55, 95% CI [1.40, 1.70], p<0.001) were associated with shorter overall labour duration. Secundiparae with planned VBAC and the type of documentation was not significantly associated with overall labour duration.

The complete final shared frailty Cox regression models with the outcome variable 'duration of first stage of labour' showed that meconium stained liquor (HR=0.82, 95% CI [0.73, 0.93], p=0.001), higher birthweight (HR=0.98, 95% CI [0.97, 0.99], p<0.001) and the performance of intrapartal amniotomy (reference intrapartal SROM, HR=0.84, 95% CI [0.77, 0.92], p<0.001) were associated with longer labour duration (Table 6). In contrast, secundiparae with second vaginal birth (reference primiparae, HR=2.28, 95% CI [2.10, 2.47], p<0.001), private insurance or complementary insurance with senior obstetrician (HR=1.30, 95% CI [1.14, 1.49], p<0.001), no risk factor in medical history except c-section (HR=1.15, 95% CI [1.06, 1.24], p<0.001), labour induction (HR=1.40, 95% CI [1.28, 1.53], p<0.001), higher

**Table 6:** Complete shared frailty Cox regression model for first stage of labour

| Variable | Hazard ratio | 95% CI | p-value |
|---|---|---|---|
| Secundiparae with pVBAC with reference primiparae | 0.92 | [0.77, 1.08] | 0.303 |
| Secundiparae with second vaginal birth with reference primiparae | 2.28 | [2.10, 2.47] | <0.001 |
| Maternal age in years | 1.00 | [0.99, 1.00] | 0.432 |
| Private insurance or complementary insurance with senior obstetrician | 1.30 | [1.14, 1.49] | <0.001 |
| No risk factors in medical history except c-section | 1.15 | [1.06, 1.24] | <0.001 |
| Labour induction | 1.40 | [1.28, 1.53] | <0.001 |
| Meconium stained liquor | 0.82 | [0.73, 0.93] | 0.001 |
| Cervical dilation at admission | 1.22 | [1.20, 1.24] | <0.001 |
| Birthweight in 100g | 0.98 | [0.97, 0.99] | <0.001 |
| Prelabour SROM, reference intrapartal SROM | 1.40 | [1.26, 1.55] | <0.001 |
| Intrapartal ARM, reference intrapartal SROM | 0.84 | [0.77, 0.92] | <0.001 |
| Prelabour ARM, reference intrapartal SROM | 3.39 | [2.38, 4.83] | <0.001 |
| Retrospective documentation, reference prospective documentation | 1.15 | [1.00, 1.34] | 0.057 |

pVBAC=planned VBAC; SROM=spontaneous rupture of the membranes, ARM=amniotomy

cervical dilatation on admission (HR=1.2, 95% CI [1.20, 1.24], p<0.001), prelabour SROM (reference intrapartal SROM (HR=1.40, 95% CI [1.26, 1.55], p<0.001) and prelabour amniotomy (reference intrapartal SROM, HR=3.39, 95% CI [2.38, 4.83], p<0.001). Secundiparae with planned VBAC, maternal age and the type of documentation were not significantly associated with the duration of first stage of labour.

The complete final shared frailty Cox regression models with the outcome variable 'duration of second stage of labour' showed that maternal age (HR=0.97, 95% CI [0.96, 0.98], p<0.001), higher cervical dilatation on admission (HR=0.95, 95% CI [0.93, 0.97], p<0.001), higher birthweight (HR=0.95, 95% CI [0.95, 0.96], p<0.001), episiotomy (HR=0.73, 95% CI [0.67, 0.80], p<0.001), prelabour SROM (reference intrapartal SROM, HR=0.89, 95% CI [0.80, 0.99], p=0.031), the later timing of oxytocin (HR=0.71, 95% CI [0.62, 0.80], p<0.001), the later timing of epidural (HR=0.42, 95% CI [0.35, 0.50], p<0.001) and the interaction between secundiparae with second vaginal birth and the later timing of oxytocin (HR=0.80, 95% CI [0.67, 0.95], p=0.011) were associated with longer duration of second stage of labour (Table 7).

**Table 7:** Complete shared frailty Cox regression model for second stage of labour

| Variable | Hazard ratio | 95% CI | p-value |
|---|---|---|---|
| Secundiparae with pVBAC with reference primiparae | 1.34 | [1.05, 1.71] | 0.019 |
| Secundiparae with second vaginal birth with reference primiparae | 3.87 | [3.45, 4.33] | <0.001 |
| Maternal age in years | 0.97 | [0.96, 0.98] | <0.001 |
| Cervical dilation at admission | 0.95 | [0.93, 0.97] | <0.001 |
| Birthweight in 100g | 0.95 | [0.95, 0.96] | <0.001 |
| Episiotomy | 0.73 | [0.67, 0.80] | <0.001 |
| Prelabour SROM, reference intrapartal SROM | 0.89 | [0.80, 0.99] | 0.031 |
| Intrapartal ARM, reference intrapartal SROM | 1.01 | [0.92, 1.11] | 0.816 |
| Prelabour ARM, reference intrapartal SROM | 1.81 | [1.26, 2.60] | 0.001 |
| Timing oxytocin | 0.71 | [0.62, 0.80] | <0.001 |
| Timing epidural analgesia | 0.42 | [0.35, 0.50] | <0.001 |
| Interaction secundiparae with pVBAC and timing of oxytocin | 1.02 | [0.71, 1.47] | 0.907 |
| Interaction secundiparae with second vaginal birth and timing of oxytocin | 0.80 | [0.67, 0.95] | 0.011 |
| Interaction timings oxytocin and epidural analg. | 1.27 | [1.03, 1.57] | 0.027 |
| Retrospective documentation, reference prospective documentation | 0.93 | [0.81, 1.05] | 0.245 |

pVBAC=planned VBAC; SROM=spontaneous rupture of the membranes, ARM=amniotomy

In contrast, secundiparae with planned VBAC (reference primiparae, HR=1.34, 95% CI [1.05, 1.71], p=0.019), secundiparae with second vaginal birth (reference primiparae HR=3.87, 95% CI [3.45, 4.33], p<0.001), the performance of prelabour amniotomy (reference intrapartal SROM, HR=1.81, 95% CI [1.26, 2.60], p=0.001) and the interaction between a later timing of oxytocin administration and a later timing of epidural analgesia (HR=1.27, 95% CI [1.03, 1.57], p=0.027) were significantly associated with a shorter duration of second stage of labour. The performance of intrapartal amniotomy (reference intrapartal SROM), the interaction between secundiparae with planned VBAC and later oxytocin administration and the type of documentation were not significantly associated with the duration of second stage of labour.

## 3.2. Results of the analysis of German OptiBIRTH-data

### 3.2.1. Sampling and study groups of the analysis of the German OptiBIRTH-data

The analysed study sample of observational data collected for the German part of the OptiBIRTH-study comprised n=387 participants from whom n=291 had a successful VBAC and n=96 an unplanned c-section during labour (Figure 5). The total study population of the German part of the OptiBIRTH trial comprised n=755 women from whom mode of birth was known for n=741 women. A total of n=332 participants were excluded from the current analysis because of c-section before onset of labour. Further women were excluded for preterm birth before 34 weeks (n=2), missing data for the timing of onset of labour (n=6) and no intention to give birth vaginally despite having had onset of labour (n=14). The variable'no intention to give birth vaginally' was coded with 89.9% agreement (see Chapter 2.2.2.) and identified n=19 women. Some women however had multiple exclusion criteria (n=5) leading to the exclusion of a total of n=14 participants for no intention to give birth vaginally.

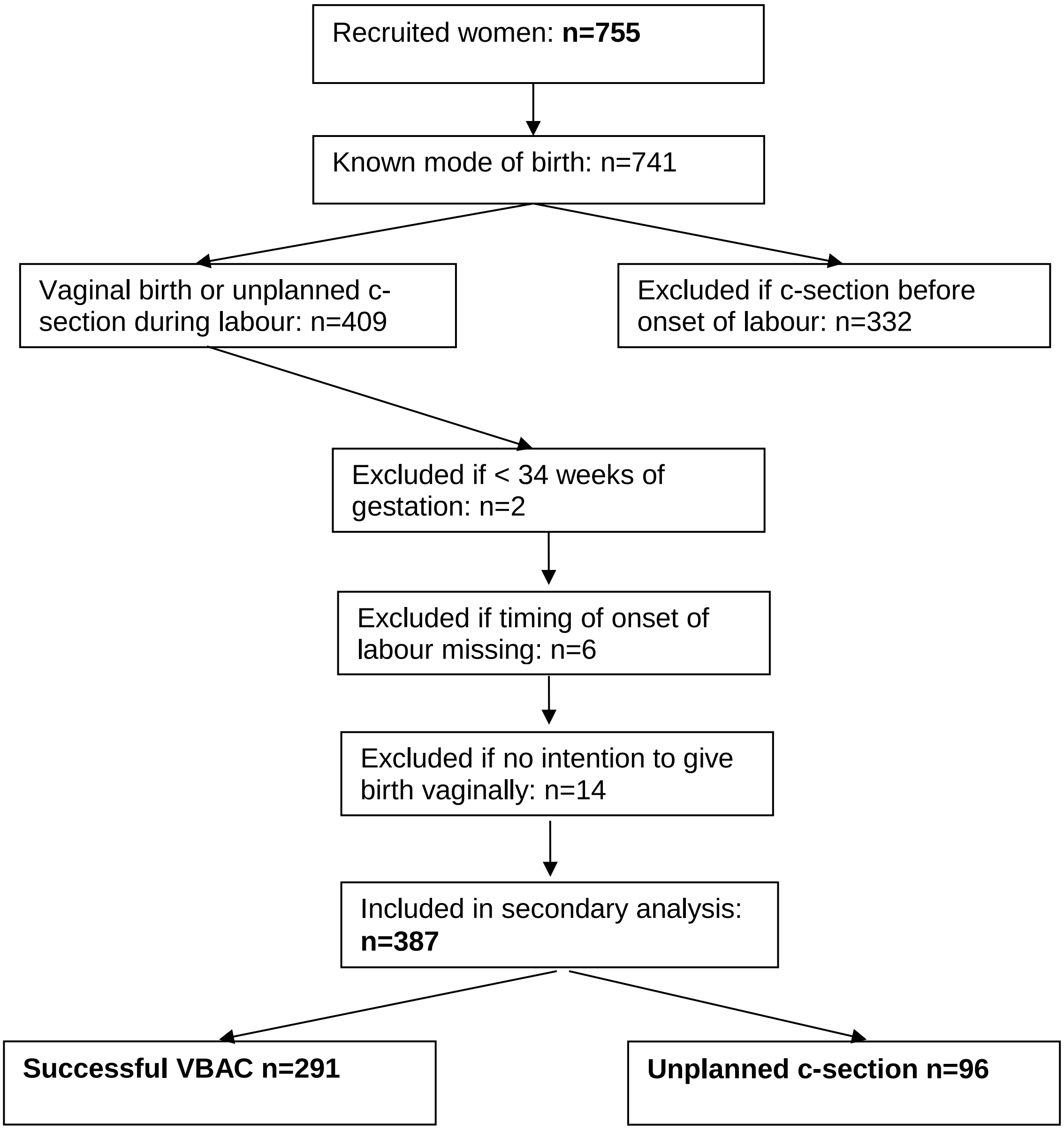


**Figure 5:** Excluded women for the current analysis of the German OptiBIRTH-data

### 3.2.2. Sociodemographic and perinatal characteristics

A similar proportion of women over 34 years had a successful VBAC compared to an unplanned c-section (39.2% versus 46.9%, p=0.184, Table 8). Marital status (94.9% versus 97.6%, p=0.299), health insurance (23.3% versus 31.8%, p=0.188), education (Bachelor degree or higher: 56.0% versus 57.7%, p=0.789) and employment status (fulltime or part-time employment: 59.2% versus 65.5%, p=0.308) did not significantly differ either between the subgroups. In contrast, women achieving successful VBAC had lower BMIs than women undergoing unplanned c-section (24.2 kg/$m^2$ versus 25.2 kg/$m^2$, p=0.045). With regard to obstetric history and perinatal characteristics, more women achieving successful VBAC than women with unsuccessful VBAC had had a previous vaginal birth (19.0% versus 5.2%, p=0.001). Gestational weeks at birth were slightly higher for women undergoing unplanned c-section (40.0 weeks (IQR=40.0-41.0 weeks) versus 40.0 weeks (IQR=39.0-41.0 weeks), p=0.004). Infant birthweights were higher in parturients undergoing unplanned c-section than in those achieving VBAC (3.69 kg versus 3.42 kg, p<0.001). Adverse outcomes were rare in both groups. Three babies had Apgar scores below 7 after five minutes (VBAC: 1 (0.4%) versus c-section: 2 (2.1%), p=0.094), and arterial pH was significantly higher in unplanned c-section cases than in successful VBAC (md c-section: 7.28 versus md VBAC: 7.25, p=0.006). One complete uterine rupture (0.3%) occurred in the study population analysed, however with positive outcomes for mother and child.

**Table 8:** Sociodemographic and perinatal characteristics of the OptiBIRTH-study participants

| **Variable** | **Whole sample** (n=387) | **Successful VBAC** (n=291) | **Unplanned c-section** (n=96) | **p-value** |
|---|---|---|---|---|
| **Sociodemographic data** | | | | |
| Age > 35 years, n (%) | 159 (41.09) | 114 (39.18) | 45 (46.88) | 0.184 |
| BMI in kg/m$^2$, md (IQR) | 24.36 (21.83-27.73) | 24.16 (21.50-27.64) | 25.15 (22.64-28.73) | 0.045 |
| Married/living with partner[a], n (%) | 326 (95.60) | 244 (94.94) | 82 (97.62) | 0.299 |
| Private or supplementary insurance[a], n (%) | 87 (25.36) | 60 (23.26) | 27 (31.76) | 0.118 |
| Bachelor's degree or higher[a], n (%) | 194 (56.40) | 145 (55.98) | 49 (57.65) | 0.789 |
| Full-time or part-time employment, n (%) | 206 (60.77) | 151 (59.22) | 55 (65.48) | 0.308 |
| **Perinatal data** | | | | |
| Previous vaginal birth, n (%) | 60 (15.58) | 55 (19.03) | 5 (5.21) | 0.001 |
| Gestational weeks, md (IQR) | 40.00 (39.00-41.00) | 40.00 (39.00-41.00) | 40.00 (40.00-41.00) | 0.004 |
| Infant's birthweight in kg, md (IQR) | 3.49 (3.19-3.81) | 3.42 (3.16-3.74) | 3.69 (3.35-3.92) | <0.001 |
| Apgar < 7 after 5 min., n (%) | 3 (0.78) | 1 (0.35) | 2 (2.08) | 0.094 |
| Arterial pH, md (IQR) | 7.25 (7.19-7.30) | 7.25 (7.18-7.29) | 7.28 (7.22-7.31) | 0.006 |

BMI=Body mass index; IQR = interquartile range; md = median; ROM = rupture of the membranes; SROM = spontaneous rupture of the membranes

[a] 10-15% missing

### 3.2.3. Labour and birth characteristics

The success rate of women attempting a VBAC was 75.2% (Table 9). The majority (82.5%) of women achieving successful VBAC gave birth spontaneously, 17.5% had an instrumental birth using the ventouse. Unplanned c-section during labour occurred in 24.8% of women who had planned VBAC; 67.7% of c-sections were performed during the first stage of labour and 32.3% during the second stage. There were no significant differences between the subsamples in the percentages of parturients with cervical dilatation on admission ≥ 4cm (successful VBAC: 23.4% versus unplanned c-section: 16.5%, p=0.182) or of women undergoing induced labour (successful VBAC: 21.3% versus unplanned c-section: 25.0%, p=0.450). Women achieving successful VBAC experienced SROM (prelabour or intrapartal) more frequently than women undergoing unplanned c-section (81.3% versus 54.2%, p<0.001) and consequently required intrapartal amniotomy less often (18.7% versus 45.8%, p<0.001).

**Table 9:** Labour-related and birth-related characteristics of OptiBIRTH-study participants

| **Variable** | **Whole sample** (n=387) | **Successful VBAC** (n=291) | **Unplanned c-section** (n=96) | **p-value** |
|---|---|---|---|---|
| Mode of birth: | | | | |
| Spontaneous birth, n (%) | 240 (62.02) | 240 (82.47) | | |
| Ventouse, n (%) | 51 (13.18) | 51 (17.53) | | |
| Unplanned c-section, n (%) | 96 (24.81) | | 96 (100.00) | |
| C-section first stage, n (%) | | | 65 (67.71) | |
| C-section second stage, n (%) | | | 31 (32.29) | |
| Cervical dilatation at admission ≥ 4cm[a], n (%) | 74 (21.64) | 60 (23.35) | 14 (16.47) | 0.182 |
| Labour induction, n (%) | 86 (22.22) | 62 (21.31) | 24 (25.00) | 0.450 |
| Rupture of the membranes: | | | | |
| Prelabour SROM, n (%) | 108 (28.88) | 88 (31.65) | 20 (20.83) | 0.044 |
| Intrapartal SROM, n (%) | 170 (45.45) | 138 (49.64) | 32 (33.33) | 0.006 |
| Intrapartal ARM, n (%) | 96 (25.67) | 52 (18.71) | 44 (45.83) | <0.001 |
| Oxytocin, n (%) | 190 (49.10) | 141 (48.45) | 49 (51.04) | 0.660 |
| Epidural analgesia, n (%) | 144 (37.21) | 96 (32.99) | 48 (50.00) | 0.003 |
| Opioids, n (%) | 86 (22.22) | 64 (21.99) | 22 (22.92) | 0.850 |
| Bath, n (%) | 60 (15.50) | 46 (15.81) | 14 (14.58) | 0.774 |
| No medical intervention, n (%) | 96 (25.26) | 86 (30.28) | 10 (10.42) | <0.001 |

ARM = artificial rupture of the membranes; IQR = interquartile range; md = median; SROM = spontaneous rupture of the membranes

[a] 10-15% missing

Successful VBAC was also associated with lower rates of epidural analgesia than unplanned c-section (33.0% versus 50.0%, p=0.003). Neither the use of oxytocin (48.5% versus 51.0%, p=0.660) and opioids (22.0% versus 22.9%, p=0.850) nor the frequency of taking a bath during labour (15.8% versus 14.6%, p=0.774) differed significantly between women with successful VBAC and those with unplanned c-section. However, there were more women achieving successful VBAC than undergoing unplanned c-section who had no intrapartal medical intervention (either amniotomy, oxytocin, epidural analgesia or opioid administration; 30.3% versus 10.4%, p<0.001). The picture was similar when women undergoing induced labour were excluded (VBAC: 32.5% versus c-section: 11.1%, p<0.001).

The duration between onset of labour and birth was significantly longer in parturients undergoing unplanned c-section than in women achieving successful VBAC (9.24 hours versus 5.77 hours, p<0.001, Table 10). The duration of the first stage of labour (i.e. the time between the onset of labour and full cervical dilatation or unplanned c-section during the first stage of labour) also differed significantly (successful VBAC: 4.67 hours versus unplanned c-section: 8.50 hours, p<0.001). The duration of the first stage of labour in those women who reached the endpoint 'complete cervical dilatation', i.e. excluding those undergoing unplanned c-section during the first stage, also differed to a similar extent (4.67 hours versus 8.00 hours, p=0.007). Parturients achieving successful VBAC received amniotomy (4.67 hours versus 8.00 hours, p=0.055) and opioids (2.30 hours versus 3.83 hours, p=0.019) earlier than women undergoing unplanned c-section (Table 10 contiued). By contrast, the time intervals between onset of labour and oxytocin administration (5.50 hours versus 6.17 hours, p=0.598), epidural analgesia (3.72 hours versus 3.87 hours, p=0.967) and taking a bath (3.00 hours versus 2.67 hours, p=0.752) were comparable between women with successful VBAC and those with unplanned c-section during labour.

**Table 10:** Labour duration and timing of interventions of OptiBIRTH-study participants

| **Variable** | **Whole sample** (n=387) | **Successful VBAC** (n=291) | **Unplanned c-section** (n=96) | **p-value** |
|---|---|---|---|---|
| Duration onset of labour – birth, hrs, md (IQR) | 6.55 (4.15-10.07) | 5.77 (3.90-8.53) | 9.24 (5.94-12.95) | <0.001[a] |
| Duration completed first stage of labour, hrs, md (IQR) | 5.00 (3.10-7.67) | 4.67 (3.00-7.17) | 8.00 (6.33-11.50) | 0.007[b] |
| Duration first stage of labour, hrs, md (IQR) | 5.33 (3.17-8.63) | 4.67 (3.00-7.17) | 8.50 (5.81-12.21) | <0.001[a] |
| Duration second stage of labour, hrs, md (IQR) | 0.95 (0.41-1.85) | 0.85 (0.37-1.70) | 2.20 (1.30-3.15) | <0.001[a] |

**Table 10** continued

| Variable | Whole sample (n=387) | Successful VBAC (n=291) | Unplanned c-section (n=96) | p-value |
|---|---|---|---|---|
| Timing SROM, hrs, md (IQR) | 3.08 (1.00-5.35) | 3.00 (1.00-5.10) | 3.25 (0.75-7.17) | 0.112[b] |
| Timing ARM, hrs, md (IQR) | 5.87 (2.83-10.17) | 5.25 (3.00-8.22) | 8.28 (2.83-11.98) | 0.055[b] |
| Timing of oxytocin, hrs, md (IQR) | 5.70 (3.60-8.50) | 5.50 (3.50-8.50) | 6.17 (4.33-8.67) | 0.598[b] |
| Timing of epidural, hrs, md (IQR) | 3.75 (2.42-6.20) | 3.72 (2.50-6.50) | 3.87 (2.13-6.20) | 0.967[b] |
| Timing of opioids, hrs, md (IQR) | 2.33 (1.25-4.98) | 2.30 (1.27-4.20) | 3.83 (1.00-10.00) | 0.019[b] |
| Timing of bath, hrs, md (IQR) | 3.00 (1.30-4.92) | 3.00 (1.33-5.00) | 2.67 (1.08-4.25) | 0.752[b] |
| Intervention-free time interval, hrs, md (IQR) | 4.25 (2.25-7.77) | 4.07 (2.30-7.52) | 4.48 (2.00-8.08) | 0.606[b] |
| ARM first intervention, n (%) | 41 (11.02) | 21 (7.58) | 20 (21.05) | <0.001 |
| Oxytocin first intervention, n (%) | 54 (14.52) | 47 (16.97) | 7 (7.37) | 0.022 |
| Epidural first intervention, n (%) | 104 (27.96) | 66 (23.83) | 38 (40.00) | 0.002 |
| Opioids first intervention, n (%) | 77 (20.70) | 57 (20.58) | 20 (21.05) | 0.921 |

ARM = artificial rupture of the membranes; IQR = interquartile range; md = median; SROM = spontaneous rupture of the membranes;

[a]Mann-Whitney U test; [b]Log rank test

The random effects logistic regression model revealed no significant association between a maternal age of over 35 years and the success or otherwise of VBAC (OR=0.61, 95% CI [0.36, 1.03], p=0.065, Table 11). A significantly higher chance of achieving successful VBAC was found for women with a previous vaginal birth (OR=4.98, 95% CI [1.78, 13.93], p=0.002). In contrast, a decreased chance of a vaginal birth was observed among infants with a higher birthweight (OR per kg=0.39, 95% CI [0.21, 0.71], p=0.002), for women receiving intrapartal amniotomy (reference intrapartal SROM, OR=0.31, 95% CI [0.17, 0.56], p<0.001) and for those with longer labour duration (0.93 per hour, 95% CI [0.88, 0.97], p=0.001). Sensitivity analyses excluding the variable ‘previous vaginal birth’ showed no significant association between age and the success of VBAC either, and there were similar

**Table 11:** Predictors for successful VBAC in the mixed effect logistic regression

| **Predictors** | **OR [95% CI]** (Previous VB included) | **OR [95% CI]** (Sensitivity analysis without previous VB) |
|---|---|---|
| Previous vaginal birth | 4.98 [1.78, 13.93]** | |
| Age > 35 years | 0.61 [0.36, 1.03] | 0.72 [0.43, 1.19] |
| Birthweight in kg | 0.39 [0.21, 0.71]** | 0.42 [0.23, 0.75]** |
| Prelabour SROM | 1.14 [0.59, 2.22] | 1.06 [0.56, 2.02] |
| Intrapartal ARM (Reference intrapartal SROM) | 0.31 [0.17, 0.56]*** | 0.33 [0.18, 0.59]*** |
| Labour duration in hrs | 0.93 [0.88, 0.97]** | 0.92 [0.88, 0.96]*** |

ARM = artificial rupture of the membranes; CI=confidence interval; OR=Odds ratio; SROM = spontaneous rupture of the membranes; VB = vaginal birth

*p<0.05; **p<0.01; ***p<0.001

findings in respect of higher birthweight, amniotomy and longer labour duration (Table 11). The empty random effect model showed no relevant variation in the outcome between study sites (random effect parameters ε=0.147, p=0.325); in the adjusted model the random effect parameter estimate decreased almost to 0, indicating that the independent variables in the model accounted for the remaining variation between study sites.

### 3.2.4. The intervention-free time interval

The length of the intervention-free time interval, representing the interval between onset of labour and the first of amniotomy, oxytocin administration, epidural analgesia or opioid administration, did not differ significantly between successful VBAC and unplanned c-section (4.07 hours versus 4.48 hours, p=0.606, Table 10 continued). This finding did not change when women who underwent induced labour were excluded (VBAC: 4.73 hours versus c-section: 5.20 hours, p=0.541). Birth without any intervention (neither amniotomy, oxytocin, epidural analgesia nor opioid) occurred significantly more often in parturients who achieved successful VBAC (31.1%) than in those who underwent unplanned c-section (10.5%, p<0.001). Amniotomy as the first intervention was more frequent in unplanned c-section than in successful VBAC (21.05% versus 7.58%, p<0.001, Table 10 continued). However, the median timing of amniotomy as a first intervention was similar between the subsamples (VBAC: 4.07 hours versus c-section: 4.47 hours, p=0.134). By contrast, oxytocin augmentation as a first intervention was significantly more frequent in women achieving successful VBAC than in those undergoing unplanned c-section (16.97 % versus 7.37%, p=0.049), although the median time interval between onset of labour and oxytocin as the first intervention was similar (VBAC: 3.33 hours versus c-section: 3.25 hours, p=0.398). Epidural analgesia was the most frequent first intervention in both study groups, with a significant difference between the subgroups (VBAC: 23.8% versus c-section: 40.0%, p=0.002); but the median time to an epidural as the first intervention did not differ significantly (VBAC: 3.18 hours versus unplanned c-section: 4.25 hours, p=0.529). The administration of an opioid as a first intervention occurred with similar frequency in both subgroups (successful VBAC: 20.58% versus unplanned c-section: 21.05%, p=0.921) but was used significantly earlier in women achieving successful VBAC than in women who underwent unplanned c-section (2.17 hours versus 3.83 hours, p=0.004). Significantly more women who successfully achieved VBAC had SROM during the intervention-free time interval than did women who underwent unplanned c-section (37.4% versus 19.8%, p=0.002). The median timing of SROM during the intervention-free time interval did not differ significantly between the subsamples (VBAC: 2.00 hours versus unplanned c-section: 2.67 hours, p=0.226).

The Cox regression model investigating predictors for the length of the intervention-free time interval showed that induced labour resulted in a shortened intervention-free time interval in successful VBAC (HR=2.85, 95% CI [2.00, 4.08], p<0.001) but had no significant impact in unplanned c-section (HR=0.88, 95% CI [0.52, 1.49], p=0.630, Table 12). A longer gestation period was associated with a prolonged intervention-free time interval in successful VBAC (HR=0.84, 95% CI [0.76, 0.94], p=0.002) and in the whole study population (HR=0.88, 95% CI [0.80, 0.97], p=0.008). The empty shared-frailty model for unplanned c-section showed no variation in the outcome between study sites (p=1.000). The empty models for successful VBAC (p<0.001) and the whole study population (p<0.001) as well as their final multivariable counterparts (VBAC: theta=0.187, p<0.001; whole study population: theta=0.143, p<0.001) indicated that the independent variables in the model did not fully account for the variation in the outcomes between study sites.

**Table 12:** Predictors for the duration of the intervention-free time interval in the Cox regression models

| **Predictors** | **Whole sample HR [95% CI]** (n=387) | **Successful VBAC HR [95% CI]** (n=291) | **Unplanned c-section HR [95% CI]** (n=96) |
|---|---|---|---|
| Age > 35 years | 0.82 [0.64, 1.04] | 0.87 [0.65, 1.17] | 0.75 [0.49, 1.14] |
| Induction | 1.97 [1.48, 2.62]*** | 2.85 [2.00, 4.08]*** | 0.88 [0.52, 1.49] |
| Gestational weeks | 0.88 [0.80, 0.97]** | 0.84 [0.76, 0.94]** | 1.03 [0.83, 1.29] |
| Post-SROM | 1.14 [0.90, 1.44] | 1.06 [0.80, 1.41] | 1.22 [0.80, 1.87] |

CI=confidence interval; HR=Hazard ratio; SROM = spontaneous rupture of the membranes

*p<0.05; **p<0.01; ***p<0.001

# 4. Discussion

This is the first study to compare overall labour duration, duration of labour phases and timing of interventions between secundiparae with VBAC, primiparae and secundiparae with second vaginal birth, as well as between women with successful VBAC and women with unplanned c-section. Therefore, these analyses of data from the ProGeb- and OptiBIRTH-studies provide new and important insights into the labour processes of parturients planning a VBAC.

## 4.1. Main results of the thesis

### 4.1.1. Second stage of labour in secundiparae with planned VBAC

Secundiparae with planned VBAC had a shorter second stage of labour compared to primiparae (Grylka-Baeschlin et al. 2016). This was congruent with the findings of the case-control study of Faranesh & Salim (2011) as well as with observations in clinical practice. A more recent study also confirmed the shorter second stage of labour but found more frequent instrumental births in secundiparae with planned VBAC compared to primiparae (Inbar et al. 2017). The explanation of the shorter second stage of labour was not obvious, because none of these women had a previous completed second stage of labour with its stretching of the perineal tissue. It would have been expected that first stage of labour was shorter compared to primiparae, because some women had a previous unplanned c-section during labour and therefore had a previous cervical dilatation. However, the indication of the c-section was not available as a potential confounder in the secondary analysis for this PhD-thesis, but was found to be a relevant predictor for labour duration in other studies (Harlass & Duff 1990, Fagerberg et al. 2013). It was a limitation of the ProGeb-study that the indication of the first c-section and whether or not women had cervical dilatation before, could not be extracted from the dataset and, therefore, could not be taken into account. During the first stage of labour, women with quick dilatation and those with slow labour progress or dystocia probably balanced each other. Some women with slow progress during the first stage of labour even had an unplanned c-section and this “drop out” prevented these women from having a second stage. This might be one explanation for the quicker second stage of labour for secundiparae with planned VBAC. The analysis of observational data of the OptiBIRTH-study confirmed the slower labour progress of women with unplanned c-section and also showed that the c-section was mostly performed during the first stage of labour. Some women with slow progress therefore did not have a second stage of labour, which might have shortened its median duration. Additionally, all these women had already had two pregnancies with two times the pressure of the infant on the vaginal and the pelvic floor tissue. This might have softened the tissue and have facilitated the second stage of labour.

The data in this thesis are important for pregnant women with a previous c-section who need a reliable evidence base for their decisions about the mode of birth (Lundgren et al. 2012). The likelihood of a shorter second stage of labour might facilitate this decision and should be promoted during antenatal classes and antenatal care. This is an important finding for midwifery antenatal counselling. Midwifery counselling increases VBAC-rates: more women chose a planned VBAC with midwifery antenatal care compared to antenatal care provided by a family practitioner (Metz et al. 2013a). Further research in larger samples is needed to confirm the shorter second stage of labour of secundiparae with planned VBAC compared to primiparae and to investigate potential explanations for these findings.

#### 4.1.2. The association between labour duration and the success of VBAC

Another main result of this PhD thesis is that shorter labour duration was a significant predictor for the success of VBAC. This might be due to more effective uterine contractions. Earlier opioid administration after onset of labour for pain relief and more often SROM in women with successful VBAC compared to unplanned c-section were interpreted to be further features of more effective labour in successful VBAC. Janssen et al. (2016) also found that mild and moderate contractions and the perception of labour lasting longer than 24 hours were predictors for c-section among low risk primiparous women. Durations for labour overall and for the first stage among the planned VBAC resembled those of primiparae (Grylka-Baeschlin et al. 2016) and therefore these findings might be congruent. Nevertheless, the question why longer labour duration was found to be associated with an increased risk for a c-section could be raised. It remained unclear whether labour in the majority of these women was obstructed and spontaneous birth impossible or whether women with longer labour duration had still not received enough time to successfully give birth vaginally. This question might be valid for primiparae as well as for women with planned VBAC. The American College of Obstetrician and Gynecologists (ACOG 2014) stated that labour dystocia was the most common cause for c-section in primiparae and proposed revisting its definition, referring to research by Zhang et al. (2002, 2010) that labour lasted longer than was historically taught. The statement of the ACOG (2014) could be interpreted as indicating that an important part of the unplanned c-sections was due to definitions of dystocia respectively of physiological labour progress and not due to impossibilities of a vaginal birth. This is congruent with the observation that labour duration for primiparous women lasted longer in settings with low intervention and low c-section rates (Hildingsson et al. 2015). It might be possible that on an individual level, shorter labour duration is associated with an increased success chance for planned vaginal birth. On an institutional level, there are indications that hospitals with higher VBAC and vaginal birth rates also have parturients who have longer labour durations (Grylka-Baeschlin et al. 2014). Further research in multicentre settings is needed to fully understand the associations between labour duration and the success of planned vaginal birth, especially among women with planned VBAC. It would be important to investigate differences in care to understand if a labour and birth management strategy allowing women more time to give birth would enhance the rates.

#### 4.1.3. Rupture of the membranes and the success of VBAC

The analysis of observational data of the OptiBIRTH-study showed that prelabour and intrapartal spontaneous rupture of the membranes (SROM) were positively associated with the success of planned VBAC compared to amniotomy. Birara & Gebrehiwot (2013) also showed that rupture of the membranes before admission to hospital was associated with higher rates of successful VBAC. In primiparous women in contrast, Lee et al. (2010) observed that early SROM before 4 cm of cervical dilatation after spontaneous onset of labour was associated with increased c-section rates. Moreover, early amniotomy has shown a slightly positive association with lower caesarean rates and increased the chance for spontaneous birth for primiparous women in various studies (Ghafarzadeh et al., 2015; Gross et al., 2014; Wei et al., 2013). It could be supposed that the association between rupture of the membranes (ROM) and the success of VBAC differ between parturients planning a VBAC and primiparous women. A closer look at the timing of amniotomy was needed, because routine performance regardless of parity and timing was not clearly associated with the mode of birth (Smyth et al. 2013). In addition to the lower chance of giving birth vaginally if an amniotomy was performed; the analysis of the OptiBIRTH-data indicated a longer median time interval between onset of labour and amniotomy in unplanned c-section compared to successful VBAC. This result was not statistically significant with a marginal p-value of 0.055. Taking into account the relatively small sample size of the study which might have prevented the statistical significance, this could be interpreted as indicating that if amniotomy was performed, it should have been done earlier during the labour process. Performing the intervention earlier would probably have led to a higher incidence, which can probably not be recommended, because amniotomy per se was a negative predictor for the success of planned VBAC. The present findings did not allow any firm conclusions about whether an increased frequency of amniotomy which was performed early during labour would increase the success rates of VBAC. Rupture of the membranes, either spontaneous or artificial, is a key event in the process of labour (Gross 2001) and further research in larger samples is needed to investigate the association between SROM and the success of planned VBAC. This is particularly important because in contrast to amniotomy and also preterm premature rupture of the membranes, intrapartal spontaneous rupture of the membranes (SROM) was of less importance in perinatal research (Gross 2001, Brown et al. 2013, Wei et al. 2013). The ongoing lack of scientific evidence and difficulties in making clear recommendations for clinical practice, mean that future studies should especially focus on the timing of amniotomy and SROM, as well as on physiological factors which foster.

#### 4.1.4. Epidural analgesia and the success of VBAC

In a multicentre prospective observational study with 14,529 women planning a VBAC, Landon et al. (2005) found higher epidural rates in women achieving successful VBAC than in those undergoing unplanned c-section. The results of the analysis of OptiBIRTH-data for this PhD-thesis revealed the opposite association in the univariable analyses; but this finding was not confirmed in the multivariable regression model. In current clinical practice, epidural analgesia is not only administered for pain relief but is also used before oxytocin administration when labour progresses slowly (Jones et al. 2012, NICE et al. 2014). This would be congruent with the finding of this thesis that parturients undergoing unplanned c-section had a higher percentage of epidural analgesia and additionally a longer overall labour duration than women with successful VBAC. However, it was not possible to differentiate in the OptiBIRTH-data if epidural was administered for pain relief or for delays in labour progress, and it was therefore not possible to conclude if labour of women ending in unplanned c-section was more painful, or if slower labour progression caused higher epidural rates. This distinction is important when trying to fully understand the association of epidural analgesia and the success of planned VBAC. Future studies including parturients with planned VBAC, as well as primiparous and multiparous women, should assess the indication for epidural analgesia to investigate its association with the success of planned vaginal birth.

#### 4.1.5. Differences in the intervention-free time interval

The duration of the intervention-free time interval, meaning the interval between onset of labour and the first medical intervention during labour (which were, in the analyses for this PhD-thesis, either amniotomy, oxytocin, epidural or opioid administration) was similar between secundiparae with VBAC and primiparae (Grylka-Baeschlin et al. 2016) as well as between successful VBAC and unplanned c-section. Secundiparae with second vaginal birth however had significantly shorter intervention-free time intervals compared to secundiparae with planned VBAC and primiparae (Grylka-Baeschlin et al. 2016). This was congruent with the results of Petersen et al. (2011) who showed that multiparous women had shorter intervention-free time intervals than primiparous women. The results of Petersen et al. (2011) however were based on analyses of almost the same dataset as the secondary analysis of this PhD-thesis but defined the intervention-free interval until the first intervention of either amniotomy, oxytocin or epidural analgesia without taking into account opioid application. Secundiparae with second vaginal birth and multiparae in general had shorter intervention-free time intervals compared to secundiparae with VBAC and primiparae. This might be due to a labour and birth process which was generally shorter. In order to better understand the reasons for these differences, it was important to have a closer look at the end points of the intervention-free time interval, meaning the first intrapartal intervention. Petersen et al. (2013b) found that the first intervention in multiparae was most often amniotomy (33.6%). In the secondary analysis of the ProGeb-study for this PhD-thesis, the differences in the endpoints of the intervention-free time interval between secundiparae with VBAC and primiparae respectively secundiparae with second vaginal birth were not investigated, and this might be of interest for further research. Nevertheless, the differences in the endpoints of the intervention-free time interval between successful VBAC and unplanned c-sections were investigated in the analysis of observational labour and birth data of the OptiBIRTH-study and were found to be relevant. Women with successful VBAC most often did not have any intrapartal interventions before giving birth (30.3%). Epidural analgesia was the most frequent first intervention in both subgroups but occurred significantly more often in unplanned c-section. Without the distinction of whether epidural analgesia was administered for pain relief or because of slow progress, this finding was difficult to interpret (see Chapter 4.1.4.). Women with successful VBAC had oxytocin administration significantly more often and women with unplanned c-section more often amniotomy as first intervention. This might mainly be because women with successful VBAC had SROM more often, making amniotomy impossible and because of the recommendations of the NICE (2014) guidelines to first rupture the membranes before administering oxytocin for labour augmentation. Oxytocin should be used cautiously for labour augmentation in planned VBAC because of the increased risk for uterine rupture (Guise et al. 2010b, NICE 2014) and the finding in this PhD thesis that oxytocin as the first intervention was associated with successful VBAC should not lead to the conclusion that labour augmentation should be started with oxytocin when the membranes have not yet ruptured.

There is a lack of research regarding the optimal time point during labour at which intrapartal interventions should start. However, this might be of special interest, because after a first intervention, a cascade of interventions is often seen (Petersen et al. 2013b). Furthermore, the intervention-free time interval cannot be discussed without taking into consideration the heterogeneous definition of onset of labour (Hanley et al. 2016). If onset of labour is recognised before labour progresses, especially, if women are already admitted to the hospital, labour dystocia might be diagnosed too early leading to early interventions into the labour process (ACOG 2014, Neal et al. 2014). Further research investigating the duration and the endpoint of the intervention-free time interval as well as its association with the definition of onset of labour is needed to gain additional knowledge of the importance of this time interval for the success of women with planned VBAC.

## 4.2. Challenges of study management, data collection and data analysis

### 4.2.1. Project management of the German part of OptiBIRTH

The OptiBIRTH-study was designed as a cluster-randomised controlled trial to test the effectiveness of a complex intervention to enhance VBAC-rates. The cluster-randomised controlled trial design is an appropriate study design to assess the effectiveness of training programmes for health care professionals (Brierley et al. 2012) and because the OptiBIRTH-intervention included training for clinicians at each study site, individual randomisation of women might have led to contamination and spillover effects. However, cluster randomized controlled trials are vulnerable to methodological problems because potential participants have knowledge about the study group to which they will be allocated if they agree to join the study (Hahn et al. 2005). Recruitment and retention problems are a known challenge in research and can lead to doubts about the generalisability of results (Schulz & Grimes 2002). There is some evidence to overcome this, for example, in order to enhance response rates, methods such as telephone reminders were found to be effective (Treweek et al. 2013). Recruitment problems were encountered in the OptiBIRTH-study and potential participants were reminded to return the consent form and participate in the study. Nevertheless, there were substantial recruitment fluctuations (see Figure 6). This might partially be due to the natural fluctuation of potential participants but might also reflect the varying efforts of the study-employees to identify and remind potential participants. It is not clear if the control

Number of recruited participants

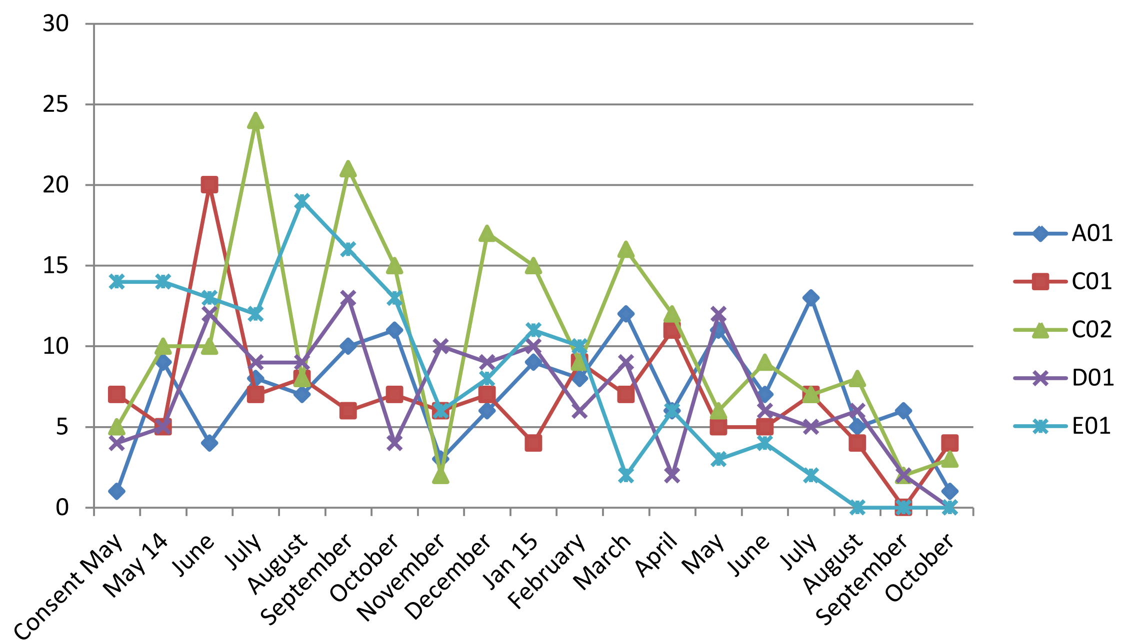


**Figure 6:** Recruitment fluctuations in the German OptiBIRTH-study sites

sites, where potential participants had knowledge about not being offered the intervention, encountered additional difficulties.

Recruitment problems are also known to extend study durations (Treweek et al. 2013). Recruitment for the main phase of the OptiBIRTH-study lasted one and half years and to take account of the time until the end of data collection, staff responsible for the study process in the sites was needed for more than two years. The tasks for the study midwives and research assistants were complex and challenging and personnel fluctuations were frequent. The study organisation had to be adapted to the individual situations at the sites and was therefore heterogeneous. In just one intervention site, one midwife mastered recruitment, implementation of the intervention and data collection on her own during the whole study period. The other two intervention sites had staff turnovers and divided the different work among various people. In one control site, collaboration between a study assistant and the midwifery team took place whereas in the other control site, the study tasks were mastered by one midwife at any one time but staff turnovers took place twice.

#### 4.2.2. Exclusion criteria for the analysis of observational data of the OptiBIRTH-study

In addition to the inclusion criteria for the OptiBIRTH-trial (pregnant women over 18 years old having had one previous c-section with transverse incision and speaking English, Italian or German), the analysis of the German data for this PhD-thesis required further inclusion criteria (see Chapter 2.2.2.). Only participants enrolled in the German study sites who had recorded onset of labour and intended to give birth vaginally after at least 34 gestational weeks were included. During the preliminary analyses, it was noted that some women were classified correctly, e.g. having spontaneous onset of labour before the planned c-section, but did not have the intention to give birth vaginally. An additional variable was then generated coding the string variable for the indication of the c-section as described in chapter 2.2.2. This disadvantage arose from using a study that also included women with planned c-section and is a challenge encountered in studies which were not primarily planned for the purpose of use and is especially frequent in secondary analyses (Cheng & Phillips 2014, Johnston 2014). Secondary analyses have the advantage of being cost-effective and accelerating the pace of research because data are already collected and time-consuming research steps can be avoided (Johnston 2014). However, disadvantages arise from data collection which did not address the research question for the secondary analysis; which means that the necessary data might be incomplete and it might not be possible to contact the participants for further information (Cheng & Phillips 2014, Johnston 2014). A further problem with a secondary analysis is sometimes that the researcher was not involved in the study process of the original trial (Johnston 2014). However, this was not the case for the analysis of the German OptiBIRTH-data, because the PhD-student was involved in most phases and steps of the OptiBIRTH-study, including designing the study instruments (see Chapter 4.4.). For the planned additional analysis of OptiBIRTH-data of all three countries with the working title “Intrapartal predictors for the success of planned VBAC in three countries”, the procedure of creating an additional variable “intention to give birth vaginally” will also be necessary for the Irish and the Italian data (see Chapter 4.5.). In further studies aiming to investigate labour processes and which also include women with planned c-section, this should be considered in the planning phase of the study so that a clear distinction can be made in the dataset with respect to the targeted mode of birth at the moment of onset of labour.

#### 4.2.3. Heterogeneity of the definition of onset of labour

The diagnosis of onset of labour is crucial in clinical practice but also in research into labour duration, because labour duration depends on this definition (Lauzon et al. 2000, Gross et al. 2009, Hanley et al. 2016). Hanley et al. (2016), in a systematic review including 62 studies, found little consensus regarding the definition of onset of labour. This heterogeneity mostly depends on how the latent and active phases of labour were considered and defined (Chelmow et al. 1993, Zhang et al. 2010, ACOG et al. 2014). Heterogeneity regarding the definition of onset of labour was noticed in the OptiBIRTH-study, between countries but also within countries, sites and even clinicians. The definition for onset of labour, which was agreed for the study purpose (regular or irregular contractions associated with progressing cervical dilatation, assessed by the midwife, see Chapter 2.2.3.), did not include a threshold of cervical dilatation respecting current findings and recommendations questioning onset of labour at 3-4 centimetre of cervical dilatation (Zhang et al. 2002, Bailit et al. 2005, ACOG 2014).

Despite this definition, remarkable variations in the overall labour duration and the duration of the first stage of labour were noticed. Overall labour durations of more than 80 hours or first stage of labour of zero hours were computed with the date and time entered in the German database. Having an exact examination of the other variables and reading birth stories in the dataset, it was observed that the time point of onset of labour was not always plausible (see Table 13 and Tables 15 and 16 in Appendix 8.2.). The most common inconsistencies were the simultaneous onset of labour with the spontaneous rupture of the membranes or with hospital admission without considering when labour progress started. A further problem was onset of labour at the time of the start of ineffective uterine contractions and before labour progressed. Time and date of outliers and implausible data were checked and if necessary edited (see Chapter 2.2.3.). Data cleaning, including data editing, is a controversial topic and some have seen it as being borderline to data manipulation (Van den Broeck et al. 2005).

However, errors on data entry are always possible and Van den Broeck et al. (2005) propose a three-step process of data cleaning starting with a screening phase which is followed by a diagnostic and a treatment phase. For the OptiBIRTH-study, the screening phase corresponded to the identification of implausible values for the duration of labour. During the screening phase, birth stories were read in the dataset (see Table 13 and Tables 15 and 16 in Appendix 8.2.). There are limited options for the treatment phase such as editing, deleting or leaving data unchanged (Van de Broeck et al. 2005). Van de Broeck et al. (2005) also stated that impossible values should not be left unchanged but should be corrected if a correct value can be found. Going back to the medical records of the OptiBIRTH-participants to check and edit data for onset of labour was in line with these recommendations. Additionally data were downloaded monthly and all data downloads were stored, enabling an understanding and audit trail for all the changes.

**Table 13:** Examples of birth stories for the three longest labour durations

| Study number | Overall labour duration | Duration first stage | Onset of labour | ROM[1] | Birth | Other | Plausibility |
|---|---|---|---|---|---|---|---|
| C02011 | **747.75 hrs** | 747.00 hrs | 17.07.14, 2.00 | 17.08.14, 02.00 SROM[2] | 17.08.14, 5.45 spontaneously | | No, probably error in month |
| C01037 | **86.28 hrs** | Endpoint not reached | 12.07.14, 12.00 | 12.07.14, 12.00 SROM[2] | 16.07.14, 9.30 Emergency c-section, Uterine rupture | | No, probably prelabour SROM[2] |
| A01015 | **61.77 hrs** | Endpoint not reached | 12.07.14, 10.00 | 13.07.14, 20.20 SROM[2] | 14.07.14, 23.46 Emergency c-section | Simulta-neous onset of labour and induction | No, onset of labour was probably not at start of induction |

[1] ROM=rupture of membranes; [2] SROM=spontaneous rupture of the membranes

As a methodological feedback and lesson learned from this experience: the definition of onset of labour plays a crucial role for the accuracy and validity of the data and results of studies investigating labour duration and time intervals between onset of labour and events respectively interventions. This should be considered carefully in the planning of future studies. A definition of onset of labour which provides a margin for cases where the time point has to be estimated because of limited information is important. Additionally, study midwives and assistants need exact instructions on how this estimation and data entry should be completed. If similar problems occur in future studies, sensitivity analyses might be done of data before and after editing data in order to compare results. This would indicate the dimension of the error and provide insights into methodological aspects of data cleaning.

#### 4.2.4. Censored data for a whole sub sample

During the planning phase of the OptiBIRTH-analyses, further challenges with the methods used were encountered. Comparing women achieving successful VBAC with women undergoing unplanned c-sections led to the situation that in the unplanned c-section subsample, all cases were right censored, because the endpoint, spontaneous birth, was not reached. Prinja et al. (2010) describe the problem precisely: “The censored individuals are excluded from the denominator of 'at risk' individuals at the point when they are censored, however, are included at each preceding point. They are not included in numerator at any point”. Calculating median overall labour duration or median duration of the second stage of labour with Kaplan-Meier estimates was therefore impossible for the unplanned c-section sub group, because none of the cases reached the endpoint of spontaneous birth and none was therefore included in the numerator at any time point. This led to results of zero minutes of durations for all time intervals with endpoints which were not reached by the whole study sub group. Time intervals for which the whole c-section group would have been censored were then calculated with usual statistics and compared with Mann-Whitney-U tests. This was first seen as an inconsistency in the methods used for this PhD-thesis but was then accepted considering the relevance of the topic and the lack of alternative options. The PhD-candidate does not have knowledge about further methodological possibilities, but this could be investigated in future studies of the dataset.

#### 4.2.5. Time-dependent predictors for the rupture of membranes

A methodological aim of the secondary analysis of the ProGeb-data was the inclusion of time-dependent covariables in the Cox regression models with episode splitting to avoid the time at risk before the interventions occurred being taken into account (Shintani et al. 2009, Daniel et al. 2015, Jones & Fowler 2016). Time-dependent bias was found to be common in observational studies using survival analysis (van Walraven et al. 2004). Unexpected but instructive challenges were encountered during the analysis of the ProGeb-data when the inclusion of time-dependent variables for SROM and amniotomy led to Hazard ratios over 100 (see Chapter 2.1.3. and Table 14). It was noticed that two time-varying covariables for a mandatory event of the process (rupture of the membranes) which exclude each other could not be included in a single model. Women with SROM were not further at risk for amniotomy and vice versa. Prior studies included time-dependent variables for amniotomy only (Gross et al. 2014). The results of these studies should be interpreted cautiously, because women with SROM were not at further risk of amniotomy. New insights into the methods used were therefore gained in this PhD research when experimenting with the Cox regression modelling with the outcome variable labour duration and including time-dependent covariables for rupture of the membranes. Including a categorical variable for rupture of the membranes which distinguished between prelabour SROM, prelabour amniotomy, intrapartal SROM and intrapartal amniotomy allowed a limited distinction in the timing and kind of rupture of the membranes to be taken into account. However, time-dependence was not considered statistically. Future studies should consider that rupture of the membranes cannot be included as time-dependent predictors for labour duration.

#### 4.2.6. Simultaneous timing of interventions and events

The recording of simultaneous timings of interventions or events with onset of labour, birth or each other were observed in both datasets used for the analyses of this PhD-thesis and also in previous studies (Petersen 2013b). These simultaneous timings were unlikely and were probably due to insufficient attention to the precision of timings for documentation in the medical records and for data entry. It also led to the computation of time intervals of zero minutes of durations, which would have negatively affected the analysis for Kaplan-Meier estimates with STATA, which excludes durations of zero minutes. For this reason, it was supposed that events and interventions occurred one minute apart. The observations of this PhD -thesis support the findings of Gross (2001) who emphasised the importance of the exact recording of the timings of all interventions and events during labour. This is important in clinical practice, but even more in research investigating labour as a dependent process and using survival analysis. The accuracy of documentation should be at a very high level as a matter of routine. Maternity units should give more importance to the documentation of events and interventions occurring during labour for childbirth.

### 4.3. Critical appraisal of the methods used

#### 4.3.1. The graphical representation of labour progression

Overall labour duration and the duration of labour phases for secundiparae planning a VBAC, primiparae and secundiparae planning a second vaginal birth were graphically represented in the secondary analysis of the ProGeb-data (Grylka-Baeschlin et al. 2016). The Kaplan-Meier curves showed the “survival probability” depending on the time or, in other words, the percentiles of women who already gave birth at a certain time-point after onset of labour (Blossfeld 2007, Sedgwick 2014). This is a different approach to the methods used by Friedman (1954, 1955) and Zhang et al. (2002) who drew labour curves plotting cervical dilatation in relation to time. Both authors also assigned the time to the x-axes and the cervical dilatation (rather than the percentage of women who already gave birth) to the y-axis. As mentioned in chapter 1.2.1., the methodological challenges of drawing labour curves were not completely solved by Friedman (1954, 1955) or Zhang (2002, 2010), because the repeated-measures regression with an eighth and tenth degree polynomial functions used by Zhang et al. (2002) were based on mean labour durations and on a historical dataset (Zhang et al. 2002, Vahratian et al. 2006). This is a problem because the characteristics of parturients have changed over the last five decades and labour of today’s women probably lasts longer than Zhang et al. (2002, 2010) described (Laughon et al. 2012). Kaplan-Meier curves in contrast are based on median durations and current datasets can be used because the method allows the inclusion of incomplete data of c-sections as censored data (Sedgwick 2014). However, the approach of graphical appraisal of labour duration used in this thesis does not provide accurate labour curves for cervical dilatation of today´s women and further research using recent data is needed to solve the methodological challenges encountered by Zhang et al. (2002, 2010).

### 4.3.2. The investigation of labour duration

The main analysis used for this PhD-thesis to investigate labour duration was survival analysis including Kaplan-Meier estimate, log rank tests and shared frailty Cox regression models. Labour is a dynamic, dependent process and therefore survival analyses seemed to be the appropriate statistical method for its investigation (Gross 2001, Zhang et al. 2002, Vahratian et al. 2006). However, different types of survival analyses were used by Gross (2001) and Zhang et al. (2002). Gross et al. (2001, 2005, 2014) researched labour as a process and used Kaplan-Meier estimates, log-rank-tests, piecewise constant exponential models and Cox regression models including time-dependent predictors. For this PhD-thesis, Kaplan-Meier analysis and shared frailty Cox regression modelling with the outcome variables overall labour duration, duration of first and second stage of labour and the intervention-free time interval were used. Kaplan-Meier estimates and Cox regression modelling are the most commonly used methods of survival analysis in public health literature (Prinja et al. 2010). Kaplan-Meier analyses are non-parametric analyses and use all information of censored cases until the moment they were censored (Prinja et al. 2010). With respect to the research on labour duration this seemed very useful, because women with c-section and instrumental birth did not have to be excluded from the analysis, but their data before the termination of the birth process could be used. Moreover, the Cox regression models enabled the inclusion of time-varying covariables with episode splitting, which had the huge advantage of minimising bias that can occur when using time-fixed methodology to analyse the effect of time-varying exposure (Shintani et al. 2009, Daniel et al. 2015, Jones & Fowler 2016). Additionally, the shared frailty Cox regression models enabled a consideration of the variations of maternity care related factors (Wienke 2003), which were observed between the OptiBIRTH sites prior to the study (Gross et al. 2015) and could also be supposed for the 47 sites of the ProGeb-study. This was not done in previous analyses and secondary analyses of the ProGeb-dataset (Petersen et al. 2011, Petersen et al. 2013a, Petersen et al. 2013b, Gross et al. 2014) and increases the validity of the current secondary analysis of the ProGeb-dataset done for this PhD-thesis, because it enabled adjustments in the analysis for cluster-related differences (Wienke 2003).

The research team of Zhang et al. (2002) also used survival analysis but computed interval censored regression for labour progression from one centimetre of cervical dilatation to the next. The exact time point when each centimetre of dilatation was reached could not be determined and their interval censoring dealt with this by right and left censoring (Zhang et al. 2002, Vahratian et al. 2006). The results showed the accelerated progression of cervical dilatation which increased from 0.3 cm/hour between two and three centimetres to 2.5cm/ hour between nine and ten centimetres of dilatation (Zhang et al. 2002). Taking into account speeding up during labour seems to be the advantage of this method compared to the Cox-regression used to investigate overall labour duration and longer labour intervals. Time-fixed covariables for maternal characteristics and intrapartal intervention were also included in interval-censored models (Vahratian et al. 2004). The inclusion of time-varying covariables in the interval-censored models would theoretically be possible and was done in other research fields (Zeng et al. 2016), but does not seem meaningful for the short time intervals from one centimetre of cervical dilatation to the next. No study was found using time-varying predictors to investigate labour progression with interval censored regression and the results would probably be difficult to interpret. The meaningful inclusion of time-dependent covariables in the Cox regression models seems to be the advantage of the method used in this thesis compared to the methods of Zhang et al. (2002). Nevertheless, the statistical analyses done for this PhD-thesis did not add new insights into the threshold of slow labour progression for a revised definition of labour dystocia as deemed necessary by the American College of Obstetricians and Gynecologists (2014). The results of Zhang et al. (2002) in contrast suggested that it was not uncommon before 7cm of cervical dilatation that labour lasted for more than two hours without perceived change, which questioned the findings of Friedman (1955). Large differences in the methods used by Zhang et al. (2002) and the methods used by Gross et al. (2014) and this PhD-thesis were therefore noticed. The comparison of all methods in the same dataset could be interesting for further research. Further studies for assessing physiological labour duration and progress are needed to address the ongoing scientific discussion about revising the definitions of labour dystocia (ACOG 2014).

#### 4.3.3. Censoring of c-section and instrumental births

Censoring of cases which did not reach the endpoint of interest has the advantage that all cases can be included in the analyses and no exclusions because of incomplete data are required (Bland & Altman1998, Blossfeld et al. 2007, Prinja et al. 2010, Sedgwick 2014). In treatment studies, right censoring usually occurs because of drop outs or because of cases with no event during the observed time interval (Bland & Altman 1998, Sedgwick 2014). It is assumed that the censored cases have the same “survival prospects as those who continue to be followed” (Bland & Altman 1998). Censoring women with c-section or instrumental birth when investigating labour duration or the duration of labour phases with the endpoints cervical dilatation complete or birth could be questioned, because birth had already occurred in these cases. These women have no further chance to give birth spontaneously. Additionally, the indication for the termination of the birth process is not taken into account. It cannot be assumed that women with c-section or with instrumental birth would have had the same probability of giving birth at a given time point after being censored compared to women without c-section or instrumental birth. Labour dystocia was found to be the leading cause for c-section (ACOG 2014) and labour was found to be longer in unplanned c-section during labour for planned VBAC compared to successful VBAC in the analysis of observational labour and birth data of the OptiBIRTH-study for this PhD-thesis. This indicates that the probability of giving birth spontaneously after the moment of censoring would probably have been lower for censored cases. However, excluding these women from the analysis instead of censoring would have increased the inaccuracy of the results. This would have led to the exclusion of women with long labour durations or slow labour progression and would have resulted in median labour durations that were too short. Taking into consideration the high c-section rates of today's parturients (EURO-PERISTAT 2013) it seems important to obtain a picture of all women going into the labour process of planned vaginal birth. Excluding c-sections was one of the criticisms of Zhang's calculations of labour progression and labour curves (Zhang et al. 2002, Zhang et al. 2010, see Chapter 4.3.1.). Vahratian et al. (2004) used interval regression to research labour progression of obese and overweight women and included data of women with c-section before the c-section occurred. This approach led to the conclusion that labour progression of advanced cervical dilatation might have been underestimated because women with slow progression "dropped out" from the analysis at the moment of surgery and therefore results for advanced cervical dilatation were mainly based on women with quicker progress. This is congruent with the idea for the survival analysis used in this PhD-thesis that excluding women with c-section would have led to an under-estimation of labour duration. Censoring women with c-section and instrumental birth for Kaplan-Meier analyses and Cox regression modelling and therefore assuming a hypothetical natural endpoint probably led to more accurate estimations of labour duration and the duration of labour phases than excluding them. Despite its limitations, this might have been the best approach taking into consideration the current available knowledge.

#### 4.3.4. The interpretation of the effect of time-dependent predictors

With respect to labour duration, it would be of special interest to investigate if labour is accelerated or slowed after the use of interventions and occurrence of events in order to gain knowledge about their optimal timing. This would be a key point for using the findings of longitudinal analyses considering labour duration and process-oriented labour management. Gross et al. (2014) found an accelerating effect of amniotomy which was less pronounced if amniotomy was performed more than five hours after onset of labour. They also observed that epidural in primiparae accelerated labour further if administered between seven and eleven hours after onset of labour. The Hazard ratio was plotted with respect to time after onset of labour and was found to be constant over time for some interventions but increased or decreased for others during the process of labour and birth. In the analysis for the current thesis, time-dependent covariables were included in the shared-frailty Cox regression to adjust the models. The accelerating or slowing effects of the time-dependent covariables were used for the adjustment of the models but no interpretation of the results for clinical practice was done. All interventions showed accelerations after the intervention was performed when women with the intervention were compared to women without it, calculated using the duration from the start of the interval to the intervention or the whole time interval of interest, if no intervention occurred. In interpreting these findings, it is important to take into consideration the natural acceleration of the process of labour which Zhang et al. (2002, 2010) showed with the increasing speed of cervical dilatation during first stage of labour, and which can also be observed in clinical practice with women recognising stronger uterine contractions when labour progresses. It could be supposed that a baseline accelerating effect exists which interacts with the effects after interventions and events. It would be conceivable to control the Cox regression models for this effect by generating a variable which splits labour duration into equal time-intervals (e.g. two to four hours) and including this variable into the models. Interactions of this equal interval-split variable with other time-dependent covariables should be tested, and if significant, included in the model according to the model-building strategy proposed by Hosmer and Lemeshow (2000). However, this additional predictor would increase the required sample size. In order to test this suggestion, further research in larger samples should control for the supposed baseline acceleration of labour progress and investigate how the accelerating or slowing effect of intrapartal interventions and events could be interpreted for clinical practice. It would be an important step toward the applicability of process-oriented labour and birth research if the accelerating and slowing effects could be used to generate recommendation for clinical practice.

#### 4.3.5. Causal relationship in observational studies

A fundamental goal in observational studies, but also one of the most important challenges of them, is the interpretation of the results with respect to causal relationship (Rasmussen 2001). The famous question about which was first, “the chicken or the egg” can very often not be answered, because of confounding by indication. One of the examples encountered during the analysis for the PhD-thesis was the observation that oxytocin is used in practice to speed up labour but the secondary analysis of the ProGeb-dataset (Grylka-Baeschlin et al. 2016) showed a significant longer median labour duration in women with intrapartal oxytocin administration compared to women without intrapartal oxytocin administration (whole study population, n=3,963, 9.00 vs 4.92 hrs, $p<0.001$, see Figure 7). This observation should not lead to the conclusion that oxytocin administration slowed the labour process. Rather, because oxytocin is a drug to accelerate labour (O'Driscoll et al. 1970, Wei et al. 2013), its use was associated with longer labour duration because slower labour progress was the indication for its administration.

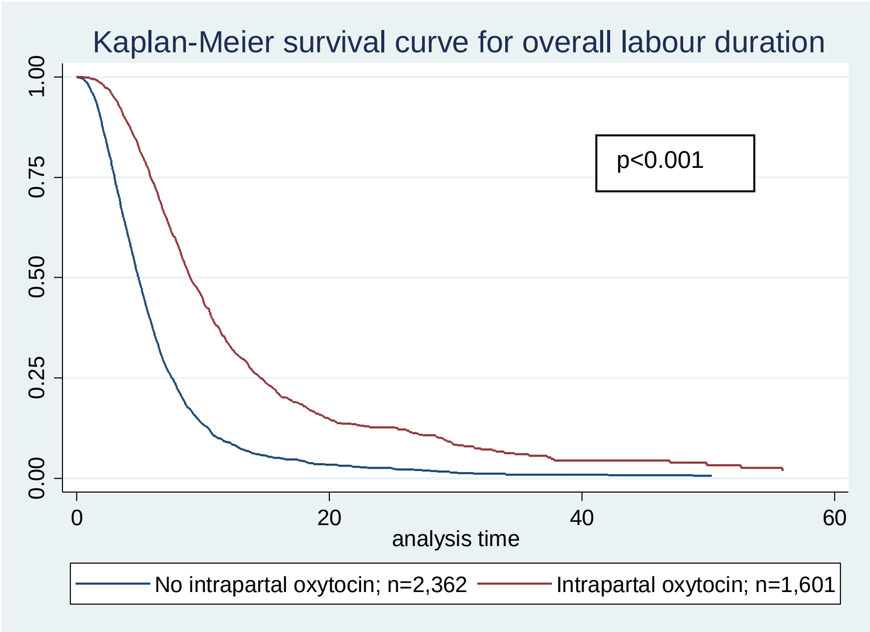


**Figure 7:** Labour duration for women with and without intrapartal oxytocin administration

A further example encountered in the analysis of the German OptiBIRTH-data was the earlier administration of opioids in women with successful VBAC compared to women with unplanned c-section. This finding could indicate that women with successful VBAC, who also had shorter labour duration than those with unplanned c-section, experienced earlier strong uterine contractions and needed pain relief medication. It therefore could not be concluded that opioids should be administered earlier to enhance the success rates of VBAC. The dynamic process of labour and birth was found to be very complex. The attempt to visualise causal relationship with labour duration in a directed acyclic graph (Hernan et al. 2002) resulted in multiple associations with no determined direction (Figure 8). For time-dependent covariables, this direction could be defined considering the sequence of interventions and events. This was done in a descriptive way by Petersen et al. (2013b). Exploratory multivariable analysis could investigate the effect of time-dependent variables on labour duration in subsamples of women who had single interventions and in subsamples of parturients with different sequences of interventions. Consequently, the subdivision of a study population into subsamples which consider sequences would require a larger sample size. However, the exploration of those associations would allow a deeper understanding of the impact of interventions on the labour process. The planned publication of the analysis of the German part of the OptiBIRTH-study for this PhD-thesis underwent several review processes and was criticised for confounding by indication (see Annexe 8.4). One reviewer proposed latent or instrumental variable analysis, a method for controlling for unmeasured confounding (Baiocchi et al. 2014). Subsequently, potential variables for latent variables analysis were discussed with Dr. André Karch, statistical and methodological advisor of this

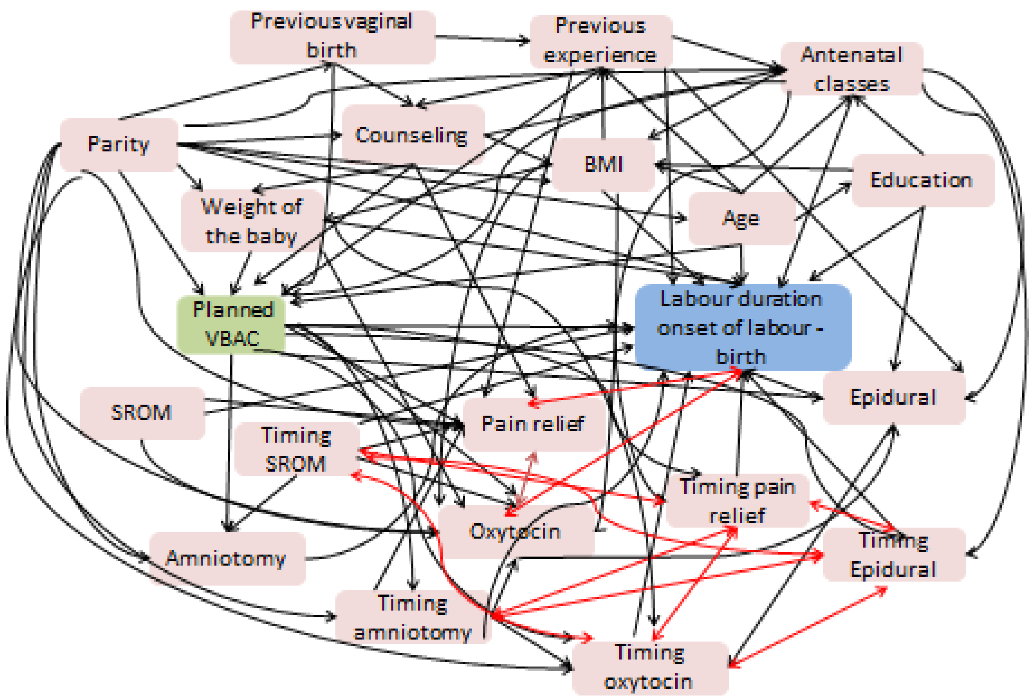


**Figure 8:** Directed acyclic graph for labour duration of VBAC as a dependent process

PhD-thesis and the main supervisor Prof. Dr. Mechthild Gross. Potential latent or instrumental variables in observational studies investigating the process of labour and birth could be care related such as the identity of the midwives who provided the largest proportion of care, the identity of the doctor who attended birth, the provision of one-to-one care or the workload of midwives. These potential latent variables should be associated with the intervention of interest (e.g. timing of oxytocin, epidural or opioid administration) and, through this intervention, with the outcome variables (e.g. labour duration or mode of birth), but not with the risk factor or indication which potentially caused the intervention and not directly with the outcome variable (only through the intervention which is investigated, Figure 9). A significant association between the latent variable and the outcome variable would then indicate the association between the intervention and the outcome and facilitate the interpretation of the results with respect to causal relationship. Future studies could collect several potential latent variables to investigate which one would be most appropriate for this purpose.

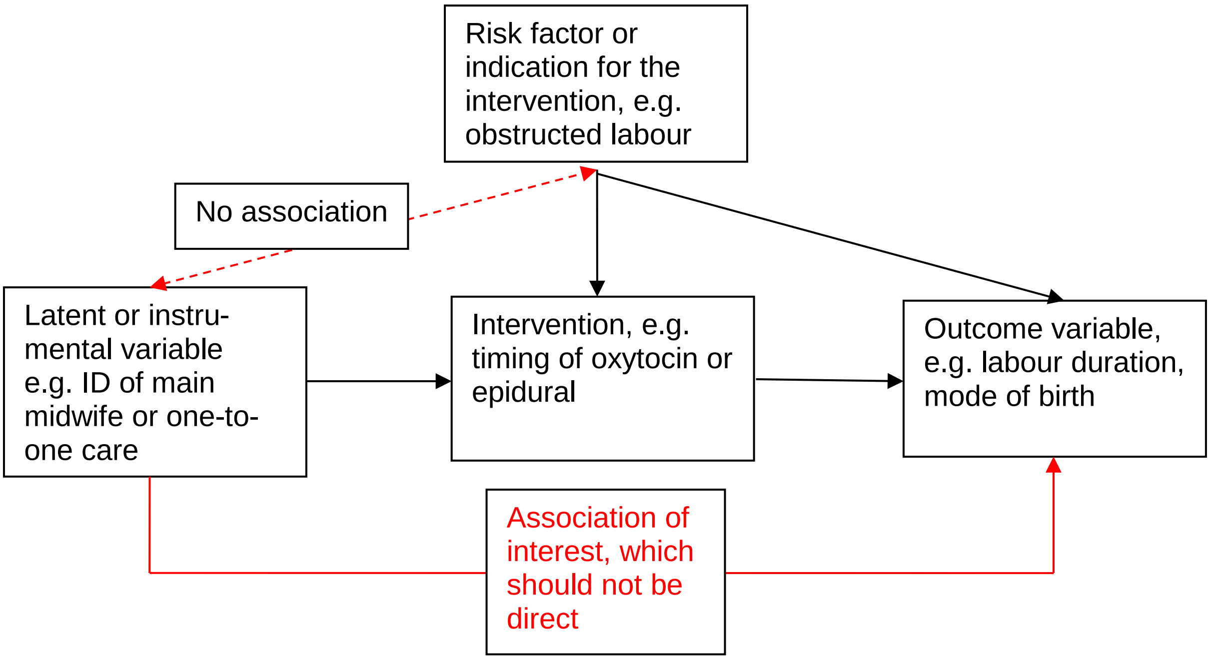


**Figure 9:** Associations between latent variable and risk factor/indication, intervention and outcome

### 4.4. Strengths and limitations

A strength of this PhD-thesis was that two different datasets were used for the analyses, and that these reflect current clinical practice. This enabled the comparison of labour processes of secundiparae with planned VBAC versus those of primiparae and secundiparae with second vaginal birth in a large study population. Additionally, the data of the OptiBIRTH-study with a larger sample of parturients planning a VBAC allowed the comparison of successful VBAC with unplanned c-sections. A strength of both analyses was the use of regression modelling taking into account variabilities in the sites (shared frailty Cox regression models in the analyses of both datasets and random effect logistic regression model in the analysis of the German part of the OptiBIRTH-study). A further benefit of both datasets was the documentation of events and interventions to the nearest minute, enabling precise computations of durations and intervals. The points in time during labour at which events and interventions such as spontaneous and artificial ruptures of the membranes, oxytocin, epidural and opioid administration occurred could therefore be computed with minute precision. Time-dependent covariables (timing of oxytocin, epidural analgesia and opioids) and the outcome variables (overall duration of labour and duration of first and second stage of labour in the ProGeb-analyses, as well as the timing of SROM with the outcome variable duration of intervention-free time interval in the OptiBIRTH-analyses) could be included in the Cox regression models with episode splitting to avoid the time at risk before the interventions being taken into account (Shintani et al. 2009, Daniel et al. 2015). Minimising this risk of bias enhanced the validity of the findings of this research.

The total sample size of the ProGeb-study of 3,963 participants, of whom 3,239 were included in the analysis (with only 724 who gave birth to their third or later child being excluded) was a strength of this secondary analysis. A strength of the data from the OptiBIRTH study was its rigorous collection as part of a cluster-randomised controlled trial. Moreover, the study was designed specifically for women planning VBAC and did not include other parturients. A further strength of this thesis overall was the involvement of the PhD-candidate in the management of the German part of the OptiBIRTH-study, which provided a very close insight into the variables to investigate in the analysis and allowed data cleaning to focus on its use for survival analysis. A particularly relevant example of this was data entry for the timing of onset of labour where heterogeneity in the definition of onset of labour was observed and the outliers could be corrected, which enhanced the accuracy of the data (see Chapter 2.2.3. and 4.2.2.).

Limitations of this thesis were the relatively small sample sizes for women planning a VBAC in both datasets. For this reason, it may not have been possible to achieve statistical significance for rare events and interventions, or where the effects of events and interventions were moderate. This means that any generalisation of the findings must be done with caution. A potential limitation of the secondary analysis of the ProGeb-study was the inclusion of prospective and retrospective data, which showed significant differences (see Chapter 3.1.2.), but related bias was minimised by adjusting the models by the variable “type of documentation”. The inclusion of late preterm births (between 34 and 37 gestational weeks) in the analyses of both datasets could be debated because lower infant´s birthweight impacts on labour duration (Albers 1999, Zhang et al. 2002), but labour management of these late preterm births did not differ from the management for birth at term (DGGG 2006, DGGG 2012), and the multivariable Cox regression models were adjusted for infant´s birthweight as a possible confounder. Further challenges in the analyses of both datasets for this PhD-thesis were the multicentre character of the studies with differences in maternity care between the sites but the associated risk of bias was minimised by using shared frailty Cox regression and random effect logistic regression (as described above in this chapter), and the use of multiple sites is likely to add to the generalisability of the findings.

Another limitation of the secondary analysis of the ProGeb-study was that no indication for the c-section was recorded in the dataset and, therefore, the stage of labour progress at which the c-section was performed, could not be taken into account. Additionally, in the OptiBIRTH-trial, participants eager to participate in the study were likely to be motivated to plan for a VBAC and may have differed from the general population, weakening generalisability because of the potential for selection bias. Furthermore, the impact of missing data in the OptiBIRTH-dataset had to be minimised through multiple imputation. As described in chapter sections 4.3.4 and 4.3.5, the causal relationship and the interpretation of the results were challenging. Without the collection of data for variables which could be used as latent variables and without including a time-splitting variable into the model to control for the supposed baseline acceleration of the labour progress, the interpretation of the results was challenging and supports only cautious conclusions. Therefore, the potential value of both studies and of the contribution made by the women who took part in them, might not have been fully exploited because of these issues with the collected data, which was beyond the control of the PhD-student.

## 4.5. Implications for clinical practice

Scott (2014) reviewed evidence and experiences, and concluded that a safe and successful VBAC is feasible with a conscious intrapartal management. The findings presented in this PhD-thesis help to move this forward by providing knowledge about the process of labour for women with planned VBAC, enabling improved decision making for optimal labour and birth management. Although further research in larger samples, with additional variables and using alternative statistical methods, will help to improve the evidence base further and support the drawing of more conclusions, this thesis adds important new insights into labour and birth processes of women with planned VBAC. It shows that timing of interventions and events in secundiparae with planned VBAC resemble those of primiparae and differ significantly from those of secundiparae with second vaginal birth. This will help to prevent too high expectations regarding the labour progress of secundiparae with planned VBAC and avoid diagnoses of labour dystocia when only patience and time are required for a successful vaginal birth (ACOG 2014). Shorter labour durations and stronger and more effective endogenous uterine contraction were found to be associated with higher odds for a vaginal birth. Again, these findings will impact on labour management, because on one hand, labour management should aim to foster endogenous uterine contraction and on the other hand, there is a further indication that parturients with a previous c-section should be allowed enough time to give birth vaginally and the unnecessary termination of the labour process by c-section should be avoided (ACOG 2014). This evidence adds to the existing evidence base that clinicians and midwives should motivate women to change positions and use upright positions to shorten labour in a physiological way (Lawrence et al. 2013, Desseauve et al. 2017). In contrast, although lithotomy positions might facilitate the monitoring of fetal heart rate and uterine contractions, as well as the performance of interventions, these have been found to have effects on the course of labour and the comfort of the women even if the biomechanical mechanisms for these effects are not clear (Desseauve et al. 2017).

Women who are pregnant following a c-section have been described as “groping through the fog” when deciding on the mode of birth and need evidence-based and consistent information (Lundgren et al. 2012). The finding of the secondary analysis of the ProGeb-study (Grylka-Baeschlin et al. 2016) that the second stage of labour for secundiparae with planned VBAC might be shorter than for primiparae can be used to motivate women to start labour. This information should be promoted in antenatal counselling and antenatal classes. Even if unplanned c-sections were found to be associated with increased risks compared to elective c-sections (El-Sayed et al. 2007), previous experience of onset of labour seems to help the long-term outcomes of mother and child (Mesquita et al. 2013, Stokholm et al. 2016, Sevelsted et al. 2016). The microbiome of the child was found to be more physiological after vaginal birth and also after c-sections which were performed after spontaneous rupture of the membranes and later immune-mediated diseases were less frequent (Stokholm et al. 2016, Sevelsted et al. 2016). VBAC rates can only be increased and overall c-section rates decreased, if more women try VBAC and go into labour (ACOG 2014). Going into labour also has the advantage for future pregnancies and births, because the risk of uterine rupture, stillbirth and haemorrhage in subsequent pregnancies and birth are lower if the c-section was performed after onset of labour (Kok et al. 2014). Additionally, avoiding multiple c-sections decreases relevant risks for the mother (Marshall et al. 2011). Improving access to reliable, evidence-based information encouraging women to plan a VBAC might help to increase VBAC rates and should therefore be part of the counselling process for pregnant women who have had a previous c-section.

### 4.6. Outlook

Future studies should continue to compare labour processes between secundiparae with planned VBAC, primiparae and secundiparae with second vaginal birth, as well as comparing successful VBAC and unplanned c-section in larger samples. This would allow a more in-depth investigation of the hypotheses generated by the analysis of both datasets for this PhD-thesis, given that these had sample sizes that were too small for some topics. An opportunity for the comparison of successful VBAC and unplanned c-section will arise in the near future because the OptiBIRTH-consortium has agreed to extend the analysis of the effect of intrapartal predictors on the success of VBAC that were done by the PhD-candidate using the German data of the OptiBIRTH-study. This has been included in the dissemination plan of OptiBIRTH, using the data from all three trial countries with the working title "Intrapartal predictors for the success of planned VBAC in three countries" and will be led by the PhD-candidate using methods developed for this PhD-thesis but will also draw on additional input from other investigators. This further analysis of the OptiBIRTH-study will investigate factors associated with the success of VBAC in a larger sample and give the opportunity to compare the results from the three European countries: Ireland, Italy and Germany. The larger sample might provide sufficient power for statistically significant results for rare events or interventions and the comparison between the countries may highlight the impact and relevance of different clinical practices. This further analysis of the OptiBIRTH-data will address some of the issues raised during the unsuccessful submission of the planned second publication of this PhD-thesis (see Annex 8.4.). The comments from reviewers, which became more demanding with lower ranked journals, highlighted three areas: 1) complexity of the research questions relating to predictors for the success of VBAC and the comparison of the intervention-free time-interval which did not lead to a straightforward aim for a single journal article, 2) too small a sample size for publication in a high-impact journal and 3) statistical analyses which made the article too complex for low ranked and more practical oriented journals. The proposed publication based on the whole OptiBIRTH-dataset and focusing on the predictors for the success of VBAC would have a clearer aim, larger sample size and an international perspective which should make it more likely to be published in a high-impact journal.

Future cohort studies to investigate the dynamic of labour and birth should collect variables which have the potential to be used as latent or instrumental variables in order to check which variables would be appropriate for this purpose (see Chapter 4.3.5.). This would pre-empt criticism of confounding by indication in future studies. Additionally, variables for controlling the suspected baseline accelerating effect of the labour progress should be included in Cox regression models to facilitate the interpretation of the accelerating or slowing down effects of time-dependent covariables. It is also unclear which methodologic approach would be most appropriate to research labour duration (Zhang et al. 2002, Gross et al. 2014) and future studies could compare different statistical methods. Therefore, these studies should collect the exact timing of events and interventions and of vaginal examinations for the assessment of cervical dilatations. This would enable Cox regression modelling with the outcome variables of overall duration of labour and the duration of labour stages as well interval-censored regression modelling with the outcome variables ‘time to progress from one centimetre of cervical dilatation to the next’ (Zhang et al. 2002, Gross et al. 2014). Having both these analyses for the same dataset would strengthen the discussion of the impact of the variables.

## 4.7. Conclusion

The dynamic nature of the methods used in the secondary analysis of the ProGeb-study and the analysis of observational data from the German part of OptiBIRTH provided new and important insights into the labour processes of women with planned VBAC. Labour and birth characteristics of secundiparae with planned VBAC differed from those of primiparae and secundiparae with second vaginal birth, suggesting that secundiparae with planned VBAC should be considered as a distinct category of birthing mothers. In the future, pregnant women who have had a previous c-section could be motivated to plan VBAC by the finding that their second stage of labour might be shorter than that for primiparous women and this finding should be integrated into antenatal courses and antenatal care. Knowledge about intrapartal predictors for the success of VBAC is important for optimal labour and birth management. Future parturients with planned VBAC may benefit from a management fostering endogenous uterine contractions to enhance the chances of success. The results of this PhD-thesis are also important for scientific progress by refining the need for further research on the labour and birth process of women planning a VBAC in larger samples. The study also confirmed the boundaries of observational studies in this topic area. The identification of causal relationships from significant results and the interpretation of the accelerating or slowing effects of time-dependent predictors were challenging and require further research, as highlighted in this thesis. In summary, the findings of this PhD-thesis provide new evidence and knowledge on how women with a previous c-section give birth in current practice and open avenues for further studies to investigate the areas of ongoing uncertainty that the candidate’s research has identified.

## 5. References

Abdel Aziz, A., Abd Rabbo, A., Sayed Ahmed, W.A. et al. 2016, "Validation of the close-to-delivery prediction model for vaginal birth after cesarean delivery in a Middle Eastern cohort", *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics,* vol. 134, no. 1, pp. 75-78.

Abildgaard, H., Ingerslev, M.D., Nickelsen, C. & Secher, N.J. 2013, "Cervical dilation at the time of cesarean section for dystocia -- effect on subsequent trial of labor", *Acta Obstetricia et Gynecologica Scandinavica,* vol. 92, no. 2, pp. 193-197.

Ajadi, M.A., Kuti, O., Orji, E.O. et al. 2006, "The effect of amniotomy on the outcome of spontaneous labour in uncomplicated pregnancy", *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology,* vol. 26, no. 7, pp. 631-634.

Albers, L.L., Schiff, M. & Gorwoda, J.G. 1996, "The length of active labor in normal pregnancies", *Obstetrics and gynecology,* vol. 87, no. 3, pp. 355-359.

Albers, L.L. 1999, "The duration of labor in healthy women", *Journal of perinatology: official journal of the California Perinatal Association,* vol. 19, no. 2, pp. 114-119.

Almgren, M., Schlinzig, T., Gomez-Cabrero, D. et al.. 2014, "Cesarean delivery and hematopoietic stem cell epigenetics in the newborn infant: implications for future health?", *American Journal of Obstetrics and Gynecology,* vol. 211, no. 5, pp. 502.e1-502.e8.

Al-Shaikh, G. & Al-Mandeel, H. 2013, "The outcomes of trial of labour after cesarean section following induction of labour compared to spontaneous labour", *Archives of Gynecology and Obstetrics,* vol. 287, no. 6, pp. 1099-1103.

Al-Zirqi, I., Stray-Pedersen, B., Forsen, L. et al. 2016, "Uterine rupture: trends over 40 years", *BJOG : an international journal of obstetrics and gynaecology,* vol. 123, no. 5, pp. 780-787.

Al-Zirqi, I., Daltveit, A.K., Forsen, L. et al. 2017, "Risk factors for complete uterine rupture", *American Journal of Obstetrics and Gynecology,* vol. 216, no. 2, pp. 165.e1-165.e8.

American College of Obstetricians and Gynecologists (ACOG), Society for Maternal-Fetal Medicine, Caughey, A.B. et al. 2014, "Safe prevention of the primary cesarean delivery", *American Journal of Obstetrics and Gynecology,* vol. 210, no. 3, pp. 179-193.

Annessi, E., Del Giovane, C., Magnani, L. et al. 2016, "A modified prediction model for VBAC, in a European population", *The journal of maternal-fetal & neonatal medicine: the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* vol. 29, no. 3, pp. 435-439.

Arulkumaran, S., Gibb, D.M., Lun, K.C. et al. 1984, "The effect of parity on uterine activity in labour", *British journal of obstetrics and gynaecology,* vol. 91, no. 9, pp. 843-848.

Ashwal, E., Wertheimer, A., Aviram, A. et al. 2016, "Prediction of successful trial of labor after cesarean - the benefit of prior vaginal delivery", *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* vol. 29, no. 16, pp. 2665-2670.

Aune, I., Hoston, M.A., Kolshus, N.J. & Larsen, C.E.G. 2017, "Nature works best when allowed to run its course. The experience of midwives promoting normal births in a home birth setting", *Midwifery,* vol. 50, pp. 21-26.

Bailit, J.L., Dierker, L., Blanchard, M.H. & Mercer, B.M. 2005, "Outcomes of women presenting in active versus latent phase of spontaneous labor", *Obstetrics and gynecology,* vol. 105, no. 1, pp. 77-79.

Baiocchi, M., Cheng, J. & Small, D.S. 2014, "Instrumental variable methods for causal inference", *Statistics in medicine,* vol. 33, no. 13, pp. 2297-2340.

Balachandran, L., Vaswani, P.R. & Mogotlane, R. 2014, "Pregnancy outcome in women with previous one cesarean section", *Journal of clinical and diagnostic research : JCDR,* vol. 8, no. 2, pp. 99-102.

Bangal, V.B., Giri, P.A., Shinde, K.K. & Gavhane, S.P. 2013, "Vaginal birth after cesarean section", *North American journal of medical sciences,* vol. 5, no. 2, pp. 140-144.

Baranov, A., Gratacos, E., Vikhareva, O. & Figueras, F. 2017, "Validation of the prediction model for success of vaginal birth after cesarean delivery at the university hospital in Barcelona", *The Journal of Maternal-Fetal & Neonatal Medicine,* [Epub ahead of print].

Beloosesky, R., Khatib, N., Ganem, N., Matanes, E. et al. 2017, "Cervical length measured before delivery and the success rate of vaginal birth after cesarean (VBAC)", *The Journal of Maternal-Fetal & Neonatal Medicine,* [Epub ahead of print].

Betran, A.P., Merialdi, M., Lauer, et al. 2007, "Rates of caesarean section: analysis of global, regional and national estimates", *Paediatric and perinatal epidemiology,* vol. 21, no. 2, pp. 98-113.

Bhide, A., Caric, V. & Arulkumaran, S. 2016, "Prediction of vaginal birth after cesarean delivery", *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics,* vol. 133, no. 3, pp. 297-300.

Bickford, C.D. & Janssen, P.A. 2015, "Maternal and newborn outcomes after a prior cesarean birth by planned mode of delivery and history of prior vaginal birth in British Columbia: a retrospective cohort study", *CMAJ open,* vol. 3, no. 2, pp. E158-65.

Baiocchi, M., Cheng, J. & Small, D.S. 2014, "Instrumental variable methods for causal inference", *Statistics in medicine,* vol. 33, no. 13, pp. 2297-2340.

Birara, M. & Gebrehiwot, Y. 2013, "Factors associated with success of vaginal birth after one caesarean section (VBAC) at three teaching hospitals in Addis Ababa, Ethiopia: a case control study", *BMC pregnancy and childbirth,* vol. 13, pp. 31-2393-13-31.

Bland, J.M. & Altman, D.G. 1998, "Survival probabilities (the Kaplan-Meier method)", *BMJ (Clinical research ed.),* vol. 317, no. 7172, pp. 1572.

Blossfeld, H.-., Golsch, K. & Rohwer, G. 2007, *Event History Analysis with Stata,* Psychology Press, Tayler & Francis Group, New York, London.

Brierley, G., Brabyn, S., Torgerson, D. & Watson, J. 2012, "Bias in recruitment to cluster randomized trials: a review of recent publications", *Journal of evaluation in clinical practice,* vol. 18, no. 4, pp. 878-886.

Brown, H.C., Paranjothy, S., Dowswell, T. & Thomas, J. 2013, "Package of care for active management in labour for reducing caesarean section rates in low-risk women", *The Cochrane database of systematic reviews,* vol. 9, pp. CD004907.

Bugg, G.J., Siddiqui, F. & Thornton, J.G. 2013, "Oxytocin versus no treatment or delayed treatment for slow progress in the first stage of spontaneous labour", *The Cochrane database of systematic reviews,* vol. 6, pp. CD007123.

Bundeszentrale für politische Bildung (BPB*). Alter der Mütter bei der Geburt ihrer Kinder*. Available: http://www.bpb.de/nachschlagen/zahlen-und-fakten/soziale-situation-in-deutschland/61556/alter-der-muetter [Accessed 01.01.2017].

Centres for Disease Control and Prevention (CDC). 2010, “Increasing Questionnaire Response Rates”, Evalution Briefs, Available from: https://www.cdc.gov/healthyyouth/evaluation/pdf/brief21.pdf, [Accessed 26.06.2017].

Chelmow, D., Kilpatrick, S.J. & Laros, R.K. 1993, "Maternal and neonatal outcomes after prolonged latent phase", *Obstetrics and gynecology,* vol. 81, no. 4, pp. 486-491.

Chen, H.H., Lai, J.C., Hwang, S.J. et al. 2017, "Understanding the relationship between cesarean birth and stress, anxiety, and depression after childbirth: A nationwide cohort study", *Birth (Berkeley, Calif.),* [Epub ahead of print].

Cheng, H.G. & Phillips, M.R. 2014, "Secondary analysis of existing data: opportunities and implementation", *Shanghai archives of psychiatry,* vol. 26, no. 6, pp. 371-375.

Cheng, Y.W., Eden, K.B., Marshall, N. et al. 2011, "Delivery after prior cesarean: maternal morbidity and mortality", *Clinics in perinatology,* vol. 38, no. 2, pp. 297-309.

Christmann-Schmid, C., Raio, L., Scheibner, K. et al. 2016, "Back to "once a caesarean: always a caesarean"? A trend analysis in Switzerland", *Archives of Gynecology and Obstetrics,* vol. 294, no. 5, pp. 905-910.

Clark, S.M., Carver, A.R. & Hankins, G.D. 2012, "Vaginal birth after cesarean and trial of labor after cesarean: what should we be recommending relative to maternal risk: benefit?", *Women's health (London, England),* vol. 8, no. 4, pp. 371-383.

Clarke, M., Savage, G., Smith, V. et al. 2015, "Improving the organisation of maternal health service delivery and optimising childbirth by increasing vaginal birth after caesarean section through enhanced women-centred care (OptiBIRTH trial): study protocol for a randomised controlled trial (ISRCTN10612254)", *Trials,* vol. 16, pp. 542-015-1061-y.

Clarke, M., Devane, D., Gross, M.M., Morano, S., Lundgren, I., Sinclair, M., Putman, K., Beech, B.L., Vehvilinen-Julkunen, K., Nieuwenhuijze, M., Wiseman, H., Smith, V., Daly, D., Savage, G., Newell, J., Grylka-Baeschlin, S. et al. submitted, "OptiBIRTH: a cluster randomised trial of a complex intervention to increase vaginal birth after caesarean section (ISRCTN10612254)", *in preparation.*

Colmorn, L.B., Krebs, L., Klungsoyr, K. et al. 2017, "Mode of first delivery and severe maternal complications in the subsequent pregnancy", *Acta Obstetricia et Gynecologica Scandinavica,* [Epub ahead of print].

Cragin, E.B. 1916, "Conservatism in Obstetrics", *The New York Medical Journal,* vol. 104, pp. 1-3.

Curtin, S.C., Gregory, K.D., Korst, L.M. & Uddin, S.F. 2015, "Maternal Morbidity for Vaginal and Cesarean Deliveries, According to Previous Cesarean History: New Data From the Birth Certificate, 2013", *National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System,* vol. 64, no. 4, pp. 1-13, back cover.

Dahlen, H.G., Kennedy, H.P., Anderson, et al. 2013, "The EPIIC hypothesis: intrapartum effects on the neonatal epigenome and consequent health outcomes", *Medical hypotheses,* vol. 80, no. 5, pp. 656-662.

Daniel, S., Koren, G., Lunenfeld, E. & Levy, A. 2015, "Immortal time bias in drug safety cohort studies: spontaneous abortion following nonsteroidal antiinflammatory drug exposure", *American Journal of Obstetrics and Gynecology,* vol. 212, no. 3, pp. 307.e1-307.e6.

Davey, M.A., McLachlan, H.L., Forster, D. & Flood, M. 2013, "Influence of timing of admission in labour and management of labour on method of birth: results from a randomised controlled trial of caseload midwifery (COSMOS trial)", *Midwifery,* vol. 29, no. 12, pp. 1297-1302.

Dekker, G.A., Chan, A., Luke, C.G. et al. 2010, "Risk of uterine rupture in Australian women attempting vaginal birth after one prior caesarean section: a retrospective population-based cohort study", *BJOG: an international journal of obstetrics and gynaecology,* vol. 117, no. 11, pp. 1358-1365.

Desseauve, D., Fradet, L., Lacouture, P. & Pierre, F. 2017, "Position for labor and birth: State of knowledge and biomechanical perspectives", *European journal of obstetrics, gynecology, and reproductive biology,* vol. 208, pp. 46-54.

Dogu, S., Kaycan, N., Karsli, B. & Bigat, Z. 2016, “The Effects of Early and Late Epidural Analgesia on Delivery Period and Labour Practice”, *International Journal of Clinical Anesthesiology,* vol. 4, no. 1, pp. 1053.

El-Sayed, Y.Y., Watkins, M.M., Fix, M. et al. 2007, "Perinatal outcomes after successful and failed trials of labor after cesarean delivery", *American Journal of Obstetrics and Gynecology,* vol. 196, no. 6, pp. 583.e1-5; discussion 583.e5.

Enkin, M. 1989, "Labour and delivery following previous caesarean section, Chapter 70" in *Effective Care during Pregnancy and Birth, Vol. II*, ed. Chalmers I., Enkin M., Keirse M.J.N.C., Oxofrd University Press, Oxford, pp. 1196-1215.

Enkin, M.W., Keirse, M.J., Renfrew, M.J. & Neilson, J.P. 1995, "Effective care in pregnancy and childbirth: a synopsis", *Birth (Berkeley, Calif.),* vol. 22, no. 2, pp. 101-110.

EURO-PERISTAT. 2013, “European Perinatal Health Report, Health and Care of Pregnant Women and Babies in Europe in 2010”. Available from: http://www.europeristat.com/reports/european-perinatal-health-report-2010.html, [Accessed 25.12.2016].

Fagerberg, M.C., Marsal, K., Ekstrom, P. & Kallen, K. 2013, "Indications for first caesarean and delivery mode in subsequent trial of labour", *Paediatric and perinatal epidemiology,* vol. 27, no. 1, pp. 72-80.

Fagerberg, M.C., Marsal, K. & Kallen, K. 2015, "Predicting the chance of vaginal delivery after one cesarean section: validation and elaboration of a published prediction model", *European journal of obstetrics, gynecology, and reproductive biology,* vol. 188, pp. 88-94.

Faranesh, R. & Salim, R. 2011, "Labor progress among women attempting a trial of labor after cesarean. Do they have their own rules?", *Acta Obstetricia et Gynecologica Scandinavica,* vol. 90, no. 12, pp. 1386-1392.

Fawsitt, C.G., Bourke, J., Greene, R.A. et al. 2013, "At what price? A cost-effectiveness analysis comparing trial of labour after previous caesarean versus elective repeat caesarean delivery", *PloS one,* vol. 8, no. 3, pp. e58577.

Flamm, B.L. 2001, "Vaginal birth after caesarean (VBAC)", *Best practice & research.Clinical obstetrics & gynaecology,* vol. 15, no. 1, pp. 81-92.

Friedman, E. 1954, "The graphic analysis of labor", *American Journal of Obstetrics and Gynecology,* vol. 68, no. 6, pp. 1568-1575.

Friedman, E.A. 1955, "Primigravid labor; a graphicostatistical analysis", *Obstetrics and gynecology,* vol. 6, no. 6, pp. 567-589.

Friedman, E.A. & Sachtleben, M.R. 1963, "Amniotomy and the Course of Labor", *Obstetrics and gynecology,* vol. 22, pp. 755-770.

Gagnon-Gervais, K., Bujold, E., Iglesias, M.H. et al. 2012, "Early versus late amniotomy for labour induction: a randomized controlled trial", *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* vol. 25, no. 11, pp. 2326-2329.

German Society of Obstetrics and Gynaecology (DGGG). 2006, “Procedure with premature rupture of the membranes, AWMF guideline Nr. 015/029”, Available from: https://www.dggg.de/fileadmin/documents/leitlinien/archiviert/federfuehrend/015029_Empfehlungen_zum_Vorgehen_beim_vorzeitigen_Blasensprung/015029_2010.pdf , [Accessed 12.06.2017].

German Society of Obstetrics and Gynaecology (DGGG). 2012, “Application of the CTG during pregnancy and birth, AWMF guideline Nr. 015/036”, Available form: https://www.dggg.de/fileadmin/documents/leitlinien/archiviert/federfuehrend/015036_Anwendung_von_CTG_waehrend_Schwangerschaft_und_Geburt/015036_2012.pdf [Accessed 12.06.2017].

Ghafarzadeh, M., Moeininasab, S. & Namdari, M. 2015, "Effect of early amniotomy on dystocia risk and cesarean delivery in nulliparous women: a randomized clinical trial", *Archives of Gynecology and Obstetrics,* vol. 292, no. 2, pp. 321-325.

Goel, M.K., Khanna, P & Kishore, J. 2010, “Understanding survival analysis: Kaplan-Meier estimate”, *International Journal of Ayurveda Research,* vol. 1, no. 4, pp. 274-278.

Graseck, A.S., Odibo, A.O., Tuuli, M. et al. 2012, "Normal first stage of labor in women undergoing trial of labor after cesarean delivery", *Obstetrics and gynecology,* vol. 119, no. 4, pp. 732-736.

Grobman, W.A., Lai, Y., Landon, M.B. et al. 2007, "Development of a nomogram for prediction of vaginal birth after cesarean delivery", *Obstetrics and gynecology,* vol. 109, no. 4, pp. 806-812.

Gross, M.M. 2001, *Gebären als Prozess: Empirische Befunde für eine wissenschaftlicheNeuorientierung,* Verlag Hans Huber, Bern; Göttingen; Toronto; Seattle.

Gross, M.M., Drobnic, S. & Keirse, M.J. 2005, "Influence of fixed and time-dependent factors on duration of normal first stage labor", *Birth (Berkeley, Calif.),* vol. 32, no. 1, pp. 27-33.

Gross, M.M., Schwarz, C., Burian, R.A. et al. 2007, "Midwifery teams differ in their opinions regarding study participation", *Birth Issues,* vol. 15, no. 3/4, pp. 77-82.

Gross, M.M., Burian, R.A., Fromke, C. et al. 2009, "Onset of labour: women's experiences and midwives' assessments in relation to first stage duration", *Archives of Gynecology and Obstetrics,* vol. 280, no. 6, pp. 899-905.

Gross, M.M., Fromke, C. & Hecker, H. 2014, "The timing of amniotomy, oxytocin and neuraxial analgesia and its association with labour duration and mode of birth", *Archives of Gynecology and Obstetrics,* vol. 289, no. 1, pp. 41-48.

Gross, M.M., Matterne, A., Berlage, S. et al. 2015, "Interinstitutional variations in mode of birth after a previous caesarean section: a cross-sectional study in six German hospitals", *Journal of perinatal medicine,* vol. 43, no. 2, pp. 177-184.

Grylka-Baeschlin, S., van Teijlingen, E. & Gross, M.M. 2014, "Cultural differences in postnatal quality of life among German-speaking women - a prospective survey in two countries", *BMC pregnancy and childbirth,* vol. 14, pp. 277-2393-14-277.

Grylka-Baeschlin, S., Petersen, A., Karch, A. & Gross, M.M. 2016, "Labour duration and timing of interventions in women planning vaginal birth after caesarean section", *Midwifery,* vol. 34, pp. 221-229, DOI: 10.1016/j.midw.2015.11.004.

Guise, J.M., Denman, M.A., Emeis, C. et al. 2010a, "Vaginal birth after cesarean: new insights on maternal and neonatal outcomes", *Obstetrics and gynecology,* vol. 115, no. 6, pp. 1267-1278.

Guise, J.M., Eden, K., Emeis, C., Denman, M.A. et al. 2010b, "Vaginal birth after cesarean: new insights", *Evidence report/technology assessment,* vol. (191), no. 191, pp. 1-397.

Guiterrez, R.G. & and Stata Cooperation 2002, “Parametric frailty and shared frailty survival models”, *The Stata Journal*, vol. 2, no. 1, pp. 22-44.

Gurol-Urganci, I., Bou-Antoun, S., Lim, C.P. et al. 2013, "Impact of Caesarean section on subsequent fertility: a systematic review and meta-analysis", *Human reproduction (Oxford, England),* vol. 28, no. 7, pp. 1943-1952.

Hahn, S., Puffer, S., Torgerson, D.J. & Watson, J. 2005, "Methodological bias in cluster randomised trials", *BMC medical research methodology,* vol. 2, pp. 5-10.

Hanley, G.E., Munro, S., Greyson, D. et al. 2016, "Diagnosing onset of labor: a systematic review of definitions in the research literature", *BMC pregnancy and childbirth,* vol. 16, no. 1, pp. 71-016-0857-4.

Harlass, F.E. & Duff, P. 1990, "The duration of labor in primiparas undergoing vaginal birth after cesarean delivery", *Obstetrics and gynecology,* vol. 75, no. 1, pp. 45-47.

Healy, P., Smith, V., Savage, G., Clarke, M., Devane, D., Gross, M.M., Morano, S., Daly, D., Grylka-Baeschlin, S. et al. submitted, "Process Evaluation for OptiBIRTH, a Randomised Controlled Trial of a Complex Intervention designed to increase rates of vaginal birth after caesarean section", *under review by Trials*.

Hernan, M.A., Hernandez-Diaz, S., Werler, M.M. & Mitchell, A.A. 2002, "Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology", *American Journal of Epidemiology,* vol. 155, no. 2, pp. 176-184.

Hildingsson, I., Blix, E., Hegaard, H. et al. 2015, "How Long Is a Normal Labor? Contemporary Patterns of Labor and Birth in a Low-Risk Sample of 1,612 Women from Four Nordic Countries", *Birth (Berkeley, Calif.),* vol. 42, no. 4, pp. 346-353.

Holland, J.G., Dupre, A.R., Blake, P.G. et al. 1992, "Trial of labor after cesarean delivery: experience in the non-university level II regional hospital setting", *Obstetrics and gynecology,* vol. 79, no. 6, pp. 936-939.

Hosmer, D.W. & Lemeshow, S. 2000, *Applied Logistic Regression,* 2nd edition edn, John Wiley and Sons, New York, Toronto.

Inbar, R., Mazaaki, S., Kalter, A. et al. 2017, "Trial of labour after caesarean (TOLAC) is associated with increased risk for instrumental delivery", *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology,* vol. 37, no. 1, pp. 44-47.

Janssen, P.A., Stienen, J.J., Brant, R. & Hanley, G.E. 2016, "A Predictive Model for Cesarean Among Low-Risk Nulliparous Women in Spontaneous Labor at Hospital Admission", *Birth (Berkeley, Calif.),* vol. 44, no. 1, pp. 21-28.

Johnsten, M.P. 2014, "Secondary Data Analysis: A Method of which the Time Has Come", *Qualitative and Quantitative Methods in Libraries (QQML),* vol. 3, pp.619 –626.

Jones, L., Othman, M., Dowswell, T. et al. 2012, "Pain management for women in labour: an overview of systematic reviews", *The Cochrane database of systematic reviews,* vol. 3, pp. CD009234.

Jones, M. & Fowler, R. 2016, "Immortal time bias in observational studies of time-to-event outcomes", *Journal of critical care,* vol. 36, pp. 195-199.

Kainu, J.P., Halmesmaki, E., Korttila, K.T. & Sarvela, P.J. 2016, "Persistent Pain After Cesarean Delivery and Vaginal Delivery: A Prospective Cohort Study", *Anesthesia and Analgesia,* vol. 123, no. 6, pp. 1535-1545.

Kaplanoglu, M., Bulbul, M., Kaplanoglu, D. & Bakacak, S.M. 2015, "Effect of multiple repeat cesarean sections on maternal morbidity: data from southeast Turkey", *Medical science monitor: international medical journal of experimental and clinical research,* vol. 21, pp. 1447-1453.

Karlstrom, A., Lindgren, H. & Hildingsson, I. 2013, "Maternal and infant outcome after caesarean section without recorded medical indication: findings from a Swedish case-control study", *BJOG : an international journal of obstetrics and gynaecology,* vol. 120, no. 4, pp. 479-86; discussion 486.

Kealy, M.A., Small, R.E. & Liamputtong, P. 2010, "Recovery after caesarean birth: a qualitative study of women's accounts in Victoria, Australia", *BMC pregnancy and childbirth,* vol. 10, pp. 47-2393-10-47.

Knight, H.E., Gurol-Urganci, I., van der Meulen, J.H. et al. 2014, "Vaginal birth after caesarean section: a cohort study investigating factors associated with its uptake and success", *BJOG : an international journal of obstetrics and gynaecology,* vol. 121, no. 2, pp. 183-192.

Kok, N., Wiersma, I.C., Opmeer, B.C. et al. 2013, "Sonographic measurement of lower uterine segment thickness to predict uterine rupture during a trial of labor in women with previous Cesarean section: a meta-analysis", *Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology,* vol. 42, no. 2, pp. 132-139.

Kok, N., Ruiter, L., Hof, M. et al. 2014, "Risk of maternal and neonatal complications in subsequent pregnancy after planned caesarean section in a first birth, compared with emergency caesarean section: a nationwide comparative cohort study", *BJOG : an international journal of obstetrics and gynaecology,* vol. 121, no. 2, pp. 216-223.

Kok, N., Ruiter, L., Lindeboom, R. et al. 2015, "Elective repeat cesarean delivery compared with trial of labor after a prior cesarean delivery: a propensity score analysis", *European journal of obstetrics, gynecology, and reproductive biology,* vol. 195, pp. 214-218.

Kolip, P., Nolting, H. & Zich, K. 2012, "Faktencheck Gesundheit Kaiserschnittgeburten – Entwicklung und regionale Verteilung, Erstellt im Auftrag der Bertelsmann Stiftung", Available from: https://www.bertelsmann-stiftung.de/de/publikationen/publikation/did/faktencheck-gesundheit-kaiserschnitt/, [Accessed 24.12.2016].

Kyvernitakis, I., Reichelt, J., Kyvernitakis, A. et al. 2014, "Trends of vaginal birth after cesarean delivery in Germany from 1990 to 2012: a population-based study", *Zeitschrift fur Geburtshilfe und Neonatologie,* vol. 218, no. 5, pp. 203-209.

Landon, M.B., Hauth, J.C., Leveno, K.J., et al. 2004, "Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery", *The New England journal of medicine,* vol. 351, no. 25, pp. 2581-2589.

Landon, M.B., Leindecker, S., Spong, C.Y. et al. 2005, "The MFMU Cesarean Registry: factors affecting the success of trial of labor after previous cesarean delivery", *American Journal of Obstetrics and Gynecology,* vol. 193, no. 3, pp. 1016-1023.

Laughon, S.K., Branch, D.W., Beaver, J. & Zhang, J. 2012, "Changes in labor patterns over 50 years", *American Journal of Obstetrics and Gynecology,* vol. 206, no. 5, pp. 419.e1-419.e9.

Lauzon, L. & Hodnett, E. 2000, "Antenatal education for self-diagnosis of the onset of active labour at term", The Cochrane database of systematic reviews, vol. 2, pp. CD000935.

Lawrence, A., Lewis, L., Hofmeyr, G.J. & Styles, C. 2013, "Maternal positions and mobility during first stage labour", *The Cochrane database of systematic reviews*, vol. 10, pp. CD003934.

Lee, S.M., Lee, K.A., Lee, J. et al. 2010, "Early rupture of membranes" after the spontaneous onset of labor as a risk factor for cesarean delivery", *European journal of obstetrics, gynecology, and reproductive biology,* vol. 148, no. 2, pp. 152-157.

Lewkowitz, A.K., Nakagawa, S., Thiet, M.P. & Rosenstein, M.G. 2015, "Effect of stage of initial labor dystocia on vaginal birth after cesarean success", *American Journal of Obstetrics and Gynecology,* vol. 213, no. 6, pp. 861.e1-861.e5.

Lundgren, I., Begley, C., Gross, M.M. & Bondas, T. 2012, "'Groping through the fog': a metasynthesis of women's experiences on VBAC (Vaginal birth after Caesarean section)", *BMC pregnancy and childbirth,* vol. 12, pp. 85-2393-12-85.

Lundgren, I., Smith, V., Nilsson, C. et al. 2015a, "Clinician-centred interventions to increase vaginal birth after caesarean section (VBAC): a systematic review", *BMC pregnancy and childbirth,* vol. 15, pp. 16-015-0441-3.

Lundgren, I., van Limbeek, E., Vehvilainen-Julkunen, K. & Nilsson, C. 2015b, "Clinicians' views of factors of importance for improving the rate of VBAC (vaginal birth after caesarean section): a qualitative study from countries with high VBAC rates", *BMC pregnancy and childbirth,* vol. 15, pp. 196-015-0629-6.

Macfarlane, A.J., Blondel, B., Mohangoo, A.D. et al. 2016, "Wide differences in mode of delivery within Europe: risk-stratified analyses of aggregated routine data from the Euro-Peristat study", *BJOG: an international journal of obstetrics and gynaecology,* vol. 123, no. 4, pp. 559-568.

Macones, G.A., Hausman, N., Edelstein, R. et al. 2001, "Predicting outcomes of trials of labor in women attempting vaginal birth after cesarean delivery: a comparison of multivariate methods with neural networks", *American Journal of Obstetrics and Gynecology,* vol. 184, no. 3, pp. 409-413.

Macones, G.A., Cahill, A., Stamilio, D.M. & Odibo, A.O. 2012, "The efficacy of early amniotomy in nulliparous labor induction: a randomized controlled trial", *American Journal of Obstetrics and Gynecology,* vol. 207, no. 5, pp. 403.e1-403.e5.

Maykin, M.M., Mularz, A.J., Lee, L.K. & Valderramos, S.G. 2017, "Validation of a Prediction Model for Vaginal Birth after Cesarean Delivery Reveals Unexpected Success in a Diverse American Population", *AJP reports,* vol. 7, no. 1, pp. e31-e38.

Menacker, F., Declercq, E. & Macdorman, M.F. 2006, "Cesarean delivery: background, trends, and epidemiology", *Seminars in perinatology,* vol. 30, no. 5, pp. 235-241.

Marshall, N.E., Fu, R. & Guise, J.M. 2011, "Impact of multiple cesarean deliveries on maternal morbidity: a systematic review", *American Journal of Obstetrics and* Gynecology, vol. 205, no. 3, pp. 262.e1-262.e8.

Masinter, L.M., Feinglass, J., Grobman, W.A. & Simon, M.A. 2014, "Likelihood of continued childbearing after cesarean delivery in the United States", *Obstetrics and gynecology,* vol. 124, no. 1, pp. 111-119.

Metz, T.D., Stoddard, G.J., Henry, E. et al. 2013a, "How do good candidates for trial of labor after cesarean (TOLAC) who undergo elective repeat cesarean differ from those who choose TOLAC?", American Journal of Obstetrics and Gynecology, vol. 208, no. 6, pp. 458.e1-458.e6.

Metz, T.D., Stoddard, G.J., Henry, E. et al. 2013b, "Simple, validated vaginal birth after cesarean delivery prediction model for use at the time of admission", Obstetrics and gynecology, vol. 122, no. 3, pp. 571-578.

Mesquita, D.N., Barbieri, M.A., Goldani, H.A. et al. 2013, "Cesarean Section Is Associated with Increased Peripheral and Central Adiposity in Young Adulthood: Cohort Study", *PloS one,* vol. 8, no. 6, pp. e66827.

Mikolajczyk, R.T., Schmedt, N., Zhang, J. et al. 2013, "Regional variation in caesarean deliveries in Germany and its causes", *BMC pregnancy and childbirth,* vol. 13, pp. 99-2393-13-99.

Miller, E.S. & Grobman, W.A. 2016, "Does the interval since vaginal delivery influence the chance of vaginal birth after cesarean?", *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians,* vol. 29, no. 2, pp. 294-297.

Moster, D., Lie, R.T. & Markestad, T. 2008, "Long-term medical and social consequences of preterm birth", *The New England journal of medicine,* vol. 359, no. 3, pp. 262-273.

Nair, M., Soffer, K., Noor, N. et al. 2015, "Selected maternal morbidities in women with a prior caesarean delivery planning vaginal birth or elective repeat caesarean section: a retrospective cohort analysis using data from the UK Obstetric Surveillance System", *BMJ open,* vol. 5, no. 6, pp. e007434-2014-007434.

Naji, O., Wynants, L., Smith, A. et al. 2013, "Predicting successful vaginal birth after Cesarean section using a model based on Cesarean scar features examined by transvaginal sonography", *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology,* vol. 41, no. 6, pp. 672-678.

Neal, J.L., Lamp, J.M., Buck, J.S. et al. 2014, "Outcomes of nulliparous women with spontaneous labor onset admitted to hospitals in preactive versus active labor", *Journal of midwifery & women's health,* vol. 59, no. 1, pp. 28-34.

NICE, National Institute for Health and Care Excellence 2014, *Intrapartum care: care of healthy women and their babies during childbirth*. Available: http://www.nice.org.uk/guidance/cg190/resources/guidance-intrapartum-care-care-of-healthy-women-and-their-babies-during-childbirth-pdf [Accessed 04.02.2017].

Nilsson, C., Lundgren, I., Smith, V. et al. 2015, "Women-centred interventions to increase vaginal birth after caesarean section (VBAC): A systematic review", *Midwifery,* vol. 31, no. 7, pp. 657-663.

Nilsson, C., van Limbeek, E., Vehvilainen-Julkunen, K. & Lundgren, I. 2017a, "Vaginal Birth After Cesarean: Views of Women From Countries With High VBAC Rates", *Qualitative health research,* vol. 27, no. 3, pp.325-340.

Nilsson, C., Lalor, J., Begley, C. et al. 2017b, "Vaginal birth after caesarean: Views of women from countries with low VBAC rates", *Women and Birth: journal of the Australian College of Midwives,* [Epub ahead of print].

Obeidat, N., Meri, Z.B., Obeidat, M. et al. 2013, "Vaginal birth after caesarean section (VBAC) in women with spontaneous labour: predictors of success", *Journal of obstetrics and gynaecology: the journal of the Institute of Obstetrics and Gynaecology,* vol. 33, no. 5, pp. 474-478.

O'Driscoll, K., Jackson, R.J. & Gallagher, J.T. 1970, "Active management of labour and cephalopelvic disproportion", *The Journal of obstetrics and gynaecology of the British Commonwealth,* vol. 77, no. 5, pp. 385-389.

Omole-Ohonsi, A., Muhammad, Z. & Iliyasu, Z. 2007, "Value of partogram in vaginal birth after caesarean section", *Journal of obstetrics and gynaecology: the journal of the Institute of Obstetrics and Gynaecology,* vol. 27, no. 3, pp. 264-266.

Palatnik, A. & Grobman, W.A. 2015, "Induction of labor versus expectant management for women with a prior cesarean delivery", *American Journal of Obstetrics and Gynecology,* vol. 212, no. 3, pp. 358.e1-358.e6.

Petersen, A., Ayerle, G.M., Fromke, C. et al. 2011, "The timing of interventions during labour: descriptive results of a longitudinal study", *Midwifery,* vol. 27, no. 6, pp. e267-73.

Petersen, A., Penz, S.M. & Gross, M.M. 2013a, "Women's perception of the onset of labour and epidural analgesia: a prospective study", *Midwifery,* vol. 29, no. 4, pp. 284-293.

Petersen, A., Poetter, U., Michelsen, C. & Gross, M.M. 2013b, "The sequence of intrapartum interventions: a descriptive approach to the cascade of interventions", *Archives of Gynecology and Obstetrics,* vol. 288, no. 2, pp. 245-254.

Petrou, S., Kim, S.W., McParland, P. & Boyle, E.M. 2017, "Mode of Delivery and Long-Term Health-Related Quality-of-Life Outcomes: A Prospective Population-Based Study", *Birth (Berkeley, Calif*.), vol. 44, no. 2, pp. 110-119.

Prinja, S., Gupta, N. & Verma, R. 2010, "Censoring in clinical trials: review of survival analysis techniques", *Indian journal of community medicine: official publication of Indian Association of Preventive & Social Medicine,* vol. 35, no. 2, pp. 217-221.

Radin, R.G., Mikkelsen, E.M., Rothman, K.J. et al. 2016, "Brief Report: Cesarean Delivery and Subsequent Fecundability", *Epidemiology (Cambridge, Mass.),* vol. 27, no. 6, pp. 889-893.

Rasmussen, K. 2001, "Is There a Causal Relationship between Iron Deficiency or Iron-Deficiency Anemia and Weight at Birth, Length of Gestation and Perinatal Mortality?", *The Journal of nutrition,* vol. 131, no. 2S-2, pp. 590S-601S; discussion 601S-603S.

Regan, J., Thompson, A. & DeFranco, E. 2013, "The influence of mode of delivery on breastfeeding initiation in women with a prior cesarean delivery: a population-based study", *Breastfeeding medicine: the official journal of the Academy of Breastfeeding Medicine,* vol. 8, pp. 181-186.

Rogers, A.J., Rogers, N.G., Kilgore, M.L. et al. 2017, "Economic Evaluations Comparing a Trial of Labor with an Elective Repeat Cesarean Delivery: A Systematic Review", *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research,* vol. 20, no. 1, pp. 163-173.

Rossen, J., Ostborg, T.B., Lindtjorn, E., Schulz, J. & Eggebo, T.M. 2016, "Judicious use of oxytocin augmentation for the management of prolonged labor", *Acta Obstetricia et Gynecologica Scandinavica,* vol. 95, no. 3, pp. 355-361.

Royal College of Obstetricians and Gynaecologist (RCOG) 2015, “Birth After Previous Caesarean Birth, Green-top Guideline No. 45” [online], Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_45.pdf, [Accessed 23.04.2017].

Richards, M., Hardy, R., Kuh, D. & Wadsworth, M.E. 2001, "Birth weight and cognitive function in the British 1946 birth cohort: longitudinal population based study", *BMJ (Clinical research ed.),* vol. 322, no. 7280, pp. 199-203.

Rutayisire, E., Huang, K., Liu, Y. & Tao, F. 2016, "The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review", *BMC gastroenterology,* vol. 16, no. 1, pp. 86-016-0498-0.

Sabol, B., Denman, M.A. & Guise, J.M. 2015, "Vaginal birth after cesarean: an effective method to reduce cesarean", *Clinical obstetrics and gynecology,* vol. 58, no. 2, pp. 309-319.

Schlinzig, T., Johansson, S., Gunnar, A. et al. 2009, "Epigenetic modulation at birth - altered DNA-methylation in white blood cells after Caesarean section", *Acta Paediatrica (Oslo, Norway: 1992),* vol. 98, no. 7, pp. 1096-1099.

Schulz, K.F. & Grimes, D.A. 2002, "Sample size slippages in randomised trials: exclusions and the lost and wayward", *Lancet (London, England),* vol. 359, no. 9308, pp. 781-785.

Scott, J.R. 2014, "Intrapartum management of trial of labour after caesarean delivery: evidence and experience", *BJOG: an international journal of obstetrics and gynaecology,* vol. 121, no. 2, pp. 157-162.

Sedgwick, P. 2014, "How to read a Kaplan-Meier survival plot", *BMJ (Clinical research ed.),* vol. 349, pp. g5608.

Sedgwick, P. 2015, "Interpreting hazard ratios", *BMJ (Clinical research ed.),* vol. 351, pp. h4631.

Sevelsted, A., Stokholm, J. & Bisgaard, H. 2016, "Risk of Asthma from Cesarean Delivery Depends on Membrane Rupture", *The Journal of pediatrics,* vol. 171, pp. 38-42.e4.

Shatz, L., Novack, L., Mazor, M. et al. 2013, "Induction of labor after a prior cesarean delivery: lessons from a population-based study", *Journal of perinatal medicine,* vol. 41, no. 2, pp. 171-179.

Shintani, A.K., Girard, T.D., Eden, S.K. et al. 2009, "Immortal time bias in critical care research: application of time-varying Cox regression for observational cohort studies", *Critical Care Medicine,* vol. 37, no. 11, pp. 2939-2945.

Shorten, A. & Shorten, B. 2012, "The importance of mode of birth after previous cesarean: success, satisfaction, and postnatal health", *Journal of midwifery & women's health,* vol. 57, no. 2, pp. 126-132.

Siddiqui, S.A. 2013, "Obstetric factors for unsuccessful trial of labor in second-order birth following previous cesarean", *Annals of Saudi medicine,* vol. 33, no. 4, pp. 356-362.

Singh, S.K., Yahya, N., Misiran, K. et al. 2016, "Combined spinal-epidural analgesia in labour: its effects on delivery outcome", *Brazilian journal of anesthesiology (Elsevier),* vol. 66, no. 3, pp. 259-264.

Smith, G.C. 2001, "Use of time to event analysis to estimate the normal duration of human pregnancy", *Human reproduction (Oxford, England),* vol. 16, no. 7, pp. 1497-1500.

Smith, G.C., Pell, J.P., Cameron, A.D. & Dobbie, R. 2002, "Risk of perinatal death associated with labor after previous cesarean delivery in uncomplicated term pregnancies", *JAMA : the journal of the American Medical Association,* vol. 287, no. 20, pp. 2684-2690.

Smith, G.C., White, I.R., Pell, J.P. & Dobbie, R. 2005, "Predicting cesarean section and uterine rupture among women attempting vaginal birth after prior cesarean section", *PLoS medicine,* vol. 2, no. 9, pp. e252.

Smyth, R.M., Markham, C. & Dowswell, T. 2013, "Amniotomy for shortening spontaneous labour", *The Cochrane database of systematic reviews,* vol. 6, pp. CD006167.

Sondgeroth, K.E., Stout, M.J., Graseck, A.S. et al. 2015, "Progress of induced labor in trial of labor after cesarean delivery", *American Journal of Obstetrics and Gynecology,* vol. 213, no. 3, pp. 420.e1-420.e5.

Stata online. *stcox*. Available: http://www.stata.com/manuals13/ststcox.pdf, [Accessed 17.06.2017.

Stata service online. *RE: st: Survival analysis: Interpretation of Cox regression.* Available: RE: st: Survival analysis: Interpretation of Cox regression, [Accessed 17.06.2017.]

Statista - das Statistik-Portal. *Mittelwerte von Körpergröße, -gewicht und BMI bei Frauen in Deutschland nach Altersgruppe im Jahr 2011*. Available: https://de.statista.com/statistik/daten/studie/260916/umfrage/mittelwerte-von-groesse-gewicht-und-bmi-bei-frauen-nach-alter/, [Accessed 01.01.2017].

Stokholm, J., Thorsen, J., Chawes, B.L. et al. 2016, "Cesarean section changes neonatal gut colonization", *The Journal of allergy and clinical immunology,* vol. 138, no. 3, pp. 881-889.e2.

Studsgaard, A., Skorstengaard, M., Glavind, J. et al. 2013, "Trial of labor compared to repeat cesarean section in women with no other risk factors than a prior cesarean delivery", *Acta Obstetricia et Gynecologica Scandinavica,* vol. 92, no. 11, pp. 1256-1263.

Tessmer-Tuck, J.A., El-Nashar, S.A., Racek, A.R. et al. 2014, "Predicting vaginal birth after cesarean section: a cohort study", *Gynecologic and obstetric investigation,* vol. 77, no. 2, pp. 121-126.

Therneau, T., Crowson, C. & Atkinson, E. 2017, “Using Time Dependent Covariates and Time Dependent Coefcients in the Cox Model, [Online], Available from: https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf, [Accessed 30.04.2017].

Timofeev, J., Reddy, U.M., Huang, C.C. et al. 2013, "Obstetric complications, neonatal morbidity, and indications for cesarean delivery by maternal age", *Obstetrics and gynecology,* vol. 122, no. 6, pp. 1184-1195.

Tollanes, M.C., Moster, D., Daltveit, A.K. & Irgens, L.M. 2008, "Cesarean section and risk of severe childhood asthma: a population-based cohort study", *The Journal of pediatrics,* vol. 153, no. 1, pp. 112-116.

Treweek, S., Lockhart, P., Pitkethly, M. et al. 2013, "Methods to improve recruitment to randomised controlled trials: Cochrane systematic review and meta-analysis", *BMJ open,* vol. 3, no. 2, pp. 10.1136/bmjopen-2012-002360.

Ugwumadu, A. 2005, "Does the maxim "once a Caesarean, always a Caesarean" still hold true?", *PLoS medicine,* vol. 2, no. 9, pp. e305.

Vahratian, A., Zhang, J., Troendle, J.F. et al. 2004, "Maternal prepregnancy overweight and obesity and the pattern of labor progression in term nulliparous women", *Obstetrics and gynecology,* vol. 104, no. 5 Pt 1, pp. 943-951.

Vahratian, A., Troendle, J.F., Siega-Riz, A.M. & Zhang, J. 2006, "Methodological challenges in studying labour progression in contemporary practice", *Paediatric and perinatal epidemiology,* vol. 20, no. 1, pp. 72-78.

Van den Broeck, J., Cunningham, S.A., Eeckels, R. & Herbst, K. 2005, "Data cleaning: detecting, diagnosing, and editing data abnormalities", *PLoS medicine,* vol. 2, no. 10, pp. e267.

van Walraven, C., Davis, D., Forster, A.J. & Wells, G.A. 2004, "Time-dependent bias was common in survival analyses published in leading clinical journals", *Journal of clinical epidemiology,* vol. 57, no. 7, pp. 672-682.

Virani, S., Dolinoy, D.C., Halubai, S. et al. 2012, "Delivery type not associated with global methylation at birth", *Clinical epigenetics,* vol. 4, no. 1, pp. 8-7083-4-8.

Wang, T.T., Sun, S. & Huang, S.Q. 2017, "Effects of Epidural Labor Analgesia With Low Concentrations of Local Anesthetics on Obstetric Outcomes: A Systematic Review and Meta-analysis of Randomized Controlled Trials", *Anesthesia and Analgesia,* vol. 124, no. 5, pp. 1571-1580.

Wei, S., Wo, B.L., Qi, H.P. et al. 2013, "Early amniotomy and early oxytocin for prevention of, or therapy for, delay in first stage spontaneous labour compared with routine care", *The Cochrane database of systematic reviews,* vol. 8, pp. CD006794.

Wienke, A. 2003. “Frailty Models, MPIDR Working Paper WP 2003-032”, Available: http://www.ressources actuarielles.net/EXT/ISFA/1226.nsf/0/37d8815030298678c125737b002e1b13/$FILE/wp-2003-032.pdf, [Accessed 04.05.2017].

Yee, L.M., Liu, L.Y. & Grobman, W.A. 2015, "Relationship between obstetricians' cognitive and affective traits and delivery outcomes among women with a prior cesarean", *American Journal of Obstetrics and Gynecology,* vol. 213, no. 3, pp. 413.e1-413.e7.

Ye, J., Zhang, J., Mikolajczyk, R. et al. 2016, "Association between rates of caesarean section and maternal and neonatal mortality in the 21st century: a worldwide population-based ecological study with longitudinal data", *BJOG : an international journal of obstetrics and gynaecology, vol.* 123, no. 5, pp. 745-53.

Zeng, D., Mao, L. & Lin, D.Y. 2016, "Maximum likelihood estimation for semiparametric transformation models with interval-censored data", *Biometrika,* vol. 103, no. 2, pp. 253-271.

Zhang, J., Troendle, J.F. & Yancey, M.K. 2002, "Reassessing the labor curve in nulliparous women", *American Journal of Obstetrics and Gynecology,* vol. 187, no. 4, pp. 824-828.

Zhang, J., Troendle, J., Mikolajczyk, R. et al. 2010, "The natural history of the normal first stage of labor", *Obstetrics and gynecology,* vol. 115, no. 4, pp. 705-710.

## 6. Personal contribution

The required contribution of the PhD-candidate in this research project consisted of the management of the German part of the OptiBIRTH-study, a cluster randomized controlled trial in Ireland, Italy and Germany. The PhD-candidate was involved fully in the development of all questionnaires and partially in the development of the intervention. She led the trial project and data management, data collection, implementation of the intervention including fidelity check in the intervention sites and the subsequent roll-out of the intervention in the control sites in Germany. The PhD-candidate also participated in the consortium and study-team meetings during the last three-and-a-half years of the four-and-a-half year trial period, and contributed to the trial processes on a regular basis.

The aims of the analyses for this PhD-thesis and the methods to be used were planned by the candidate, taking account of suggestions from the supervisors of the PhD-thesis. The PhD-candidate analysed both datasets herself with the support of Dr. André Karch, epidemiologist of the Helmholtz Centre of Infection Research HZI in Braunschweig. It was particularly important for the PhD-candidate to understand the methods and analyses used, to develop the statistical analysis plan and to write the syntax herself before seeking additional support as needed.

The PhD-candidate prepared two manuscripts for publication to present the main findings of this research. She drafted both papers herself, revised them after review by the supervisors, submitted the articles and revised the finally published first article for publication after peer review. The article presenting the analysis of observational data from the German part of the OptiBIRTH-study was submitted to a total of four journals by the PhD-candidate but was declined by each following peer review (for reasons provided in Chapter 4.5). All co-authors on both manuscripts contributed appropriately to the planning, writing and publication processes but the lead for both remained with the PhD-candidate.

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# 8. Appendices

## 8.1. Experimental modelling with time-dependent covariables

Experimenting with the inclusion of time-dependent covariables for spontaneous rupture of the membranes (SROM) and for amniotomy, implausible high results for the Hazard ratios for theses variables were obtained (Table 14). It was then realised that two time-dependent predictors excluding each other for an event that occurs in all cases of a dataset (in this case rupture of the membranes (ROM), either spontaneous or artificial) cannot be included in the same multivariable models. As a consequence, ROM was then included in the models as a time-constant variable.

**Table 14:** Example of a preliminary shared frailty Cox regression model with the dependent variable overall labour duration and time-dependent covariables for SROM and amniotomy

| **Variable** | **Hazard ratio** | **p-value** | **96% CI** |
|---|---|---|---|
| Secundiparae with pVBAC compared primiparae | 0.987 | 0.920 | 0.766-1.272 |
| Secundiparae with pVBAC compared secundiparae | 0.313 | <0.001 | 0.243-0.403 |
| Age | 0.989 | 0.004 | 0.981-0.996 |
| Private insurance or complementary with senior obstetrician | 1.220 | 0.007 | 1.056-1.410 |
| No risk in medical history except c-section | 1.153 | 0.001 | 1.061-1.253 |
| Induction | 1.520 | <0.001 | 1.380-1.667 |
| Cervical dilation at admission | 1.182 | <0.001 | 1.161-1.204 |
| Meconium stained liquor | 0.763 | <0.001 | 0.670-0.870 |
| Birthweight | 0.982 | 0.003 | 0.971-0.994 |
| Circumference head | 0.948 | 0.008 | 0.911-0.986 |
| Timing SROM | 115.680 | <0.001 | 65.526-204.222 |
| Timing amniotomy | 111.958 | <0.001 | 63.331-197.920 |
| Timing epidural | 0.739 | <0.001 | 0.645-0.846 |
| Timing opioids | 1.347 | <0.001 | 1.188-1.527 |
| Interaction parity and timing of opioids | | | |
| Secundiparae with pVBAC | 1.033 | 0.861 | 0.719-1.484 |
| Secundiparae | 0.816 | 0.023 | 0.685-0.972 |
| Interaction timings epidural and opioids | 0.668 | <0.001 | 0.536-0.833 |

pVBAC=planned VBAC; SROM=spontaneous rupture of membranes

### 8.2. Analysis of the outliers of the variable "labour duration"

**Table 15:** Reading birth stories of the longest labour durations as a working tool for data cleaning, data download May 2015, examples

| **Studien-nummer** | **Gesamte Geburtsdauer** | **Dauer EP** | **Geburtsbeginn** | **Blasensprung** | **Geburt** | **Anderes** | **Plausibilität** |
|---|---|---|---|---|---|---|---|
| C02011 | **747.75 Std** | 747.00 Std. | 17.07.14, 02.00 | 17.08.14, 02.00 SROM | 17.08.14, 05.45 spontan | | Eher nicht, ein Monat zu früh |
| C01037 | **86.28 Std** | keine | 12.07.14, 12.00 | 12.07.14, 12.00 SROM | 16.07.14, 09.30 Emergency CS, Uterusruptur | | Eher nicht, vorz. BS, Ko Geburts-beginn |
| A01015 | **61.77 Std** | keine | 12.07.14, 10.00 | 13.07.14, 20.20 SROM | 14.07.14, 23.46 Emergency CS | Geburtsbeginn gleichzeitig Einleitung | Eher nicht, Ko Geburtsbeginn, Wehen und nicht Einleitung |
| D01035 | **59.37 Std** | keine | 29.06.14, 16.00 | Keine Angaben | 02.07.14, 03.22 Emergency CS Drohende Uterusruptur, Blutung | MM am 01.07.14 erst 1 cm | Eher nicht, Ko Geburtsbeginn wahrscheinlich erste Wehe und nicht Geburts-fortschritt |
| E01050 | **56.73 Std** | keine | 26.05.14, 23.30 | Keine Angaben | 29.05.14, 08.14 Emergency CS Geburtsstillstand 7 cm nach 2.5 Tagen Wehen | Keine Schmerzmittel, kein MM dokumentiert | Fraglich, wahrscheinlich erste Wehe und nicht Geburts-fortschritt |
| C01001 | **45.85 Std** | 44.00 Std. | 26.02.14, 03.00 | 26.02.14, 03.00 | 28.02.14, 00.51 spontan | | Eher nicht, vorz. BS, Ko Geburts-beginn |
| A01126n | **45.42 Std** | keine | 12.02.15, 01.50 | Keine Angaben | 13.02.15, 23.15 Emergency CS, frustrane Einleitung | Immer 1 cm MM Eröffnung | Kein Geburtsbeginn, Geburtsmodus korrigieren! |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C01003 | **45.13 Std** | keine | 22.03.14, 14.00 | 22.03.14.00 | 24.03.14, 11.08 Emergency CS, Frustrane Einleitung | MM nur 0-1 cm | Kein Geburtsbeginn, Geburtsmodus korrigieren |
| E01094 | **41.83 Std** | 40.25 Std. | 21.07.14, 04.00 | 20.07.14, 05.00 | 22.07.15, 21.15 spontan | MM Veränderungen erst am 22.7.15 | Eher nicht, Geburtsbeginn kontr. Erste Wehen ohne Forschritt |
| C01059 | **40.35 Std** | keine | 07.08.14, 01.00 | 07.08.14, 01.00 | 08.08.14, 17.21 Emergency CS vorz. BS, keine Wehen | | Eher nicht, vorz. BS kein Geburtsbeginn, Geburtsmodus korrigieren |
| E01048 | **36.35 Std** | keine | 15.07.14, 10.45 | Keine Angaben | 16.07.14, 23.06 Emergency CS, Geburtsstillst. | Keine MM dokumentiert | Fraglich, keine Anhaltspunkte |
| C01012 | **35.40 Std** | 35.00 Std. | 28.05.14, 08.00 | 28.05.14, 8.00 SROM | 29.05.14, 19.40 spontan | MM-Veränderungen erst am 29.5.14 | Eher nicht, vorz. BS, Ko Geburts-beginn |
| A01026 | **35.12 Std** | 34.17 Std. | 17.06.14, 16.00 | 17.06.14, 16.00 SROM | 19.06.14, 03.07 spontan | VU erst ab 18.6. nachmittags | Nein, vorz. BS, Ko Geburts-beginn |
| A01019 | **32.67 Std** | 31.83 Std. | 14.08.14, 14.00 | SROM, Zeit-punkt missing | 15.08.14, 22.40 spontan | Keine VU dokumentiert, | Fraglich, zu wenige An-gaben, Geburt in anderer Klinik |

CS= Caesarean section, BS=Blasensprung, Ko=Kontrolle, MM=Muttermund, SROM=Spontanous rupture of membranes, Std=Stunden, VU=Vaginale Untersuchung

**Table 16:** Reading birth stories of the shortest labour durations as a working tool for data cleaning, data download May 2015, examples

| Studien-nummer | Gesamte Geburtsdauer | Dauer EP | Geburtsbeginn | Blasensprung | Geburt | Anderes | Plausibilität |
|---|---|---|---|---|---|---|---|
| C01167 | **0.57 Std** | missing | 09.03.15, 15.40 | missing | 09.03.14, 16.14 Emergency CS, path. CTG | | Ja, ok |
| D01093 | **0.77 Std** | 0.00 Std. | 22.12.14, 14.50 | 22.12.14, 13.00 | 22.12.14, 15.36 spontan | Klinikeintritt mit MMV als Geburtsbeginn | Eher nicht, Ko Geburtsbeginn |
| C01047 | **0.80 Std** | 0.75 Std. | 07.06.14, 03.00 | 07.06.14, 3.00 | 07.06.14, 03.48 spontan | | Ja, ok |
| C02243 | **1.03 Std** | 0.5 Std. | 23.03.15, 13.50 | 23.03.15, 13.50 SROM | 23.03.15, 14.52 spontan | Drittes Kind, ungeplante Hausgeburt | Ja, ok |
| C02007 | **1.03 Std** | keine | 26.04.14, 11.10 | Keine Angabe | 26.04.14, 12.12 Emergency CS, Wunsch | Kontraktionen seit 9 Uhr, MM 3 cm um 11.10 | Wahrscheinlich ok, Kontrolle Wehenbeginn gemäß Hebamme |
| C01170 | **1.08 Std** | 0.75 Std. | 22.02.15, 21.00 | 22.02.15, 21.45 ARM | 22.02.15, 22.05 spontan | Keine Angaben MM, WT gemäß Mutter 22.02.15, morgens | Schwierig zu beurteilen |
| C01223 | **1.23 Std** | 0.62 Std | 13.04.15, 15.30 | 13.04.15, 16.35 SROM | 13.04.15, 16.07 Vakuum wegen CTG | Wehen gemäß Mutter 13.04.15, 13.30. Um 16.00 Uhr MM 9cm | Fraglich, Ko Geburtsbeginn |
| A01111 | **1.25 Std** | 0.97 Std. | 01.02.15, 02.30 | Keine Zeitangabe | 01.02.15, 03.45 spontan | Keine Angaben VU | Schwierig zu beurteilen |
| C02003 | **1.28 Std** | 0.58 Std. | 21.06.14, 22.35 | 21.06.14, 23.10 | 21.06.14, 23.52 spontan | Keine Angaben VU | Schwierig zu beurteilen |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C01133 | **1.28 Std** | keine | 27.11.14, 04.00 | Kein BS | 27.11.14, 05.17 Emergency CS path CTG in EP | MM 1cm um 03.05 Uhr und 5 cm um 4.54 Uhr | Ja, ok |
| C01038 | **1.38 Std** | 0.25 Std. | 11.07.14, 23.15 | 11.07.14, 23.15 SROM | 12.07.14, 00.38 spontan | Um 22.05 schon 7 cm mm-Eröffnung | Eher nicht, Ko Geburtsbeginn, früher als SROM |
| E01024 | **1.42 Std** | keine | 03.09.14, 19.18 | Kein BS | 03.09.14, 19.18 Emergency CS wg BEL | MM 3cm am 03.09.14 um 19.50 | Ja, ok |
| C01040 | **1.50 Std** | 1.03 Std. | 30.05.14, 21.30 | 30.05.14, 21.30 SROM | 30.05.14, 21.30 spontan | Wehenbeginn und onset women 30.05., 21.32 | Ja, ok |
| C02044 | **1.53 Std** | 0.97 Std. | 17.04.14, 01.00 | 17.04.14, 0.00 SROM | Wehenbeginn gemäß Mutter 16.04.14, 23.30, MM 2 cm um 01.00 Uhr | 17.04.14, 02.32 Emergency CS wegen path. CTG | Wahrscheinlich ok |
| E01166 | **1.70 Std** | keine | 02.12.14, 15.30 | Kein BS | Emergency CS wegen WT und MM-Eröffnung | Geburtsbeginn gemäß Frau um 15.30 Uhr, MM 4 cm um 16.00 Uhr | Ja, ok |

ARM=Artificial rupture of membranes, CS= Caesarean section, BS=Blasensprung, Ko=Kontrolle, MM=Muttermund, SROM=Spontanous rupture of membranes, Std=Stunden, VU=Vaginale Untersuchungen, WT=Wehentätigkeit

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# Labour duration and timing of interventions in women planning vaginal birth after caesarean section

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ABSTRACT

*Objective:* understanding the labour characteristics of women attempting vaginal birth after caesarean (VBAC) may suggest how to improve intrapartum management and may enhance success rates. Promoting VBAC is a relevant factor in decreasing overall caesarean section (c-section) rates. However, the labour processes of women attempting VBAC are not well investigated. The aim of this paper is to compare multiparae planning a first VBAC (pVBAC) with primiparae and with multiparae planning a second vaginal birth, all starting to give birth vaginally, with regard to (a) perinatal characteristics, (b) the timing of intrapartal spontaneous rupture of membranes (SROM) and of interventions, and (c) labour duration, with respect to the first and second stages.
*Setting:* cohort study of women planning vaginal birth in 47 obstetric units in Lower Saxony, Germany.
*Participants:* 1897 primiparae, 211 multiparae with one previous c-section and 1149 multiparae with one previous vaginal birth.
*Measurements:* secondary analysis of data from an existing cohort study. Kaplan–Meier estimates, log rank test, Wilcoxon test and shared frailty Cox regression models including time-varying covariates were used to compare the timing of interventions and labour duration between the subsamples. Analyses were done with the statistics programme Stata 13.
*Findings:* perinatal and labour characteristics of multiparae with pVBAC mainly resembled those of primiparae and differed from those of multiparae planning a second vaginal birth. However, compared to primiparae, multiparae with pVBAC received oxytocin less often (48.82 versus 56.95%, $p=0.024$) and gave birth vaginally significantly less often (69.19 versus 83.40%, $p<0.001$). The timing of intrapartal SROM (2.67 versus 3.42 hours, $p=0.112$) and of interventions (amniotomy: 5.50 versus 5.83 hours, $p=0.198$; oxytocin: 5.75 versus 6.00 hours, $p=0.596$; epidural: 4.00 versus 4.67 hours, $p=0.416$; opioids: 3.83 versus 3.78, $p=0.851$) was similar to that in primiparae although timings of all interventions but not of SROM differed significantly from that in multiparae with second vaginal birth (SROM: 2.67 versus 2.67 hours, $p=0.481$; amniotomy: 5.50 versus 3.93 hours, $p<0.001$; oxytocin: 5.75 versus 4.25 hours, $p<0.001$; epidural: 4.00 versus 3.50 hours, $p=0.009$; 3.83 versus. 2.75 hours, $p=0.026$). Overall and first-stage labour duration were comparable to primiparae (overall labour duration: 8.83 versus 8.57 hours, HR=0.998, 95% CI=0.830–1.201, $p=0.987$; first stage: 7.42 versus 7.00 hours, HR=0.916, 95% CI=0.774-1.083, $p=0.303$) but significantly longer than in other multiparae (overall labour duration: 8.83 versus 4.63 hours, HR=0.319, 95% CI=0.265–0.385, $p<0.001$; first stage: 7.42 versus 4.25 hours, HR=0.402, 95% CI=0.339-0.478, $p<0.001$). However, the second stage of labour was significantly shorter in multiparae with pVBAC than in primiparae (0.55 versus 0.77 hours, HR=1.341, 95%

*Abbreviations:* Primiparae, primiparous women; Other multiparae, multiparous women planning their second vaginal birth; Multiparae with pVBAC, multiparous women with first planned vaginal birth after one previous caesarean section; c-section, caesarean section; ERCS, elective repeat caesarean section; VBAC, vaginal birth after caesarean section; pVBAC, planned vaginal birth after caesarean section; SROM, spontaneous rupture of the membranes; ARM, artificial rupture of the membranes; IQR, interquartile range; HR, hazard ratio; CI, confidence interval

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CI=1.049–1.714, $p=0.019$), but longer than in multiparae with second vaginal birth (0.55 versus 0.22 hours, HR=0.334, 95% CI=0.262–0.426, $p<0.001$).
*Key conclusion:* labour patterns of multiparous women planning a VBAC differ from those of primiparae and other multiparous women. Multiparae with pVBAC should be considered as a distinct group of parturients.
*Implication for practice:* expectations regarding labour progression for multiparae with first pVBAC should be similar to those for primiparae. However, the chance that the second stage of labour might be shorter than in primiparae is relevant and motivating information for pregnant women with a previous c-section in deciding the planned mode of birth.


## Introduction

Understanding labour characteristics of women planning vaginal birth after caesarean section (VBAC) may suggest how to improve intrapartum management. This is relevant for achieving a successful and safe VBAC (Scott, 2014). Promoting VBAC is a relevant factor in decreasing overall caesarean section (c-section) rates (Cheng et al., 2011; Sabol et al., 2015) and supports efforts to avoid multiple c-sections with increasingly adverse outcomes (Marshall et al., 2011). Rising c-section rates are of international concern and cannot be explained by risk factors such as age and parity (EURO-PERISTAT, 2013; ACOG et al., 2014).

The absolute risks for women planning a VBAC and for their children are low (Landon et al., 2004; Nair et al., 2015). Maternal mortality is three times higher with elective repeat c-section (ERSC) than with planned VBAC (pVBAC) (0.013 versus 0.004%, Guise et al., 2010). The risk of infant loss, however, is higher for VBAC than for elective repeat c-section (ERCS) (0.13 versus 0.05%) but comparable to that for women giving birth to their first child (Smith et al., 2002). Uterine rupture is more frequent with pVBAC than with ERCS (Guise et al., 2010). The risk of uterine rupture is lower with spontaneous labour than with induced labour (Dekker et al., 2010; Palatnik and Grobman, 2015). Hospital stays have been found to be shorter, satisfaction with the mode of birth higher, recovery after birth better, quality of life as determined by physical health higher, breast-feeding initiation rates higher and the costs lower with pVBAC than with ERCS (Guise et al., 2010; Kealy et al., 2010; Shorten and Shorten, 2012; Fawsitt et al., 2013; Karlström et al., 2013; Regan et al., 2013; Prick et al., 2015). With conscientious intrapartum management there is a high probability of a safe and successful vaginal birth outcome meaning that caution is needed with induction and augmentation of labour to avoid overstimulation of contractions and that a thorough surveillance regarding signs of uterine rupture is necessary (RCOG, 2007; Scott, 2014). Several studies found that 60–85% of women planning VBAC did indeed give birth vaginally (Balachandran et al., 2014; Knight et al., 2014; Tessmer-Tuck et al., 2014), including even women at high risk (Regan et al., 2015); it is therefore asserted that women should be informed about the high likelihood of a successful outcome (King et al., 2015).

Uterine activity differs according to parity (Arulkumaran et al., 1984). This has a significant impact on labour duration, which is shorter with the second baby than with the first one (Albers et al., 1996; Vahratian et al., 2006; Zhang et al., 2010; Petersen et al., 2011). So far, no other study investigating timing of interventions was found. In the overall sample of the same cohort study including 3963 participants, amniotomy, oxytocin and epidural were performed slightly earlier in multiparae than in primiparae (Petersen et al., 2011). Consequently the median intervention-free time span after onset of labour has been found to be shorter for multiparae than for primiparae (Petersen et al., 2011) and the sequence of interventions differs (Petersen et al., 2013b). There is less evidence on the labour patterns of women with a previous c-section. Graseck et al. (2012) found no difference in cervical dilatation between women with pVBAC and women without a previous c-section. Multiparous women who had had a previous c-section because of dystocia were found to have a similar or longer labour duration than primiparous women (Harlass and Duff, 1990). Grantz et al. (2015) found that labour progression from 4 to 10 cm cervical dilatation was slower in multiparae with first VBAC where labour was induced than in primiparae. Faranesh and Salim (2011) by contrast found shorter active phases of the first stage and shorter second stages of labour for multiparous women with VBAC as compared to primiparae. Multiparous women with second vaginal births by contrast had shorter active phases and second stages than multiparae with first VBAC (Faranesh and Salim, 2011). The frequency and timing of interventions in the cases of women with pVBAC have however not been investigated in previous studies.

The aim of this paper is to compare multiparous women planning a first VBAC with primiparous women and multiparous women planning a second vaginal birth in respect of:

(a) baseline and perinatal characteristics
(b) the timing of intrapartal SROM, amniotomy, oxytocin, epidural and opioid administration
(c) the overall duration of labour and the durations of the first and second stages of labour.

## Methods

### *Study design and setting*

This study is based on a secondary analysis of the ProGeb dataset, which was derived from a cohort study undertaken between April and October 2005 in 47 of the 96 maternity units in Lower Saxony with birth rates ranging from 500 to 2000 births per year (Gross et al., 2007, 2009; Petersen et al., 2011, 2013a, 2013b; Gross et al., 2014). Women were eligible for this study if they were expecting a singleton in vertex presentation, were over 34 weeks of gestation and had started to give birth vaginally after onset of labour assessed by the midwife in terms of regular or irregular contractions associated with cervical dilatation (Gross et al., 2009). Parturients over 34 weeks were included because recommendations in German guidelines consider them together with women at term as one target group (DGGG, 2006, 2010b, 2012). Midwives in the current study defined onset of labour as the moment when labour started to progress without being tied to exact centimetres of dilatation. This approach was chosen, because there is no homogenous definition which addresses the complexity of onset of labour appropriately (Hanley et al., submitted for publication). In general, German perinatal statistics count labour duration from the onset of regular contraction (Aqua, 2015).

Prospective data was collected from 47 hospitals, and also in addition retrospective data from the medical records of seven of these hospitals relating to all eligible women for whom prospective data was lacking (Petersen et al., 2011). The prospective sample consisted of 1169 participants (29.50%), the retrospective one of 2794 participants (70.50%), giving a total of 3963 women. A theoretical figure of $n=25{,}028$ births in Lower Saxony was calculated for the six months of data collection (Petersen et al., 2011). The whole study sample therefore comprised of about 16% of eligible parturients giving birth during the six months period in the federal state. Within the study population, there were 302 women with a history of c-section who were planning a VBAC; 211 of these were multiparous women expecting their second child and planning a VBAC.

Multiparous women ($n=724$) giving birth for the third time or more were excluded from the analysis because they did not meet the inclusion criteria for this secondary analysis. Thus the study population investigated consisted of three subsamples: the 211 multiparous women with planned first VBAC, in the following called 'multiparae with pVBAC' for short (6.5% of the study population), who were compared with 1879 primiparous women ('primiparae', 58.01%) and 1149 multiparous women planning their second vaginal birth ('other multiparae', 35.47%). Inequalities of the sample sizes could be accepted because these differences correspond to the natural and random mixing of birthing women in the study sample, do not affect statistical analyses and because matching the subgroups would have led to sources of selection bias.

The ProGeb study received ethical approval from the Ethics Committee of Hannover Medical School and from the Ethics Committee of the Chamber of Physicians for all public hospitals in Lower Saxony.

*Data preparation*

Women not having received either amniotomy, oxytocin, epidural analgesia or opioids between onset of labour and birth were classified as having had 'No intervention during labour'. The intervention-free time span was calculated as the duration between onset of labour and the first of any one of these four interventions.

It is unlikely that any events or interventions would occur simultaneously with onset of labour or birth, and for the analysis of Kaplan–Meier estimates the Stata software excludes durations of zero minutes. As measurements were recorded in minutes, any such events or interventions were therefore deemed to have occurred one minute after onset of labour or one minute before birth.

*Data analysis*

Descriptive analysis was carried out on the baseline characteristics and on the frequencies of interventions and of spontaneous rupture of the membranes. The comparisons of the subsamples, namely multiparae with first pVBAC, primiparae and multiparae with a second vaginal birth, were computed using $\chi^2$ tests for categorical variables, one-way ANOVAs and the Tukey post-hoc tests for normally distributed metric variables and Kruskal–Wallis tests for skewed metric variables.

The medians and interquartile ranges (IQR) of the timing of spontaneous rupture of the membranes (SROM), the timing of interventions, labour duration and the durations of the first and second stages of labour were computed with Kaplan–Meier estimates. Data concerning the time span between SROM or interventions and birth, overall labour duration and the durations of the first and second stages was treated as right-censored in the case of c-section or vaginal operative delivery (for the first stage of labour only in the case of c-section). By contrast, the durations between onset of labour and SROM or interventions were considered as non-censored. Kaplan–Meier survival curves (Bland and Altman, 1998; Sedgwick, 2014) were compared either with the log rank test or with the Wilcoxon test, depending on the sensitivity region of the test and the differences in the shapes of the Kaplan–Meier curves.

Multivariable analyses were performed using shared frailty Cox regression models in order to take into account the variability between the locations (Gutierrez, 2002; Blossfeld et al., 2007; Sedgwick, 2013). Dependent variables of the models were labour duration and the durations of the first and second stages of labour respectively. Crude associations were assessed between the outcome variables and potential predictors (maternal age, health insurance, no risk factor in medical history, obesity, diabetes, gestational diabetes, induction, cervical dilatation at admission, meconium-stained liquor, rupture of the membranes, sex of the baby, birth weight, episiotomy (not for the first stage of labour), the duration of the first stage of labour (only for the model of the duration of the second stage of labour) and the type of documentation) with log rank testing for categorical variables and bivariable Cox regression models for metric variables. Variables were included in the main effect model if $p<0.25$, according to the model-building strategies of Hosmer and Lemeshow (2000). The time-dependent covariates (oxytocin, epidural analgesia and opioids) were included with episode splitting in order to avoid the time at risk before interventions occurred being taken into account (Shintani et al., 2009). If interventions occurred before the time interval of interest, this was taken into account in the models. Stepwise backward elimination was performed in the multivariable model (based on Likelihood Ratio Tests $p<0.05$). It was decided to retain maternal age and birth weight in the model, as these are known from previous studies to be valid predictors (Albers, 1999; Zhang et al., 2002). The type of documentation was retained in the model as well. Interactions were tested between the group variable and the time dependent variables and between the time dependent variables themselves. Interactions with $p<0.10$ were included in the full effects model but were eliminated again in the backward selection process if $p>0.05$.

*P*-values $<0.05$ were considered to be statistically significant and statistical analyses were conducted with Stata 13 (StataCorp, College Town, US).

## Findings

*Baseline and perinatal characteristics*

Multiparous women with previous c-section gave birth at 24 of the 47 locations and the number of participants at each location ranged between 1 and 40 (Table 1). There was no statistically significant difference compared to primiparous women (45 out of 47 sites, range = 1–309, $p=0.439$) or multiparous with a previous vaginal birth (42 out of 47 sites, range 1–178, $p=0.253$).

The multiparae with pVBAC were significantly older than the primiparae (31.55 versus 27.97 years, $p<0.001$) but the same age as the multiparae planning a second vaginal birth (31.55 versus 30.74 years, $p=0.104$). Similar percentages of women in each of the study groups had private insurance or complementary private insurance with a senior medical consultant attending birth ($p=0.244$). The proportion of women who were risk-factor free was highest among multiparae with pVBAC, the difference being significant as against other multiparae (67.77 versus 58.92%, $p=0.016$), but not significant as against primiparae (67.77 versus 62.21%, $p=0.113$). Obesity ($p=0.459$), diabetes ($p=0.407$) and gestational diabetes in history ($p=0.282$) did not differ significantly between the study groups.

**Table 1**
Baseline and perinatal characteristics.

| Variable | Primiparae (n=1879) | Multiparae with pVBAC* (n=211) | Multiparae† (n=1149) | p-Value‡ |
|---|---|---|---|---|
| **General information** | | | | |
| No. of locations/47 (range *n* of births) | 45 (1–309) | 24 (1–40) | 42 (1–178) | $p=0.047^{c}$ |
| Retrosp. documentation, *n* (%)§ | 1317 (70.09) | 163 (77.25) | 807 (70.23) | $p=0.090^{a,b}$ |
| **Socio-demographic and medical history related characteristics** | | | | |
| Age in years; mean (min–max) | 27.97 (14–46) | 31.55 (18–45) | 30.74 (18–45) | $p<0.001^{a,c}$ |
| Private insurance; n (%)¶ | 144 (7.66) | 18 (8.53) | 108 (9.40) | $p=0.244$ |
| No risk factor in history; *n* (%) | 1169 (62.21) | 143 (67.77) | 677 (58.92) | $p=0.028^{b}$ |
| Obesity; *n* (%) | 73 (3.89) | 10 (4.74) | 55 (4.79) | $p=0.459$ |
| Diabetes; *n* (%) | 12 (0.64) | 1 (0.47) | 12 (1.05) | $p=0.407$ |
| Gestational diabetes; *n* (%) | 59 (3.14) | 11 (5.21) | 38 (3.31) | $p=0.282$ |
| **Perinatal characteristics** | | | | |
| Induction of labour; *n* (%) | 546 (29.06) | 66 (31.28) | 278 (24.19) | $p=0.006^{b,c}$ |
| Cervical dilation at admission in cm; median (IQR) | 2.00 (1.00–4.00) | 2.00 (1.00–3.00) | 3.00 (2.00–5.00) | $p=0.513$ |
| Meconium-stained liquor; *n* (%) | 217 (11.55) | 31 (14.69) | 128 (11.14) | $p=0.332$ |
| Rupture of the membranes: | | | | $p<0.001^{b,c}$ |
| Prelabour SROM; *n* (%) | 481 (25.69) | 50 (23.92) | 191 (16.62) | |
| Prelabour ARM; *n* (%) | 23 (1.23) | 0 (0.00) | 14 (1.22) | |
| Intrapartal SROM; *n* (%) | 719 (38.41) | 90 (43.06) | 464 (40.38) | |
| Intrapartal ARM; *n* (%) | 649 (34.41) | 69 (33.01) | 480 (41.78) | |
| Oxytocin; *n* (%) | 1070 (56.95) | 103 (48.82) | 367 (31.94) | $p<0.001^{a,b,c}$ |
| Epidural analgesia, *n* (%) | 651 (34.65) | 76 (36.02) | 164 (14.27) | $p<0.001^{b,c}$ |
| Opioids; *n* (%) | 919 (48.91) | 91 (43.13) | 333 (28.98) | $p<0.001^{b,c}$ |
| Episiotomy; *n* (%)** | 799 (50.99) | 71 (48.63) | 220 (19.98) | $p<0.001^{b,c}$ |
| No intrapartal interventions; *n* (%) | 255 (13.57) | 35 (16.59) | 328 (28.55) | $p<0.001^{b,c}$ |
| Birth weight in g; mean (min–max) | 3407.71 (1720–5370) | 3466.29 (2060–4900) | 3532.10 (1760–5240) | $p<0.001^{c}$ |
| Female sex; *n* (%) | 918 (48.88) | 105 (49.76) | 557 (48.48) | $p=0.936$ |
| Mode of birth: | | | | $p<0.001^{a,b,c}$ |
| Spontaneous; *n* (%) | 1366 (72.70) | 131 (62.09) | 1078 (93.82) | |
| Vacuum; *n* (%) | 151 (8.04) | 12 (5.69) | 19 (1.65) | |
| Forceps; *n* (%) | 50 (2.66) | 3 (1.42) | 4 (0.35) | |
| C-section; *n* (%) | 312 (16.60) | 65 (30.81) | 48 (4.18) | |

ARM, amniotomy; IQR, interquartile range; SROM, spontaneous rupture of the membranes.
[a]Significant difference between multiparae with first pVBAC and primiparae.
[b]Significant difference between multiparae with first pVBAC and multiparae with second vaginal birth.
[c]Significant difference between primiparae and multiparae with second vaginal birth.

* Multiparous women expecting their second child planning a VBAC.
† Multiparous women expecting their second child planning a second vaginal birth.
‡ Tukey post-hoc tests after ANOVA, Kruskal–Wallis tests or chi squared tests.
§ Retrospective as opposed to prospective documentation.
¶ Private insurance or complementary insurance with senior medical consultant in contrast to statutory insurance.
** For vaginal births.

The number of women whose labour, whether electively or because of indications, was induced either with oxytocin, prostaglandin, amniotomy, misoprostol or castor oil, differed significantly overall between the subgroups ($p=0.006$): the difference was not significant as between multiparae with pVBAC and primiparae (31.28 versus 29.06%, $p=0.501$), but was significant as between multiparae with pVBAC and multiparae with second vaginal birth (31.28 versus 24.19%, $p=0.030$). Median cervical dilatation at admission did not differ significantly between the subgroups (multiparae with pVBAC: 2.00 cm, primiparae: 2.00 cm, other multiparae: 3.00 cm, $p=0.513$) and meconium-stained liquor occurred in similar frequencies ($p=0.332$). The frequency with which multiparae with pVBAC had spontaneous rupture of the membranes (SROM) before onset of labour was similar to that in primiparae (23.92 versus 25.69%, $p=0.578$) but significantly higher as compared to other multiparae (23.92 versus 16.62%, $p=0.011$). Amniotomy before onset of labour was not performed in multiparae with pVBAC and also only rarely in the other subgroups ($p=0.274$). Intrapartal SROM occurred more often in multiparae with pVBAC (43.06%) than in primiparae (38.41%) or other multiparae (40.38%), but the difference was not significant ($p=0.300$). Amniotomy during labour was performed with similar frequency in multiparae with pVBAC and primiparae (33.01 versus 34.67%, $p=0.633$), but significantly less often in multiparae with pVBAC than in other multiparae (33.01 versus 41.78%, $p=0.018$).

Multiparae with first pVBAC (48.82% in total and 42.65% during labour) received oxytocin significantly less often than primiparae (56.95% in total with $p=0.024$ and 53.54% during labour with $p=0.003$) but significantly more often than multiparae women with second vaginal birth (31.94% in total and 27.15% during labour, both differences $p<0.001$). The frequency of epidural analgesia also differed significantly overall between the subsamples ($p<0.001$), being administered most often in multiparae with pVBAC (36.02% in total, 35.07% during labour) as compared to primiparae (34.65% in total, 33.90% during labour) and other multiparae (14.27% in total, 13.84% during labour). However, in the comparisons of the individual subgroups the difference was significant only as between multiparae with pVBAC and other multiparae ($p<0.001$) and not as between multiparae with pVBAC and primiparae (total $p=0.691$, during labour $p=0.734$). The administration of opioids, either pethidine, meptazinol or pentazocine, also differed between the subsamples ($p<0.001$). Multiparae with pVBAC (43.13% in total, 41.23% during labour) received opioids slightly but not significantly less often than primiparae (48.91% in total with $p=0.111$ and 47.10% during labour with $p=0.105$) but significantly more often than other multiparae (28.98% in total and 28.11% during labour, $p<0.001$). The proportions of multiparous women planning a first VBAC and of primiparae who did not have either amniotomy, oxytocin, epidural or opioids during labour were similar (16.59 versus 13.57%, $p=0.229$); there was however a significant difference between multiparae with pVBAC and other multiparae in this respect (16.59 versus 28.55%, $p<0.001$).

The frequency with which multiparae who actually achieved their first VBAC received episiotomies was similar to that for primiparae (48.63 versus 50.99%, $p=0.586$) but significantly higher than that for multiparae with second vaginal birth (48.63 versus 19.98%, $p<0.001$). The birth weights of multiparae with pVBAC did not differ significantly from those of primiparae ($p=0.206$) and other multiparae ($p=0.154$), and neither did the sex of neonates ($p=0.936$). However, there were highly significant differences in the modes of birth between multiparae with pVBAC and primiparae ($p<0.001$) and between multiparae with pVBAC and other multiparae ($p<0.001$). Multiparae with pVBAC had a significantly lower proportion of vaginal births in comparison to both primiparae (69.19 versus 83.40%, $p<0.001$) and other multiparae (69.19 versus 98.82%, $p<0.001$), and consequently the highest c-section rate of the subsamples (30.81 versus 16.60% for primiparae and 4.18% for other multiparae).

*The timing of intrapartal SROM and interventions*

Spontaneous rupture of the membranes (SROM) for multiparous women with first pVBAC occurred at a median time of 2.67 hours after onset of labour and was not significantly earlier than the timing of SROM for primiparous women (3.42 hours, $p=0.112$, Table 2) or multiparous women planning a second vaginal birth (2.67 hours, $p=0.481$). A significant difference was found between the subsamples regarding the time between SROM and birth ($p<0.001$), with not significantly shorter median durations for multiparae with pVBAC than for primiparae (3.17 versus 3.53 hours, $p=0.762$) but significantly longer durations for multiparae with pVBAC than for other multiparae (3.17 versus 0.88 hours, $p<0.001$).

Amniotomy for multiparae with pVBAC was performed at a median time of 5.50 hours after onset of labour. This time span was slightly but not significantly shorter than that for primiparae (5.50 versus 5.83 hours, $p=0.198$) and significantly longer than that for other multiparae (5.50 versus 3.93 hours, $p<0.001$). The median duration from amniotomy to birth also differed between the subgroups ($p<0.001$) with a non-significant difference between multiparae with pVBAC and primiparae (3.25 versus 2.25 hours, $p=0.162$) but a significant difference between multiparae with pVBAC and other multiparae (3.25 versus 0.60 hours, $p<0.001$).

Oxytocin during labour for multiparae with pVBAC was administered at a median time of 5.75 hours after onset of labour, which was earlier, though not significantly so, than for primiparae (5.75 versus 6.00 hours, $p=0.596$), but significantly later compared to other multiparae (5.75 versus 4.25 hours, $p<0.001$). The median duration from first intrapartal oxytocin administration to birth was 2.85 hours for multiparae with pVBAC and was not significantly shorter than the duration for primiparae (2.85 versus 3.18 hours, $p=0.645$) but significantly longer than the duration for other multiparae (2.85 versus 1.37 hours, $p<0.001$).

Epidural analgesia for multiparae with pVBAC was administered at a median time of 4.00 hours after onset of labour, which was slightly but not significantly earlier than for primiparae (4.00 versus 4.67 hours, $p=0.416$) but significantly later than for other multiparae (4.00 versus 3.50 hours, $p=0.009$). The median duration between epidural and birth for multiparae with pVBAC was similar to that for primiparae (5.38 versus 5.17 hours, $p=0.315$) but significantly longer than that for other multiparae (5.38 versus 3.05 hours, $p<0.001$).

Opioids during labour were given to multiparae with pVBAC after a median time of 3.83 hours; this time interval was comparable to that for primiparae (3.83 versus 3.78 hours, $p=0.851$) but significantly longer than that for other multiparae (3.83 versus 2.75 hours, $p=0.026$). There was no significant difference as between multiparae with pVBAC and primiparae regarding the median duration between opioid administration and birth (4.55 versus 3.67 hours, $p=0.811$), but as between multiparae with pVBAC and other multiparae the difference was highly significant (4.55 versus 1.43 hours, $p<0.001$).

The intervention-free interval for multiparae with pVBAC lasted 3.67 hours; this was not significantly shorter than for primiparae (3.80 hours, $p=0.375$) but significantly longer than for other multiparae (3.08 hours, $p=0.015$). The median duration between the first intervention and birth was similar in multiparae with pVBAC and primiparae (4.52 versus 4.12 hours, $p=0.550$) but

**Table 2**
Duration of labour and the timing of intrapartal SROM and interventions.

| Duration, timing | Primiparae (n=1879) | Multiparae with pVBAC* (n=211) | Multiparae† (n=1149) | p-Value |
|---|---|---|---|---|
| Onset of labour – birth, hours; median (IQR) | 8.57 (5.60–13.42) | 8.83 (5.35–16.55) | 4.63 (2.85–7.05) | $p<0.001$ [b,c] |
| First stage of labour, hours; median (IQR) | 7.00 (4.50-10.50) | 7.42 (4.42-12.50) | 4.25 (2.60-6.50) | $p<0.001$ [b,c] |
| Second stage of labour, hours; median (IQR) | 0.77 (0.38–1.47) | 0.55 (0.27–1.28) | 0.22 (0.12–0.42) | $p<0.001$ [a,b,c] |
| Onset of labour– SROM, hours; median (IQR) | 3.42 (1.00–6.63) | 2.67 (0.48–5.83) | 2.67 (0.83–5.08) | $p<0.001$ [c] |
| SROM – birth, hours; median (IQR) | 3.53 (1.18–7.80) | 3.17 (1.15–8.98) | 0.88 (0.25–2.45) | $p<0.001$ [b,c] |
| Onset of labour – ARM, hours; median (IQR) | 5.83 (3.67–9.08) | 5.50 (3.83–7.22) | 3.93 (2.33–6.08) | $p<0.001$ [b,c] |
| ARM – birth, hours; median (IQR) | 2.25 (1.00–4.45) | 3.25 (1.03–5.55) | 0.60 (0.25–1.43) | $p<0.001$ [b,b] |
| Onset of labour – oxytocin, hours; median (IQR) | 6.00 (3.92–9.20) | 5.75 (3.98–10.25) | 4.25 (2.50–6.55) | $p<0.001$ [b,c] |
| Oxytocin – birth hours; median (IQR) | 3.18 (1.20–6.42) | 2.85 (1.27–8.32) | 1.37 (0.67–2.92) | $p<0.001$ [b,c] |
| Onset of labour – epidural, hours; median (IQR) | 4.67 (2.75–7.42) | 4.00 (2.42–7.25) | 3.50 (2.00–5.08) | $p<0.001$ [b,c] |
| Epidural – birth, hours; median (IQR) | 5.17 (3.45–8.42) | 5.38 (3.90–14.22) | 3.05 (1.75–4.53) | $p<0.001$ [b,c] |
| Onset of labour – opioids, hours; median (IQR) | 3.78 (2.00–6.67) | 3.83 (1.75–6.00) | 2.75 (1.62–5.33) | $p<0.001$ [b,c] |
| Opioids – birth, hours; median (IQR) | 3.87 (2.05–7.62) | 4.55 (1.82–7.75) | 1.43 (0.83–2.63) | $p<0.001$ [b,c] |
| Onset of labour – first intervention, hours; median (IQR) | 3.80 (2.08–6.42) | 3.67 (2.00–5.75) | 3.08 (1.67–5.17) | $p<0.001$ [b,c] |
| First intervention – birth, hours; median (IQR) | 4.12 (1.98–7.62) | 4.52 (1.75–7.75) | 1.37 (0.58–2.70) | $p<0.001$ [b,c] |

ARM, amniotomy; SROM, spontaneous rupture of the membranes.
[a]Significant difference between multiparae with first pVBAC and primiparae.
[b]Significant difference between multiparae with first pVBAC and multiparae with second vaginal birth.
[c]Significant difference between primiparae and multiparae with second vaginal birth.
* Multiparous women expecting their second child planning a VBAC.
† Multiparous women expecting their second child planning a second vaginal birth.

**Table 3**
Adjusted shared frailty Cox regression models for overall labour duration and the durations of the first and second stages of labour.

| Time interval/comparison | Hazard ratio | 95% CI | p-Value |
|---|---|---|---|
| **Overall labour duration***: | | | |
| Multiparae with first pVBAC with reference primiparae | 0.998 | 0.830–1.201 | 0.987 |
| Multiparae with first pVBAC with reference multiparae with second vaginal birth | 0.319 | 0.265–0.385 | <0.001 |
| **First stage of labour**†: | | | |
| Multiparae with first pVBAC with reference primiparae | 0.916 | 0.774–1.0831 | 0.303 |
| Multiparae with first pVBAC with reference multiparae with second vaginal birth | 0.402 | 0.339–0.478 | <0.001 |
| **Second stage of labour**‡: | | | |
| Multiparae with first pVBAC with reference primiparae | 1.341 | 1.049–1.714 | 0.019 |
| Multiparae with first pVBAC with reference multiparae with second vaginal birth | 0.334 | 0.262–0.426 | <0.001 |

* Adjusted for: maternal age, health insurance, no risk factor in history, induction, meconium-stained liquor, cervical dilatation at admission, birth weight, rupture of the membranes, timing of epidural, timing of opioid, interaction between the timing of epidural and the timing of opioids, type of documentation.
† Adjusted for: maternal age, health insurance, no risk factor in history, induction, meconium-stained liquor, cervical dilatation at admission, birth weight, rupture of the membranes, type of documentation.
‡ Adjusted for: maternal age, cervical dilatation at admission, birth weight, episiotomy, rupture of the membranes, timing of oxytocin, timing of epidural, interaction between parity and timing of oxytocin, interaction between timing of oxytocin and timing of epidural, type of documentation.

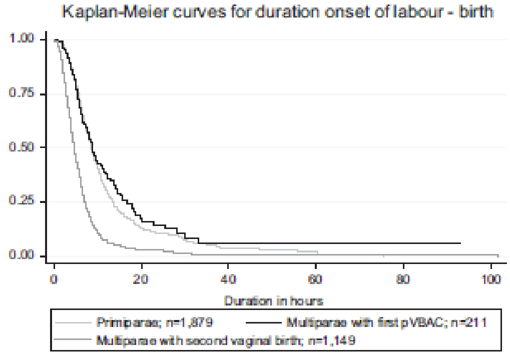


**Fig. 1.** Kaplan-Meier curves for duration onset of labour to birth.

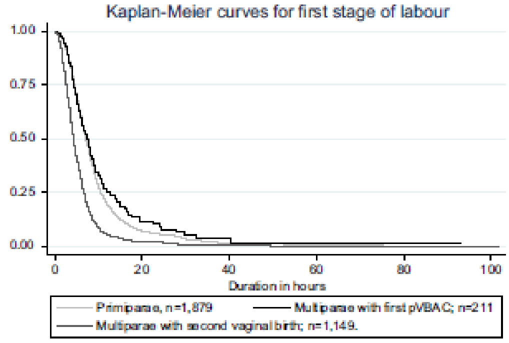


**Fig. 2.** Kaplan-Meier curves for the first stage of labour.

differed significantly as between multiparae with pVBAC and other multiparae (4.52 versus 1.37 hours, $p<0.001$).

*Overall labour duration and the durations of the first and second stages*

The multivariable shared frailty Cox regression model revealed no statistically significant difference in durations between onset of labour and birth as between multiparous women with previous c-section and primiparous women (8.83 versus 8.57 hours, HR=0.998, 95% CI=0.830–1.201, $p$=0.987, Table 3, Fig. 1). In contrast, compared to multiparae with a second vaginal birth multiparae with first pVBAC had a significant longer labour duration (8.83 versus 4.63 hours, HR=0.319, 95% CI=0.265–0.385, $p<0.001$). There was strong evidence for heterogeneity between study locations (theta=0.302, $p<0.001$).

The multivariable analyses confirmed no statistically significant difference in the duration of the first stage of labour for multiparae with pVBAC as compared to primiparae (7.42 versus 7.00 hours, HR=0.916, 95% CI=0.774-1.083, $p$=0.303, Table 3, Fig. 2). Compared to other multiparae, however, multiparae with pVBAC had a significantly longer first stage of labour (7.42 versus 4.25 hours, HR=0.402, 95% CI=0.339-0.478, $p<0.001$). Again, there was strong evidence for heterogeneity between study locations (theta=0.233, $p<0.001$).

In contrast to the comparisons of overall labour duration and the duration of first stage of labour, the multivariable shared frailty Cox regression model revealed that the second stage of labour was shorter for multiparae with pVBAC than for primiparae (0.55 versus 0.77 hours, HR=1.341, 95% CI=1.049–1.714, $p$=0.019, Table 3, Fig. 3). Compared to other multiparae however, multiparae with pVBAC had a longer second stage of labour (0.55 versus 0.22 hours, HR=0.334, 95% CI=0.262–0.426, $p<0.001$). There was also strong evidence for heterogeneity between study locations, which however was minimal (theta=0.035, $p<0.001$).

## Discussion

This was the first study investigating the timing of SROM and of interventions for multiparous women planning a first VBAC and comparing them with primiparous women and multiparous women planning a second vaginal birth. Labour characteristics of multiparae with pVBAC strongly resembled those of primiparae for most parameters but differed significantly from those of other multiparae. However, there were also obvious relevant differences between multiparae with pVBAC and primiparae: multiparae with pVBAC were older, received oxytocin less often, gave birth vaginally significantly less often and had a shorter second stage of labour.

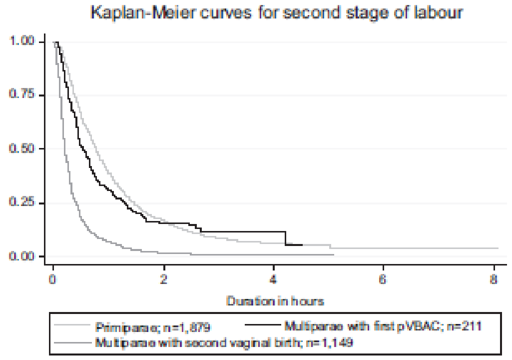


**Fig. 3.** Kaplan-Meier curves for the second stage of labour.

*Baseline and perinatal characteristics*

The similarity in age between multiparous women with first pVBAC and multiparous women with second vaginal birth, and the difference to primiparous women, were expected and naturally caused by the fact that women of both multiparae subgroups were expecting their second child. Multiparae with pVBAC had the highest rate of medical histories containing no risk factors. An explanation may be that in a country like Germany with high c-section and low VBAC rates (EURO-PERISTAT, 2013; Gross et al., 2015), women with a previous c-section and additional risk factors are more often counselled to have an elective c-section in their subsequent pregnancies than those in the other subgroups.

Induction and labour augmentation with oxytocin have been found to be associated with increased rates of uterine rupture during VBAC (Dekker et al., 2010; Guise et al., 2010), which could explain the significantly lower rates for multiparae with pVBAC as compared to primiparae in the current study. This is congruent with guidelines which recommend that oxytocin should be administered with caution to women with pVBAC because of the increased risk of uterine rupture (DGGG, 2010a; RCOG, 2007). The rate of 69.19% of successful vaginal births after previous c-section corresponded to the range of rates found in other studies (60–85%, Balachandran et al., 2014; Knight et al., 2014; Tessmer-Tuck et al., 2014).

*Timing of SROM and interventions and the duration of labour and its phases*

Regarding the timing of SROM and interventions, multiparous women with first pVBAC were similar to primiparous women for all the intervals analysed but differed significantly from multiparous women with second vaginal birth. This can be explained by the shorter overall labour duration of other multiparae, which obviously shortened the time intervals between onset of labour and events or interventions as well as birth. The differences between primiparae and multiparae have been investigated before (Petersen et al., 2011), but no previous study has investigated these aspects for multiparae with pVBAC.

Labour duration from the onset of labour until birth and the duration of the first stage of labour were very similar as between multiparae with pVBAC and primiparae. The similar first stages of labour found in the current study confirmed the findings of Graseck et al. (2012) and Harlass and Duff (1990), but not those of Faranesh and Salim (2011), who found a shorter active phase of labour in multiparae with pVBAC as compared to primiparae. However, the current study investigated the duration of the first stage of labour starting from the onset of labour as defined by the midwife in terms of regular or irregular contraction associated with cervical dilatation, and not only the active phase as Faranesh and Salim (2011). First stage of labour can be subdivided into a latent and an active phase, which is relevant for the assessment of delay in labour progression (Friedman, 1955; Zhang et al., 2010; NICE, 2014). However, there is no clearly defined cut off point (Zhang et al., 2010; NICE, 2014), what makes comparison of phases difficult. The different results regarding the comparison of the duration of first stage of labour may arise from the varying definitions of onset of labour (Hanley et al., submitted for publication) and therefore from differences in the time interval investigated. Different statistical methods or the relatively small sample size of women with pVBAC with risk of imprecise results also have to be considered as potential reasons. By contrast, the shorter second stage of labour in multiparae with pVBAC as compared to primiparae confirmed the findings of Faranesh and Salim (2011) using larger samples and time-to-event analysis. A shorter second stage of labour for multiparae with pVBAC was not to be expected and cannot be explained, because none of the women with pVBAC had previously experienced a completed second stage. However, this finding suggests that a distinction has to be made also between multiparae with pVBAC and primiparae, and not only between multiparae with pVBAC and other multiparae. Further research is needed to confirm these findings in larger samples of multiparous women with a previous c-section.

*Implication for midwifery practice*

Knowledge about the labour patterns of multiparous with first pVBAC may suggest how to improve intrapartum management, which is relevant for a safe and successful VBAC (Scott, 2014). The similarities in frequencies and timings of events and interventions as between multiparae with pVBAC and primiparae and the differences as compared to other multiparae indicate a need to beware of preconceived expectations with regard to labour progression and to exercise patience, especially during the first stage of labour. The shorter second stage of labour might be a relevant aspect for antenatal and intrapartum midwifery care. The area of support for women with a previous c-section in deciding on the mode of birth in a subsequent pregnancy is a challenging one, and there is limited evidence as to how far decision support can bring about an increase in rates of vaginal births (Horey et al., 2013). King et al. (2015) recommend informing women with a previous c-section not only about the benefits and risks of VBAC and elective c-section but also about the high likelihood of a successful VBAC. The information that the second stage of labour of multiparae with pVBAC might be shorter as compared to primiparae could be a further factor increasing the motivation for a trial of labour after a c-section. Midwives may use this information in antenatal counselling. Such knowledge regarding a shorter second stage of labour of multiparae with pVBAC as compared to primiparae might also be useful for intrapartum counselling, support and motivation. However, further research in lager samples is needed to confirm these findings.

*Strengths and limitations*

A strength of the ProGeb study was the total sample size of 3963 participants, of whom only 724 multiparaous women giving birth for at least the third time had to be excluded, so that 3239 participants could be included in this secondary analysis. Furthermore, the documentation of the timing of labour onset, birth, SROM and interventions was done with minute precision. However, the study had its limitations in that it included only 211 multiparous women with a previous c-section planning their second childbirth as a VBAC. The small sample size of this subgroup makes generalisation of the findings questionable. Using prospective as well as retrospective data could be source of reporting bias. This aspect was considered in the regression model as a possible confounder. The inclusion of late preterm births between 34 and 37 gestational weeks could be questioned because of lower birth weights. However labour management of these births does not differ from the one at term (DGGG, 2006, 2012). In order to account for this, birth weight was included in the regression models as a possible confounder. Further limitations were the high intervention rates making it questionable if the findings of this study are generalisable to settings with lower rates. Available national and regional figures from 2005 and 2014 however show comparably high intervention rates (epidural analgesia 18–44%; induction 22–25%, labour augmentation 32%, episiotomy 23–35%) (ZQ, 2006; EURO-PERISTAT, 2013; Aqua, 2015). Women with emergency c-section before rupture of the membranes were considered as receiving amniotomy, which enhanced amniotomy rates. Further weaknesses were that no indications for the first c-section were reported and no information was available with regard to the stage of cervical dilatation at which the c-section was performed. Additionally, the multicentre characteristics of the study may have involved a lack of uniformity in intrapartum care.

Strengths of this secondary analysis were on the one hand the shared frailty Cox regression models, which took account of the variability of the locations; and on the other hand the fact that multivariable analyses were done with the dependent variables labour duration and the durations of the first and second stages of labour, thus taking into account the varying dynamics of the different labour phases. Interventions occurring during the relevant period were included as time-varying covariates, and interventions before the time interval of interest were also taken into account. The different timings of interventions during labour could therefore be taken into account in the regression models. This maximised consideration of the dynamic nature of labour for childbirth, and was something that had not been done in previous longitudinal analyses of labour durations.

## Conclusion

The differences in labour patterns between multiparous women with previous c-section on the one hand primiparous and secundiparous women without previous c-section on the other suggest that multiparae with pVBAC should be considered as a distinct group of birthing women. Expectations regarding labour progression and the timing of events and interventions during the first stage of labour should probably for the most part be similar to those for primiparae. However, the significantly shorter second stage of labour of multiparae with pVBAC as compared to primiparae, was a surprising finding of the current study and cannot be explained. Pregnant women with a previous c-section might be motivated to undergo a trial of labour if they know that the second stage of labour could be shorter as compared to primiparae.

## Conflict of interest

This study has no competing interests.

## Acknowledgements

The ProGeb study was funded by the German Research Council. Many thanks to Professor Gérard Krause for his support as one of the supervisors of the PhD thesis and for his comments on the advanced draft of the manuscript.

## References

Albers, L.L., Schiff, M., Gorwoda, J.G., 1996. The length of active labor in normal pregnancies. Obstet. Gynecol. 87, 355–359.
Albers, L.L., 1999. The duration of labor in healthy women. J. Perinatol.: Off. J. Calif. Perinatal Assoc. 19, 114–119.
American College of Obstetricians and Gynecologists (ACOG, College), Society for Maternal-Fetal Medicine, Caughey, A.B. et al., 2014. Safe prevention of the primary cesarean delivery. Am. J. Obstet. Gynecol. 210, 179–193.
AQUA - Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen (AQUA), 16/1-Geburtshilfe, Qualitätsindikatoren, Bundesauswertung zum Verfahrensjahr 2014, 2015. ⟨https://www.sqg.de/downloads/Bundesauswertungen/2014/bu_Gesamt_16N1-GEBH_2014.pdf⟩.
Arulkumaran, S., Gibb, D.M., Lun, K.C., et al., 1984. The effect of parity on uterine activity in labour. Br. J. Obstet. Gynaecol. 91, 843–848.
Balachandran, L., Vaswani, P.R., Mogotlane, R., 2014. Pregnancy outcome in women with previous one cesarean section. J. Clin. Diagn. Res.: JCDR 8, 99–102.
Bland, J.M., Altman, D.G., 1998. Survival probabilities (the Kaplan–Meier method). Br. Med. J. (Clinical research ed.) 317, 1572.
Blossfeld, H.P., Golsh, K., Rohwer, G., 2007. Event history analysis with Stata. Erlbaum, Mahwah, NJ.
Cheng, Y.W., Eden, K.B., Marshall, N., et al., 2011. Delivery after prior cesarean: maternal morbidity and mortality. Clin. Perinatol. 38, 297–309.
Dekker, G.A., Chan, A., Luke, C.G., et al., 2010. Risk of uterine rupture in Australian women attempting vaginal birth after one prior caesarean section: a retrospective population-based cohort study. BJOG: Int. J. Obstet. Gynaecol. 117, 1358–1365.
EURO-PERISTAT, 2013. European Perinatal Health Report, Health and Care of Pregnant Women and Babies in Europe in 2010. ⟨http://www.europeristat.com/reports/european-perinatal-health-report-2010.html⟩.
Faranesh, R., Salim, R., 2011. Labor progress among women attempting a trial of labor after cesarean. Do they have their own rules? Acta Obstet. Gynecol. Scand. 90, 1386–1392.
Fawsitt, C.G., Bourke, J., Greene, R.A., et al., 2013. At what price? A cost-effectiveness analysis comparing trial of labour after previous caesarean versus elective repeat caesarean delivery. PLoS One 8, e58577.
Friedman, E.A., 1955. Primigravid labor; a graphicostatistical analysis. Obstet. Gynecol. 6 (6), 567–589.
German Society of Obstetrics and Gynaecology (DGGG), 2006. Procedure with premature rupture of the membranes, AWMF guideline Nr. 015/029. ⟨http://www.awmf.org/uploads/tx_szleitlinien/015-029_S1_Empfehlungen_zum_Vorgehen_beim_vorzeitigen_Blasensprung_06-2006_06-2011_01.pdf⟩.
German Society of Obstetrics and Gynaecology (DGGG), 2010a. Pre- and Peripartum Care in Women with Status Post Caesarean Section. ⟨http://www.dggg.de/leitlinienstellungnahmen/archivierte-leitlinien/federfuehrende-leitlinien-der-dggg/⟩.
German Society of Obstetrics and Gynaecology (DGGG), 2010b. Tocolytics to prevent preterm birth, AWMF guideline Nr. 015/025. ⟨http://www.dggg.de/leitlinienstellungnahmen/archivierte-leitlinien/federfuehrende-leitlinien-der-dggg/⟩.
German Society of Obstetrics and Gynaecology (DGGG), 2012. Application of the CTG during pregnancy and birth, AWMF guideline Nr. 015/036. ⟨http://www.awmf.org/uploads/tx_szleitlinien/015-036l_S1_CTG_Schwangerschaft_Geburt_2014-06.pdf⟩.
Grantz, K.L., Gonzalez-Quintero, V., Troendle, J., et al., 2015. Labor patterns in women attempting vaginal birth after cesarean with normal neonatal outcomes. Am. J. Obstet. Gynecol. 213, 226.e1–226.e6.
Graseck, A.S., Odibo, A.O., Tuuli, M., et al., 2012. Normal first stage of labor in women undergoing trial of labor after cesarean delivery. Obstet. Gynecol. 119, 732–736.
Gross, M.M., Schwarz, Ch, Burian, R.A., et al., 2007. Midwifery teams differ in their opinions regarding study participation. Birth Issues 15, 77–82.
Gross, M.M., Burian, R.A., Fromke, C., et al., 2009. Onset of labour: women's experiences and midwives' assessments in relation to first stage of labour. Arch. Gynecol. Obstet. 280, 899–905.
Gross, M.M., Froemke, C., Hecker, H., 2014. The timing of amniotomy, oxytocin and neuraxial analgesia and its association with labour duration and mode of birth. Arch. Gynecol. Obstet. 289, 41–48.
Gross, M.M., Matterne, A., Berlage, S., et al., 2015. Interinstitutional variations in mode of birth after a previous caesarean section: a cross-sectional study in six German hospitals. J. Perinat. Med. 43, 177–184.
Guise, J.M., Eden, K., Emeis, C., et al., 2010. Vaginal birth after cesarean: new insights. Evid. Rep./Technol. Assess. 191, 1–397.
Gutierrez, R.G., 2002. Parametric frailty and shared frailty survival models. Stata J. 2, 22–44.
Hanley, G. et al. Diagnosing onset of labour: a systematic review of definitions in the research literature , BMC Pregnancy Childbirth, submitted for publication.
Harlass, F.E., Duff, P., 1990. The duration of labor in primiparas undergoing vaginal birth after cesarean delivery. Obstet. Gynecol. 75, 45–47.
Horey, D., Kealy, M., Davey, M.A. et al., 2013. Interventions for supporting pregnant women's decision-making about mode of birth after a caesarean. Cochrane Database Syst. Rev. 7, CD010041.

Hosmer, D.W., Lemeshow, S., 2000. Chapter 4. Model-building strategies and methods for logistic regression. In: Hosmer, D.W., Lemeshow, S. (Eds.), Applied Logistic Regression, 2nd edn. John Wiley and Sons, INC.

Karlström, A., Lindgren, H., Hildingsson, I., 2013. Maternal and infant outcome after caesarean section without recorded medical indication: findings from a Swedish case–control study. BJOG: Int. J. Obstet. Gynaecol. 120, 479–486.

Kealy, M.A., Small, R.E., Liamputtong, P., 2010. Recovery after caesarean birth: a qualitative study of women's accounts in Victoria, Australia. BMC Pregnancy Childbirth 10 (47-2393-10-47).

King, V.J., Fontaine, P.L., Atwood, L.A., et al., 2015. Clinical practice guideline executive summary: labor after cesarean/planned vaginal birth after cesarean. Ann. Fam. Med. 13, 80–81.

Knight, H.E., Gurol-Urganci, I., van der Meulen, J.H., et al., 2014. Vaginal birth after caesarean section: a cohort study investigating factors associated with its uptake and success. BJOG: Int. J. Obstet. Gynaecol. 121, 183–192.

Landon, M.B., Hauth, J.C., Leveno, K.J., et al., 2004. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. N. Engl. J. Med. 351, 2581–2589.

Marshall, N.E., Fu, R., Guise, J.M., 2011. Impact of multiple cesarean deliveries on maternal morbidity: a systematic review. Am. J. Obstet. Gynecol. 205, 262. e1–262.e8.

Nair, M., Soffer, K., Noor, N., et al., 2015. Selected maternal morbidities in women with a prior caesarean delivery planning vaginal birth or elective repeat caesarean section: a retrospective cohort analysis using data from the UK Obstetric Surveillance System. Br. Med. J. Open 5, e007434-2014-007434.

National Institute for Health and Care Excellence (NICE), 2014. Intrapartum care for healthy women and babies, https://www.nice.org.uk/guidance/cg190.

Palatnik, A., Grobman, W.A., 2015. Induction of labor versus expectant management for women with a prior cesarean delivery. Am. J. Obstet. Gynecol. 212, 358. e1–358.e6.

Petersen, A., Ayerle, G.M., Fromke, C., et al., 2011. The timing of interventions during labour: descriptive results of a longitudinal study. Midwifery 27, e267–e273.

Petersen, A., Penz, S.M., Gross, M.M., 2013a. Women's perception of the onset of labour and epidural analgesia: a prospective study. Midwifery 29, 284–293.

Petersen, A., Poetter, U., Michelsen, C., Gross, M.M., 2013b. The sequence of intrapartum interventions: a descriptive approach to the cascade of interventions. Arch. Gynecol. Obstet. 288, 245–254.

Prick, B.W., Bijlenga, D., Jansen, A.J., et al., 2015. Determinants of health-related quality of life in the postpartum period after obstetric complications. Eur. J. Obstet. Gynecol. Reproduct. Biol. 185, 88–95.

Regan, J., Keup, C., Wolfe, K., et al., 2015. Vaginal birth after cesarean success in high-risk women: a population-based study. J. Perinatol.: Off. J. Calif. Perinat. Assoc. 35, 252–257.

Regan, J., Thompson, A., DeFranco, E., 2013. The influence of mode of delivery on breastfeeding initiation in women with a prior cesarean delivery: a population-based study. Breastfeed. Medicine: Off. J. Acad. Breastfeed. Med. 8, 181–186.

Royal College of Obstetrician and Gynaecologist (RCOG), 2007. Birth after previous caesarean birth. ⟨https://www.rcog.org.uk/globalassets/documents/guidelines/gtg4511022011.pdf⟩.

Sabol, B., Denman, M.A., Guise, J.M., 2015. Vaginal birth after cesarean: an effective method to reduce cesarean. Clin. Obstet. Gynecol. 58, 309–319.

Scott, J.R., 2014. Intrapartum management of trial of labour after caesarean delivery: evidence and experience. BJOG: Int. J. Obstet. Gynaecol. 121, 157–162.

Sedgwick, P., 2013. Cox proportional hazards regression. Br. Med. J. 374, f4919.

Sedgwick, P., 2014. How to read a Kaplan–Meier survival plot, Br. Med. J. (Clinical Research ed.) 349, g5608.

Shintani, A.K., Girard, T.D., Eden, S.K., et al., 2009. Immortal time bias in critical care research: application of time-varying Cox regression for observational cohort studies. Crit. Care Med. 37, 2939–2945.

Shorten, A., Shorten, B., 2012. The importance of mode of birth after previous cesarean: success, satisfaction, and postnatal health. J. Midwifery Women's Health 57, 126–132.

Smith, G.C., Pell, J.P., Cameron, A.D., et al., 2002. Risk of perinatal death associated with labor after previous cesarean delivery in uncomplicated term pregnancies. J. Am. Med. Assoc. 287, 2684–2690.

Tessmer-Tuck, J.A., El-Nashar, S.A., Racek, A.R., et al., 2014. Predicting vaginal birth after cesarean section: a cohort study. Gynecol. Obstet. Invest. 77, 121–126.

Vahratian, A., Hoffman, M.K., Troendle, J.F., Zhang, J., 2006. The impact of parity on course of labor in a contemporary population. Birth (Berkeley, CA) 33, 12–17.

Zhang, J., Troendle, J.F., Yancey, M.K., 2002. Reassessing the labor curve in nulliparous women. Am. J. Obstet. Gynecol. 187, 824–828.

Zhang, J., Landy, H.J., Branch, D.W., et al., 2010. Contemporary patterns of spontaneous labor with normal neonatal outcomes. Obstet. Gynecol. 116, 1281–1287.

ZQ Centre for quality and management in the health system, 2006. Obstetric, Anual figures for 2005, Module 16/1. ⟨https://www.aekn.de/zq-home/projekte/perinatalerhebung/download-statistiken/⟩.

## 8.4. Submission history of the analysis of the German part of the OptiBIRTH-study

Submission schedule

The envisaged publication of the analysis of observational data of the German part of the OptiBIRTH-study was submitted four times, underwent four review processes and was rejected after review from all journals.

| | |
|---|---|
| 03.10.2016 | Submission to Paediatric and Perinatal Epidemiology |
| 03.12.2016 | Submission to BIRTH |
| 06.02.2017 | Submission to Archives of Gynecology and Obstetrics |
| 25.03.2017 | Submission to Women and Birth |

Rejection comments of the editor and the reviewers

The comments of the editor and the reviewers from Paediatric and Perinatal Epidemiology were constructive and encouraged the discussion of this thesis. They are therefore shared here:

26-Nov-2016

Dear Mrs. Grylka-Baeschlin:

We are writing to you in regard to manuscript (PPE-2016-3000) entitled "Labour processes of women with successful vaginal births after caesarean section" which you submitted to Paediatric and Perinatal Epidemiology. The paper has undergone peer review, and the comments of the referees are appended to the bottom of this letter.

The editors have looked at this carefully together with the criticisms of the referees. We regret to inform you that your paper cannot be accepted for publication in Paediatric and Perinatal Epidemiology. We receive many more papers than what we can publish, and this leaves us to turn down several important papers, including yours. While the comments of the reviewers may appear favorable in general, your manuscript did not receive a priority score high enough for consideration for publication. We are sorry to give you such disappointing news, but hope the referees' comments will be helpful.

The manuscript is indeed interesting, and fairly well written. However, as reviewer 2 notes, there is serious concern for your findings to be the consequence of confounding by indication. There are methods to address confounding by indication (a latent variable analysis is one such method), which you may wish to consider.

We realize the disappointment authors face when their work is declined for publication, and hope the outcome of this specific submission will not discourage you from considering submission of future manuscripts. Thank you for giving us the opportunity to consider your work, and for choosing Paediatric and Perinatal Epidemiology for publication of your paper.

With best wishes,

Cande V. Ananth
Editor-in-Chief
Paediatric and Perinatal Epidemiology

Referee Comments to Author

Referee: 1

The authors examined women's characteristics who had a successful VBAC in comparison to those who failed and had a cesarean section using data from a clinical trial. They used multivariable models to identify potential predictors for successful VBAC. The topic is important; the analysis was well done; and the paper was clearly written. I have two minor points for the authors to consider:

1. The "labor duration" (in Table 4) as is currently calculated is not a predictor for VBAC success. It is a retrospective variable. Furthermore, I'd avoid using the word "predictor" because there is a large difference between "risk factor" and "predictor". One disease can have many risk factors but few predictors or none.
2. The authors examined " intervention-free" time interval in great detail. However, the "intervention" in this paper consisted of various procedures, each of which may have different implications to labor. Combining them together may not provide useful information for clinical practice.

Finally, the results section may be shortened.

Referee: 2

The authors present the results of a retrospective cohort study as a secondary analysis of the OptiBIRTH cluster-randomized controlled trial. The secondary analysis was designed to "investigate sociodemographic, perinatal and labor process-related characteristics of women with successful VBAC compared to those with unplanned cesarean, predictors for the success of planned VBAC and predictors and endpoints for the intervention-free time interval." The researchers used appropriate bivariable and multivariable analytic methods. They concluded "differences in intrapartal factors between the subgroups indicate that women with successful VBAC had more effective labor."

My concerns, criticisms and suggested are summarized below:

1. Abstract (p.2) and Background (p.5): The specific aim is unfocussed and unwieldy, which results in a convoluted analysis.
2. This reviewer feels that due to the limitations of the study design (see below), the study does not contribute significantly to the current body of literature and does not further inform clinicians on labor & birth management, selecting VBAC candidates or decreasing the unplanned cesarean rate, all of which were stated as goals of the research project.
3. Methods (p.6): The sample size is small (N=355 after exclusions), and therefore has limited power for identifying clinical predictors for many VBAC-related outcomes, including VBAC success.
4. Methods (p.6): "19 women were excluded from the sample…" What were the reasons for exclusion?
5. Methods (p.7), Results (p.9) and Comments (p.13): The study exposure variable "intervention-free time interval" is problematic conceptually and analytically because

the association between this exposure and the outcome of failed VBAC is fraught with considerable confounding by indication. The interventions used to define "intervention-free time interval", including amniotiomy, oxytocin, epidural analgesia and opioids, are all prescribed specifically in response or are directly related to labor disorders or longer labors. And thus, for this study's specific aim, one cannot identify these interventions with the intent of avoiding or encouraging them for the purposes of decreasing the VBAC failure rate. The association between labor length, uterotonics or labor disorders and failed VBAC have been extensively studied in two large cohort studies (MFMU Network and Macones (PI) et al).

6. Methods (p.7): More detail is needed on the amount of missing data for each variable. One can glean from the table footnotes that some variables have 10-15% missing data but this should be described for each variable.
7. Results (pp.8 and 10): Birth weight is not an appropriate covariate to assess as a predictive factor for VBAC outcomes since the variable is not available until after delivery (therefore after the preclinical period of prediction).
8. Results (p.9): "Forceps were not used in this study population." Was this by design or by chance? If by design, why?
9. Results (p.10 first paragraph): This paragraph is difficult to understand. In the 6th line, what do the authors mean by "differed similarly"? The last sentence of this paragraph is vague…"in contrast" to what?
10. Results (p. 10 second paragraph): "Maternal age over 35 years was not associated with success of VBAC." But the 95%CI for the OR point estimate approaches 1; do the authors believe that this could be a result of beta error, given prior study results?
11. Results (p.11): As written, it is a little difficult to follow and understand the results description of intervention-free time interval since the interval is similar between the two outcome groups but rates of individual interventions were different between groups when not considering time to intervention.
12. Comments (p.12): The authors state "The results of our study supplement prediction during pregnancy…with the success of women who start to give birth vaginally." This sentence is unclear with poor syntax and based on the methods limitations listed above, I disagree with the claim that the study improves prediction of successful VBAC, if that is what the authors are trying to state.
13. Comments (p.13-14): The authors state: "Labor management should therefore aim to foster labor progression." And, the authors suggest that "natural methods" be used to help foster labor progression since there was an "association between successful VBAC and no intrapartal medical intervention." As I stated above, this conclusion cannot be drawn since there is considerable potential for confounding by indication. Further, the study was not designed to evaluate a causal relationship between intervention with "natural methods" and VBAC success. Thus this study does not provide data to support such a claim or recommendation.
14. I disagree with this statement for all of the study design limitations listed above: "This study revealed new knowledge about the labor process for successful VBAC."
15. Table 1: Notable potential confounding variables that are missing from table 1 (and thus I assume from the analysis) include gestational diabetes, gestational hypertension, smoking and maternal chronic disorders.

## 8.5. Curriculum vitae and scientific activities

### 8.5.1. Curriculum vitae

Personal data:

| | |
|---|---|
| Name: | Susanne Grylka-Baeschlin |
| Address: | Hoefen 7, CH-5420 Ehrendingen |
| Mobile: | +41 78 720 36 98 |
| Email: | Grylka-Baeschlin.Susanne@mh-hannover.de |
| Date of birth: | May, 24th 1966 in Boston (USA) |

Education and further training:

| | |
|---|---|
| 2006, 2011, 2016 | International Board Certified Lactation Consultant (IBCLC) and Recertification |
| 1986 – 1989 | Midwifery training "Ecole le Bon Secours", Geneva, Switzerland |
| 1982 – 1985 | General qualification for university entrance, Matura Typus C, Kantonsschule Baden, Switzerland |

Academic career:

| | |
|---|---|
| 2013 - 2017 | PhD Programme „Epidemiology", Helmholtz Centre for Infection Research HZI Braunschweig and Hannover Biomedical Research School HBRS, Germany |
| 2010 – 2013 | European Master of Science in Midwifery, Hannover Medical School, Germany |

Professional activities:

| | |
|---|---|
| Since 2016 | Research associate, Zurich University of Applied Sciences |
| Since 2015 | Teaching European Master of Science in Midwifery Programme, Hannover Medical School |
| Since 2008 | Breastfeeding consultant in postpartum ward, Cantonal Hospital Baden |
| 2013 – 2017 | Research assistant, Midwifery Research and Education Unit, Hannover Medical School |
| 2005 - 2013 | Midwife in independent practice |
| 2003 - 2006 | Midwife in labour ward, Spital Limmattal, Schlieren |
| 1996 - 2003 | Midwife in labour ward, Cantonal Hospital Baden |
| 1992 - 1995 | Maternity leave |
| 1989 - 1992 | Midwife in labour ward, Spital Limmattal, Schlieren |

8.5.2. Scientific activities since the start of the PhD-studies

Peer reviewed publications

Nilsson C, Lalor J, Begley C, Carroll M, Gross MM, **Grylka-Baeschlin S** et al. Vaginal Birth After Caesarean: Views of women from countries with low VBAC rates. Women and Birth, 2017 [Epub ahead of print], DOI 10.1016/j.wombi.2017.04.009.

Bonzon M, Gross, MM, Karch A, **Grylka-Baeschlin, S**. Deciding on the mode of birth after a previous caesarean section - An online survey investigating women's preferences in Western Switzerland. Midwifery, 2017 [Epub ahead of print], DOI: 10.1016/j.midw.2017.04.005.

Lundgren I, Healy P, Carroll M, Begley C, Matterne A, Gross MM, **Grylka-Baeschlin S** et al. Clinicians' views of factors of importance for improving the rate of VBAC (vaginal birth after caesarean section): a study from countries with low VBAC rates. BMC Pregnancy and Childbirth. 2016 Nov 10; 16(1):350, DOI: 10.1186/s12884-016-1144-0.

Zondag DC, Gross MM, **Grylka-Baeschlin S**, Poat A, Petersen A. The dynamics of epidural and opioid analgesia during labour. Arch Gynecol Obstet. 2016 May 19, DOI: 10.1186/s12884-016-1144-0.

**Grylka-Baeschlin S**, Petersen A, Karch A, Gross MM. Labour duration and timing of interventions in women planning vaginal birth after caesarean section. Midwifery. 2016 Mar;34:221-9, DOI: 10.1016/j.midw.2015.11.004.

Clarke M, Savage G, Smith V, Daly D, Devane D, Gross MM, **Grylka-Baeschlin S** et al. Improving the organisation of maternal health service delivery and optimising childbirth by increasing vaginal birth after caesarean section through enhanced women-centred care (OptiBIRTH trial): study protocol for a randomised controlled trial (ISRCTN10612254). Trials. 2015 Nov 30;16:542,015-1061-y.

**Grylka-Baeschlin S**, van Teijlingen E, Stoll K, Gross MM. Translation and validation of the German version of the Mother-Generated Index and its application during the postnatal period. Midwifery. 2015 Jan;31(1):47-53.

**Grylka-Baeschlin S**, van Teijlingen E, Gross MM. Cultural differences in postnatal quality of life among German-speaking women - a prospective survey in two countries. BMC Pregnancy Childbirth. 2014 Aug 15;14:277,2393-14-277.

Published abstracts

**Grylka-Bäschlin S**, Petersen A, Karch A, Gross MM. Geburtsdauer und Zeitpunkte von Blasensprung und Interventionen von Zweitgebärenden mit Zustand nach Sectio (Labour duration and timing of interventions in secundiparae with previous caesarean section). 27. Deutscher Kongress für Perinatale Medizin 2015, 01.-03.12.2015, Berlin, Germany. doi: 10.1055/s-0035-1566517.

Bonzon M, Karch A, Stoll K, **Grylka-Bäschlin S**, Gross MM. Vaginal mode of birth after previous caesarean section versus elective repeat caesarean section: Factors associated with women's preferences in Western Switzerland. 27. Deutscher Kongress für Perinatale Medizin 2015, 01.-03.12.2015, Berlin, Germany. doi: 10.1055/s-0035-1566515.

Gehling H, **Grylka-Bäschlin S**, Gross MM. Der Europäische Masterstudiengang Hebammenwissenschaft an der Medizinischen Hochschule Hannover (The European Master Programme in Midwifery at Hannover Medical School) . 27. Deutscher Kongress für Perinatale Medizin 2015, 01.-03.12.2015, Berlin, Germany. doi: 10.1055/s-0035-1566490.

Zondag D, Gross MM, **Grylka-Baeschlin S**, Petersen A. Association between analgesia and labour duration as well as mode of birth. 27. Deutscher Kongress für Perinatale Medizin 2015, 01.-03.12.2015, Berlin, Germany. doi: 10.1055/s-0035-1566489.

**Grylka-Bäschlin S**, Groß MM. Postpartale Lebensqualität als Ergebnisparameter der Hebammenbetreuung und der peripartalen Versorgung (Postnatal quality of life as an outcome of midwifery and perinatal care). Zeitschrift für Hebammen-wissenschaft (Journal of Midwifery Science), 2014, 02 (Sup. 01), Doc14dghwiP1. DOI: 10.3205/14dghwi08.

Publications without peer review

**Grylka-Bäschlin S,** van Teijlingen E, Gross MM. Postpartale Lebensqualität beurteilen (Assessing postnatal quality of life). Hebamme.ch, 2017; 4:20-23.

**Grylka-Bäschlin S**, Groß MM. Die OptiBIRTH-Studie: Geburten nach Sectio (The OptiBIRTH-study: births after caesarean section). Die Hebamme 2016; 29:226-232.

Bernloehr A, **Grylka-Baeschlin S**, Schwarz C, Gross MM (Do midwives need master studies?). Brauchen Hebammen ein Masterstudium?. Hebammenforum, 2015; 6(1):130-133.

Records in Study Within A Trial (SWAT)-repository

**Grylka-Baeschlin S**. Impact of questionnaire design on response rates and satisfaction of the participants. SWAT07, 2014 May 28 1632, Available: http://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/

**Grylka-Baeschlin S**. Telephone screening versus face-to-face screening for the identification of participants in a multicentre trial. SWAT08, 2014 May 28 1645, Available: http://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/

Presentations without published abstract

Gross MM, Petersen A, Schwarz C, Weckend M, Gehling H, **Grylka-Baeschlin S**. Length of intervention free intervals during labour – an important step towards normal birth. 31st Triennial Congress of the International Confederation of Midwives, 18.-22.6.2017, Toronto, Kanada.

**Grylka S**, Pehlke-Milde J, Gross MM. Chancen und Herausforderungen von Studienhebammen am Beispiel der OptiBIRTH-Studie (Opportunities and challenges of study midwives using the example of the OptiBIRTH-study). 4. Hebammensymposium, 21.01.2017, ZHAW Winterthur, Switzerland.

**Grylka-Bäschlin S**, Gross MM. Anwendung des Mother-Generated Index in der Hebammenforschung und der Hebammenbetreuung – eine prospektive Studie in zwei deutschsprachigen Ländern (The application of the Mother-Generated Index in midwifery research and midwifery care – a prospective study in two German speaking countries). 3. Hebammensymposium, 17.01.2015, ZHAW Winterthur, Switzerland.

**Grylka-Baeschlin S**, van Teijlingen E, Gross MM. Cultural differences in postnatal quality of life among German-speaking women. COST Optimising Childbirth Across Europe conference 10.04.2014, Brussels, Belgium.

Invited presentations

**Grylka-Bäschlin S.** Stillen des späten Frühgeborenen (Breastfeeding of the late preterm infant)". Further training for midwives 14.05.2017, Hannover Medial School, Germany.

**Grylka S**. Der frühe Start ins Leben – Die Begleitung in der Frühgeburt (Early start into life – support during prematur birth). 8. Internationaler Dialog: Geburtshilfe, Hebammen, Anästhesie. und Neonatologen im Gespräch 22.-24.09.2016, AKH Wien, Austria.

**Grylka S**, Gross MM. OptiBIRTH-Studie: Vaginal gebären nach Sectio?- Eine cluster-randomisierte Multicenterstudie (OptiBIRTH-study: giving birth vaginally after caesarean section? – A cluster randomised multicenter study).. Eröffnungstagung HELIOS Universitätsklinikum Wuppertal, 02.07.2016, Wuppertal, Germany.

**Grylka-Bäschlin S**, Gross MM. OptiBIRTH-Studie: Geburten nach Kaiserschnitt (OptiBIRTH-study: Births after caesarean section). 5. Forum Geburtshilfe für Hebammen und Frauenärzte, 24.06.2016, Kassel, Germany.

**Grylka-Bäschlin S**. Die Betreuung während des Gebärens ist Kernaufgabe der Hebammen. Inputvortrag Podiumsdiskussion Zukunft der vaginalen Geburt (Intrapartum care is the key task of midwives. Input presentation for the panel discussion about the future of vaginal births). 27. Deutscher Kongress für Perinatale Medizin 2015, 01.-03.12.2015, Berlin, Germany.

**Grylka-Bäschlin S**. Der deutsche Arm der OptiBIRTH-Studie – Projektmanagement einer Multicenterstudie an der AG Hebammenwissenschaft in Hannover (The German arm of the OptiBIRTH-study – project management of a multicentre study at the midwifery research and education unit in Hannover). 27. Deutscher Kongress für Perinatale Medizin 2015, 01.-03.12.2015, Berlin, Germany.

**Grylka-Bäschlin S**, Gross MM. Pro vaginale Geburt nach Kaiserschnitt – weshalb ist sie so wichtig und wie kann sie gelingen?. (Pro vaginal birth after caesarean section- why is it so important and how can it succeed?) Input presentation for the discussion about vaginal birth after caesarean section Update Perinatalmedizin: Geburtsmodus spontan versus Sectio, 11.11.2015, Hannover, Germany.

**Grylka S**. Der Schmerz als physiologischer Wegbereiter der Geburt (Pain as a physiological precorsor of giving birth). 7. Internationaler Dialog: Geburtshilfe, Hebammen, Anästhesie und Neonatologen im Gespräch 11.-13.09.2014, AKH Wien, Austria.

**Grylka-Bäschlin S**. Die OptiBIRTH-Studie: Eine Studie für Schwangere mit Zustand nach vorangegangenem Kaiserschnitt Kaiserschnitt (The OptiBIRTH-study: a study for pregnant women with a previous caesarean section). Further training for midwives 14.05.2014, Hannover Medial School, Germany.

Posters without published abstracts

Gross MM, Weckend M, Ruescher N, Gehling H, Sitter E, Spineli L, **Grylka-Baeschlin S**. Effectiveness of self-diagnosed vaginal pH scores for the prevention of preterm birth: a systematic review. 31st Triennial Congress of the International Confederation of Midwives, 18.-22.6.2017, Toronto, Kanada.

**Grylka S,** Iglesias C, Läuppi M, Pehlke-Milde J. Finding a midwife for sure – Evaluation of Familystart Zurich. Swiss Midwifery Conference, 18.05.2017, Geneva, Switzerland.

**Grylka-Baeschlin S**, Weckend M, Gehling H, Gross MM. The OptiBIRTH-study - project management of the German arm of the trial at the Midwifery Research and Education Unit. 50 Years of Scientific Excellence in Medicine at Hannover Medical School, 25.09.2015, Hannover, Germany.

**Grylka-Baeschlin S**, Mikolajczyk, R, Karch A, Gross MM. How is timing of the rupture of the membranes associated with labour duration and oxytocin administration?. 10th Research Conference Normal Labour and Birth 15.-17.06.2015, Grange over Sands, English Lake District, UK.

Ehrendingen, 07.09.2017

## 8.7. Declaration

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