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# Low numbers of post-term pregnancy inductions result in high numbers of emergency caesarean sections

A comparison of morbidity and mortality between term and post-term deliveries in the Murmansk County Birth Registry 2006-2011

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## Abstract

**Background:** A post-term pregnancy is a pregnancy lasting 294 days or more. The incidence of post-term pregnancies world-wide varies from 1 to 13%. Births taking place post-term seem to have a higher risk of perinatal mortality and morbidity compared with term deliveries. To avoid the possible risks associated with post-term pregnancy and birth, many countries practice routine induction of labour before or when women reach the post-term limit. The aetiology of the possible increased risks from post-term pregnancies is unclear, but placental insufficiency seems to play a role. There is no test which can reveal which women will progress post-term or which babies are particularly at risk. Women with a high-risk pregnancy should not progress to post-term. This study aims to address these issues from the perspective of a delivering population in North-West Russia.

**Objective:** This thesis compares women who went into spontaneous labour at term with women who gave birth post-term with regards to five outcome variables: perinatal mortality, threatening intrauterine asphyxia, Apgar score below 7 (after 5 minutes), meconium staining and emergency caesarean section.

**Material and methods:** The thesis used data from the Murmansk County Birth Registry from 2006 to 2011. The final study group consisted of 41 417 women of which 1 895 gave birth post-term and 39 522 at term. Logistic regression analysis was used to compare the groups, which in turn were adjusted for mothers' age, civil status, education, parity, BMI, smoking, preeclampsia, birth weight and birth defects. Interaction analyses were performed for mothers' age, BMI and parity.

**Results:** The main results are that the women in the post-term group had statistically significant higher odds of emergency caesarean section (OR 1.33, 95% CI 1.16 – 1.52), threatening intrauterine asphyxia (OR 1.37, 95% CI 1.17 – 1.61) and meconium staining (OR 1.49, 95% CI 1.32 – 1.69) compared with women in the term group. The odds for perinatal mortality (OR 1.04, 95% CI 0.48 – 2.23) and Apgar score below 7 (after 5 minutes) (OR 1.17, 95% CI 0.75 – 1.83) were not statistically significant. The results were equivalent for both univariate and multivariable analysis.

**Conclusion:** The most important finding of the study is that the odds of emergency caesarean section were 33% higher for the women in the post-term group compared with the term group. The possible implications of this finding are unnecessary high costs for the health care system, and increased morbidity for the women and children in the North-West Russia. The odds of experiencing threatening intrauterine asphyxia and meconium staining were also higher for women in the post-term group compared with the term group, which can lead to interventions such as emergency caesarean section, where threatening intrauterine asphyxia would act as a mediator, and an affected baby. The birth institutions in Murmansk County should consider inducing more women for post-term pregnancy when reaching $42^{+0}$ weeks.

**Key words:** post-term pregnancy, perinatal mortality, morbidity, Murmansk, Russia, induction of labour.

## Abbreviations and terminology

| | |
|---|---|
| Apgar score | Method of classifying the condition of a baby right after birth, at 1, 5 and 10 minutes. Heart rate, colour, respiration, reflex and muscle tone are considered, giving a score of 0 to 2 for each |
| Breech delivery | When the foetus at birth presents with its buttocks first |
| CS | Caesarean section, divided in elective CS and emergency CS |
| CTG | Cardiotocography, a method of external foetal surveillance of the heartbeat and contractions |
| GA | Gestational age |
| Induction of labour | Attempt to artificially start labour by a medical or mechanical intervention |
| LMP | Last menstrual period |
| Mal-presentation | When the foetus during birth presents with any other body part than the back of the head |
| MCBR | Murmansk County Birth Registry |
| Meconium | Intestinal content of the foetus passed into the amniotic fluid |
| Oligohydramnios | When the amount of amniotic fluid surrounding the foetus is below normal level |

| | |
|---|---|
| Operative vaginal birth | When the baby is born vaginally with the help of forceps or vacuum suction |
| PM | Perinatal mortality, deaths occurring from gestational week 22 to six completed days after birth |
| Post-partum haemorrhage | Bleeding from the uterus or the birth canal after birth |
| Primiparous | A woman expecting her first child |
| SGA | Small for gestational age |
| WHO | World Health Organization |

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# 1. Introduction

Post-term pregnancy and labour are associated with higher risk of mortality and morbidity for both mother and child compared with term deliveries [1]. In order to reduce this risk, an option is to artificially induce labour once the woman approaches or passes the post-term limit. This thesis aims to address post-term related pregnancy risks from the perspective of a delivering population in Russia, by comparing women who gave birth post-term to women who went into spontaneous labour at term.

Normally, a pregnant woman will enter into a prenatal care program, consisting of consultations and examinations by midwives or doctors. During the first routine ultrasound scan she is presented with an estimated due date for the birth of the baby. This due date often becomes a mental “deadline” for the woman. Even though only 5.0% of women give birth on their actual due date [2], there is a popular misconception that if the baby is not born before or on this date, the pregnancy has progressed to post-term. Many women conceive this transition from a normal pregnancy to a post-term pregnancy as negative. They are either tired of being pregnant or believe that the health of the foetus is compromised once the due date is passed, often willing to go great lengths in order to get the labour started. A due date is only the best available estimate of when a baby should be born, while in reality, anything between three weeks before to two weeks after the due date is considered to be within term [1]. It is not clear why some women progress past term, as the aetiology behind post-term pregnancies is not well established. According to a large study by Roos et al., there seem to be positive associations between post-term deliveries and being primiparous (i.e. women who have not given birth before), being above the age of 30 and being obese [3]. The evidence of increased mortality from post-term pregnancies is ambiguous. A large study by Olesen et al. in Denmark found a 33%

increased risk of perinatal mortality (PM) (OR = 1.33) in the post-term group [4], while another large study from Norway by Morken et al. found no increased mortality risk for post-term babies compared with term babies when gestational age (GA) was decided by ultrasound [5].

For the baby, apart from PM, some of the most frequent morbidity outcomes considered in post-term studies are intrauterine asphyxia, oligohydramnios, meconium staining, transfer to a neonatal intensive care unit, neonatal encephalopathy and Apgar score below 7 (after 5 minutes). For the mother, the most studied outcomes are caesarean section (CS), operative vaginal births, perineal injury and post-partum haemorrhage [1].

Many countries practice routine induction of labour (i.e. artificially start labour) at some point after due date is passed in an attempt to reduce the above-mentioned risks of mortality and morbidity [1], because there is no uniform antenatal test which can predict which babies actually will need to be induced [6]. In addition, certain detrimental outcomes seem to vary according to population groups, such as meconium staining [7]. It is therefore difficult to arrive at an international consensus for a routine that can reduce the absolute risk of post-term pregnancies.

## 1.1 Purpose and objective

The study data are collected from the Murmansk County Birth Registry (MCBR), constituting women who gave birth between January 1st 2006 and December 31st 2011. The women have been further divided into two study groups, those who gave birth at term and those who went on to deliver post-term. If post-term deliveries carry the same risk in Murmansk County as in those populations described above and in the literature, the incidence of detrimental outcomes should be higher in the post-term group. The nullhypotheses are that there is no difference in PM, threatening intrauterine asphyxia, Apgar score below 7 (after 5 minutes), meconium staining and emergency CS for women who gave birth post-term compared with women who gave birth at term.

## 2. Theory

The average length of a pregnancy is 280 days when estimated by ultrasound, equalling 40 weeks$^{+0}$ days. The World Health Organization (WHO) and a majority of countries use this definition of pregnancy length, but some countries use other estimates based on national guidelines. Norway, for example, does not follow WHO guidelines, and determines the length of a pregnancy to be 282 days [8]. Generally, a woman is defined within term if she gives birth between 259 and 294 days of her pregnancy (week 37$^{+0}$ and 41$^{+6}$) [1]. It is within this time-period that the baby has the optimal chance of survival.

Before concluding on how to clinically manage a post-term pregnancy, it is important to correctly estimate the GA of the baby. The methods in use are: the last menstrual period (LMP), ultrasound, or a combination of both. There is no international agreement on which method to use and they all yield slightly different results. The ultrasound method estimates the GA by comparing several measurements of the foetus to a chosen reference chart of foetal growth. Ultrasound is replacing LMP worldwide, but does not provide a gold standard of measurement because the growth charts used as reference guide differ between countries and even hospitals [9]. The lack of a common method to estimate GA and the use of mixed methods makes it complicated when comparing studies.

Before ultrasound was routinely used to estimate the due date, or in settings where ultrasound is not available, GA may be decided by using information from LMP, where the days of pregnancy are counted from the first day of the last menstrual period and then adding 280 days. Using LMP, compared to ultrasound, tends to overestimate the GA, according to the study by Savitz et al., the average overestimation was 2.8 days [10]. Mongelli et al. demonstrated the importance of this differentiation in their study from

1996 when they replaced LMP with ultrasound for determining GA, the incidence of post-term pregnancies was reduced from 11.5% to 3.5% [9]. In addition to the actual overestimation, relying solely on LMP for determining GA is regarded as imprecise for several reasons. It is common that women cannot recall the exact dates in question, there are biological variations in a menstrual cycle [8] (anything between 21 and 35 days is within the normal range) and the mother might be using oral contraceptives at the time of conception [6]. Only if the woman has regular 28 days cycles and know precisely the day of the conception can this method be absolutely trusted.

The incidences of post-term pregnancies worldwide vary considerably, from 1% to 13% [11, 12]. Some variation in incidence could be expected because of biological variations or environmental impacts. A study by Patel et al. showed that the average gestation for African British and Asian British women was a week shorter compared with white British women [7]. In general, the main explanatory factors, however, are different methods used to estimate GA and inaccurate dating of pregnancy [13]. In addition to the previously mentioned predictors for post-term pregnancy, a study by Jukic et al. demonstrated other important predictors such as age of the mother (where one year increase added approximately one day to the pregnancy), mothers' birth weight, (where each 100 gr added approximately one day to the pregnancy) and previous pregnancy lasting one week longer than the average pregnancy (adding 2.5 days to the current pregnancy) [14].

Potential risks for mother and baby, if the pregnancy progresses post-term, are listed in the introduction. The importance of the five chosen outcomes considered in this thesis is explained below. PM is the primary outcome and warrants no further explanation. The secondary outcomes: threatening intrauterine asphyxia is important because it can add information on long-term prospects for the baby. A baby subjected to severe asphyxia during birth can suffer different degrees of mental impairment or other types of brain damage due to oxygen deprivation. Apgar score below 7 (after 5 minutes) may also indicate possible long-term impairments. Meconium staining can lead to meconium aspiration syndrome, which is a rare, but potential fatal condition where the lungs of the baby become swelled and inflamed caused by aspiration of thick meconium at birth [15]. Emergency CS as an outcome is important because it can have serious consequences for future pregnancies such as placenta previa (placenta covering the opening of the uterus, with high risk of bleeding and making vaginal birth impossible) and placenta accreta (the placenta has grown into the wall of the uterus, not separating after birth, potentially causing severe bleeding) [16]. Emergency CS also carry the risk of wound infection, embolism and high blood loss for the mother [17]. For babies born by emergency CS, more and more research is being published suggesting a possible link between CS and a later risk of diabetes, asthma and allergies compared to babies being born vaginally [18, 19]. The suspected cause is that babies born by CS are not exposed to the bacteria of the mother's birth canal, which influences the first colonisation of gut bacteria in the baby [20].

Although the cut-off $42^{+0}$ weeks is used in research for defining a post-term pregnancy, there is no clear threshold for when the risk of mortality and morbidity actually increases, with different studies indicating increased risk from as early as week 38 [21-23]. The presumed aetiology is believed to be placental insufficiency [24], especially for small for gestational age (SGA) foetuses [25]. A foetus being SGA means that it has a weight lower than a specific percentile, normally the $10^{th}$ percentile [26]. The lower-than-normal growth can have a genetic cause, but most commonly, it is due to pregnancy-related conditions, which can compromise the flow of oxygen and nutrients to the baby, for example preeclampsia, infections and smoking. The SGA-babies have higher mortality and morbidity compared with normal babies [26] all through the pregnancy, but most of these babies are diagnosed after birth because it is difficult to diagnose such a condition in utero [27]. Carrying a SGA-foetus  is therefore a high-risk pregnancy that should not proceed to post-term, but this will sometimes happen, as a high proportion of SGA-babies are undetected until birth.

## 2.1 Induction of labour

Inducing labour to avoid increased risk linked to post-term pregnancy is frequently performed in hospital settings [1]. It is near impossible to predict which women will give birth at week 40 or week 42, even close to delivery. The clinical solution is to induce or perform a CS in women within a certain time limit. Depending on the state of the cervix and the favoured routines of the specific hospital or country, labour is usually induced by use of drugs such as misoprostol to soften the cervix, oxytocin to create contractions, or mechanical rupture of membranes to induce contractions [1]. Detrimental side effects are linked to induction of labour just like the abovementioned possible negative effects from post-term deliveries, namely, prolonged labour, post-partum haemorrhage, emergency CS and traumatic birth [1]. Although induction of labour has been associated with an increased risk of emergency CS compared to waiting for spontaneous labour for women with a post-term pregnancy [28], this association could not be found in the reviews consulted from the last 12 year-period such as the Cochrane review [1] , Wennerholm et al. [29], Sanchez-Ramos et al. [30] and Caughey et al. [31]. It should be noted that most of these reviews consider the same trials and studies, concluding that very few, if any of the trials included, are of high quality.

The latest Cochrane review recommends induction in week 41 [1], up to seven days before the current recommendation. Adhering to this recommendation would result in a significant increase of inductions resulting in a similar increase of risks associated with induction of labour. Similarly, such a change will increase the economic burden for each hospital and the health system as a whole. An induction is, per definition, a high risk birth, which requires more surveillance, medicines, use of technology and presence of staff compared with a normal birth. For the pregnant women, the possible implications of such a change of routine can be twofold: some women might be relieved not having to pass their due date by more than a week, while for others wanting a normal birth, it can cause a higher level of stress as the time frame for giving birth at term is narrowed. Further, it can become more difficult to defend their choice not to be induced. It would be crucial to provide women with good information on the risk of an induction versus the risk of waiting, and it would be important to strongly differentiate between high risk and low risk pregnancies. Changing a routine procedure sends a strong signal to a group in a vulnerable situation and must therefore be carefully considered.

The most important outcome measure of any induction regime is how many women need to be induced to avoid one perinatal death. To calculate this, number-needed-to-treat (NNT) analysis is used. According to the latest Cochrane Review from 2012, 410 women need to be induced to avoid one perinatal death [1]. The review concludes that women should be offered induction of labour at 41 completed weeks of gestation. This practice seems to reduce the risk of perinatal death without increasing the risk of caesarean section.

If a woman is diagnosed with either a pre-existing condition or a condition acquired during pregnancy such as diabetes, high blood pressure or growth-restricted foetus, she should not be allowed to progress to a post-term state of pregnancy. According to the Cochrane review, a healthy woman, carrying a healthy foetus in a pregnancy with no complications, can, as an alternative to induction of labour, be followed closely with foetal surveillance at regular intervals by cardiotocography (CTG) and ultrasound, which is referred to as *expectant management* [1].

## 3. Background: the situation in Murmansk County

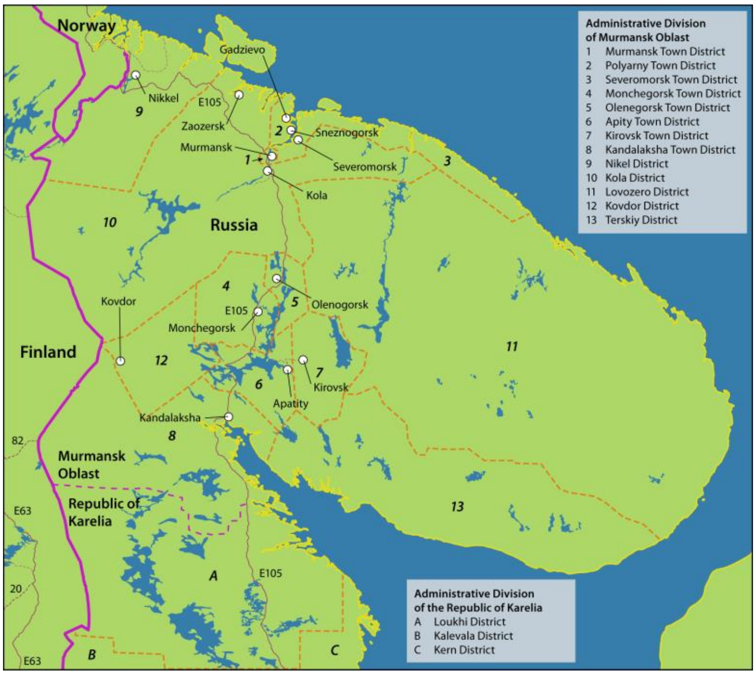


**Figure 1 - Map of the Kola Peninsula (Map produced and licensed by the graphics department at UiT, The Arctic University of Norway).**

Murmansk County is located in North-West Russia, bordering Norway and Finland. The population, mainly ethnic Russians, was estimated at 857 000 in 2008 [32], and the major city is Murmansk. There are 15 delivery departments in the county and there were a total of 8979 births in 2008 [32]. The expertise and technology, which these delivery departments can supply, classify their level of care. This means that high risk pregnancies and high risk births are transferred to the larger hospitals in Murmansk city where facilities such as neonatal intensive care units and blood banks are available [32]. Both midwives and gynaecologists are employed at the maternity wards, but births are mainly handled by gynaecologists, while midwives have an assisting role [33]. As is also the case in the rest of Russia, almost all women give birth in these institutions with skilled attendance [34].

According to a previous analysis from the MCBR, the PM was 11.2 per 1000 live births in 2009 [32]. Since there is no national birth registry in Russia, it is difficult to predict how applicable the numbers from Murmansk County are to the rest of the country. Limited research on maternal and perinatal health in Russia is available in English, but smaller research projects indicate that the PM differs by region. The PM is especially high in regions where indigenous populations are prominent [35].

The fertility rate of Murmansk county is not known, but for the whole of Russia the latest number stands at 1.5 per woman (2013) [36], well below the replacement rate of 2.1 which is needed in order to keep the population constant. Todays' medical system in Russia is influenced by its lack of internationalisation throughout the Soviet era and has resulted in a specialist-centred system with focus on pathology [37]. During the Soviet era, high numbers of health personnel and hospital beds were considered the main indicators of health care quality and their numbers were, in fact, much higher than in Western Europe [33]. After the collapse of the Soviet Union there was a sharp decrease in fertility rates creating a huge surplus of health care providers and infrastructure, which in turn lead to an over-use of antenatal check-ups and hospitalisation in maternal health care situations [34]. Antenatal care in Murmansk County is mainly provided by doctors, often different kinds of specialists, and it is not uncommon that a woman goes through 20 to 30 check-ups during one pregnancy [38]. In comparison, WHO recommends a minimum of four antenatal care visits for a normal pregnancy [39]. Because of the situation described above, any minor sign of pathology often leads to hospitalisation. According to a study by Heiberg and Skurtveit, more than 50% of women were admitted to hospital during pregnancy, often for 14 days or more. The most common causes for admittance were threatening labour, high blood pressure and oedema [38].

Several factors regarded as high risk in the Russian health system, are not treated as such in other countries. Pregnant women older than 25 years are considered high risk because of their advanced age [33]. Another example is that among Norwegian pregnant women, 4.5% were diagnosed with anaemia [40], while in the MCBR 40.1% of the women were diagnosed with some form of anaemia (mild, moderate or severe). This is a direct result of lowering the limit for what is considered anaemic in Russia to be able to admit women to hospital or prescribe drugs. An unusually high amount of women with complicated labour or pregnancies are reported in the MCBR, each requiring prescription drugs or hospitalisation. These findings resonate with studies done in other parts of Russia. Parkhurst et al. suggest the reason to be threefold: the doctor prescribing hospitalisation can be rewarded for handling a "complicated" case, the hospitalisation reduces the risk of complaints from the patients and a long-lasting hospitalisation leads to higher reimbursement to the hospital from state funding [34]. In addition, doctors in Russia are often paid by pharmaceutical companies to supply certain medicines to patients [41].

In this thesis, 1895 women were included in the post-term group. Only 99 or 5.2% of these were induced, even though according to A. Kovalenko, the directives from the Ministry of Health in Moscow state that women should be induced when they reach the limit of $42^{+0}$ weeks [Personal communication, 2015 Oct 20]. The reasons behind not complying with national guidelines are unclear and not within the scope of the thesis, but the consequences of this practice will be investigated by comparing women giving birth post-term with women giving birth at term, considering five mortality and morbidity outcomes.

# 4. Material and methods

## 4.1 Material

The data material used in the thesis stems from the Murmansk County Birth Registry (MCBR) in North-West Russia. It was established in 2006 in a joint effort between the University of Tromsø and the Murmansk County Health Department and was operational until the end of 2012. Approximately 61 000 births have been registered in the database. The aim of the registry was to monitor maternal and perinatal health, generate new procedures for maternal and perinatal health care and provide data which could be used for future research [32]. The registry is modelled after the Norwegian Birth Registry, and registration was made obligatory by decree. Already after the first year of running, 98.9% of all deliveries were included in the MCBR [32].

## 4.2 Study population

The women included in this study gave birth between January 1st 2006 and December 31st 2011, 52 806 women in total. It was not possible to obtain data from the last year, 2012, because these data were not ready when the work on the thesis started. Since this study only compares women who gave birth post-term with women who gave birth at term, those who gave birth before week 37 and after week 45 were excluded (n = 4518). The post-term upper limit was set at $45^{+0}$ weeks in line with existing literature and to avoid possible inclusion of unrealistically high GA-values [42]. Additional exclusion criteria were twin births (n= 243), as they are considered high risk pregnancies with higher mortality and morbidity than singleton pregnancies [43]. Induced labour at term (n= 1349) was excluded as a possible confounder because these women will normally have comorbidities such as diabetes, preeclampsia and small-for-gestational babies and would therefore not be allowed to progress to a post-term pregnancy. Elective CS was excluded (n= 4741) because women elected to have a CS cannot be delivered by emergency CS as the two interventions are mutually exclusive. Women with previous CS were not excluded because 93.2% of these women had a repeat elective CS in their next pregnancy according to a master's degree from 2012 [44] and would therefore be excluded through the elective CS group.

## 4.3 Variables

### 4.3.1 Dependent variables

There are five separate outcome variables included in the analysis: PM, Apgar score below 7 (after 5 minutes), threatening intrauterine asphyxia, meconium staining and emergency CS.

The primary outcome variable is:

PM, which has been created by combining three variables in the registry: status of child (miscarriage = 0, live born = 1, stillborn = 2), time of child's death (if live born, dead within 24 hours) and date of child's death (if live born, dead after 24 hours). The last variable has been filtered to leave out all deaths which occurred later than 6 completed days after delivery (the end of the perinatal period) [45].

The secondary outcome variables are:

- The variable threatening intrauterine asphyxia during birth (0= no, 1= yes) was used without any alterations.

- The variable Apgar score at 5 minutes in infant (continuous) was recoded to a dichotomous variable Apgar score below 7 (after 5 minutes). Babies with Apgar score 7 to 10 after 5 minutes = 0 and those with Apgar score from 0 to 6 after 5 minutes = 1.

- The variable meconium staining (0= no, 1= yes) was used without any alterations.

- The variable emergency CS was created from the variable was the CS planned prior to delivery? (0= no, 1= yes), where elective CS have been filtered out to leave only CS not planned. In the new variable not planned CS = 1, while all other women in the study population = 0.

#### 4.3.2 Independent variables

For the variables mothers' age, birth weight and BMI, the population mean value was used as the reference category.

- The registration method for GA was modified in 2009 and for this reason several variables had to be used and combined in order to obtain reliable GA for all women. Mainly, GA decided by ultrasound was used. The variable gestational age by ultrasound was created by computing the difference between the variable predicted date of delivery by ultrasound from the date of birth of the child. 280 days were then added to all the values. For those women who did not have a value for predicted date of delivery by ultrasound (n=3463), the LMP-value was used. The variable gestational age by LMP was created by subtracting the variable date of birth (of the baby) from the variable first day of the last menstrual period. The final variable post-term pregnancy combined the two previous variables, and was computed by selecting all women who gave birth from 294 days to 315 days, equalling $42^{+0}$ to $45^{+0}$ completed weeks, coding them as 1, while the remaining women were coded as 0.

- The variable body mass index (BMI) was computed by dividing the women's weight in kilos at first visit to the gynaecologist by height in centimetres squared. This linear variable was then categorized into five groups, according to the WHO BMI classification [46] where BMI <18.5 = group 1 is underweight, 18.5 to 24.9 = group 2 is normal weight, 25 to 29.9 = group 3 is overweight, 30 to 34.9 = group 4 is obese class I and ≥35 = group 5 is obese class II. The cut-off points for exclusion were BMI below 10 or above 60, since these values would be considered outside of range.

- The variable mothers' age at time of delivery was given in years. The mean age was then computed in the demographic table. For the analysis, the linear variable was categorized into 5 groups: <20 years = group 1, 20-24 = group 2, 25-29 = group 3, 30-34 = group 4, ≥35 = group 5. Cut-off points were set at 13 and 50 years.

- The variable birth weight is the weight of a baby at delivery measured in grams. It was computed from the variable baby's weight, which was measured in hectograms, then multiplied by 10. The mean weight was calculated by using the computed variable in grams. The variable was categorized into 5 groups in the analysis <2500 g = group 1, 2500 to 2990 g = group 2, 3000 to 3490 g = group 3, 3500 to 3990 g = group 4 and ≥4000 g = group 4. The cut-off point was set at 500 g, which is the Norwegian lower limit [43], as the Russian limit could not be found. The upper limit was set at 6000 g.

- The variable live births (total number) for each woman, was computed into the new variable parity, were women who had given birth to three or more children were collapsed into one group, while the other values were kept as in the original variable (0= 0, 1= 1, 2= 2, 3 or more children = 3). This was done to make the groups more evenly distributed in terms of numbers in each group. It was considered justifiable to do so as there is no association between increased parity and perinatal mortality for post-term births. There was, however, a higher percentage of primiparous in the post-term group, which is in line with research showing that women expecting their first child have a higher chance of post-term pregnancy compared to women who have given birth before [3].

- The variable cigarette smoking before pregnancy (0= no, 1= yes) and cigarette smoking during pregnancy (0 = no, 1 = yes) were used without alterations.
- The variables mild preeclampsia, severe preeclampsia and moderate preeclampsia were merged into one variable (0= no, 1= yes).
- The variable educational level of mother was coded into: 1= Secondary education or less, 2= Technical school and 3= Higher education (the unknown were recoded as missing). The grouping of the variable is age-dependent with younger mothers in the first category, students in the second and elder mothers in the third.
- The variable civil status was divided into four subcategories (0= unmarried, 1= married, 2= cohabitant and 3= other) and was used without alterations.
- The variable child's birth defects (0 = no, 1 = yes) was used without alterations. Exclusion of all births with birth defects was considered, but this was not performed because too many non-influential defects would have been excluded. A further consideration was to divide the variable into categories according to the seriousness of the defect, but this was not performed because of the probability

that each group would have been too small for further analysis (serious birth defects are rare events).

### 4.4 Statistical analysis

All analyses in the thesis have been performed using Statistics Package for Social Sciences (SPSS) version 22 from IBM. The demographic features of the study population were computed by both descriptive and frequency analyses. The numbers are displayed as percentages, total numbers, means and standard deviations in Table 1.

Binary logistic regression was used on five separate outcome variables which were either dichotomous in their original form (threatening intrauterine asphyxia and meconium staining) or where computed to be dichotomous with the values 0 = no, 1 = yes (PM, Apgar score below 7 (after 5 minutes) and emergency CS). All continuous variables or variables with several categories were collapsed into either customized groups to or according to normative standards.

Univariate analyses were performed by running each outcome variable separately against the main independent variable post-term to test for statistical significance of the five outcomes in the post-term group. Separate age-adjusted analysis were performed initially, but omitted from the final results, as they did not contribute significantly to the model. A multivariable model was constructed by adding all independent variables in the analysis for each outcome variable, then removing one at the time and registering how much the regression coefficient of the main covariate, post-term, changed. The criteria as to whether it should be included as a confounder, was that the coefficient changed by a minimum of 5.0%.

A model containing all relevant confounders were run together with interaction variables for post-term combined with BMI, parity and mothers' age. These three were chosen as the aetiology of post-term pregnancies is possibly associated with high BMI, primiparous women and women above 35 years of age [3]. We stratified the data by mothers' age for the outcome of PM and by BMI groups for the outcome of threatening intrauterine asphyxia, as statistically significant interaction effects were found between these two independent variables and the main exposure, post-term. Since the stratification analysis showed no cases of PM in two of the five groups in the variable of mothers' age, the variable was instead collapsed into two groups: <25 and ≥25 years to increase the number of cases in the strata. The final multivariable model for each variable was then run and the results are presented in Table 2. Results are presented along with odds ratios and confidence intervals. Significance levels are set at < 0.05 in all analyses.

### 4.5 Missing data

In total, there were 539 women in the registry who did not have either a predicted due date based on ultrasound or LMP value, thus gestational age could not be computed. Among these 539 women there were 30 perinatal deaths. After manual examination of the 30 deaths, 19 would have been excluded from the study population due to birth weight much lower than expected at term, elective CS and induction of labour at term. 11 deaths could potentially have been included. The possible ramifications of excluding these missing deaths are discussed later. The combined percentage of missing data for all variables included in the initial analysis was 4.3% for the study population. The constructed variable BMI and the variables smoking before pregnancy and smoking during pregnancy had the highest percentage of missing cases with 1.4%, 1.7% and 1.7% respectively.

## 4.6 Ethical considerations

The MCBR is approved by the Regional Ethics Committee (REK) and its equivalent in Murmansk County. The data used in this thesis are anonymized. The coupling-key used to extract the data from the original file has been deleted and no longer exists.

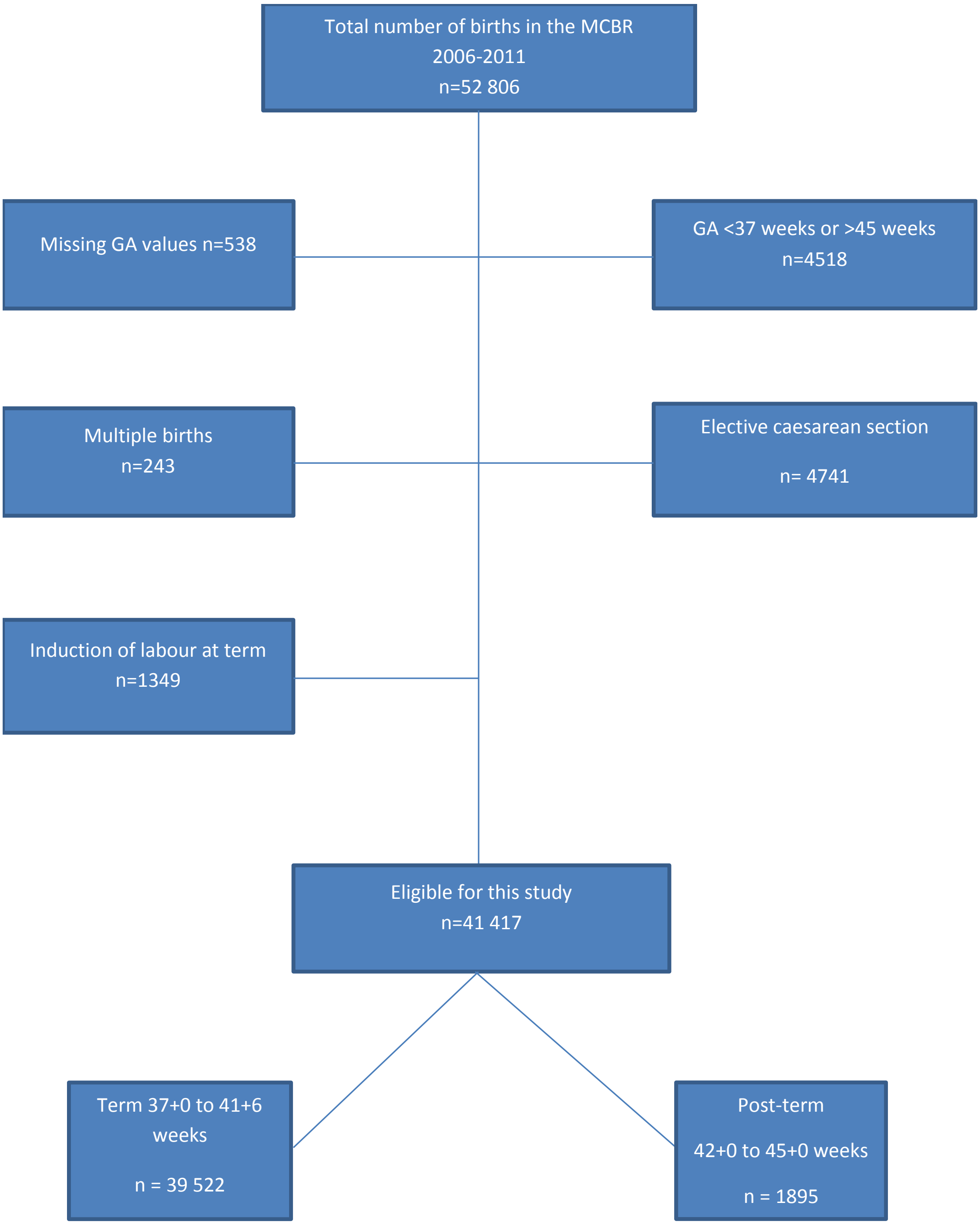


**Figure 2 - Exclusion criteria and numbers excluded in the study population.**

# 5. Results

## 5.1 Demographic characteristics

The study sample consisted of 41 417 women who gave birth from 2006 to 2011, divided into a post-term group (n=1895) and a term group (n= 39 522). All results are presented in table 1. Most of the women, 57.2%, were expecting their first child, and a very small percentage had more than two children (1.5%). The mean BMI for the two groups was 23.3 (±4.2), with more women in the post-term group with BMI over 25 compared to the term group. The percentage of smokers before pregnancy was 24.6%, while 18.3% smoked during pregnancy in both groups. The percentage of women developing preeclampsia (both mild, moderate and severe) during pregnancy was 8.1%. The mean birth weight was 3435 g (± 451.8 g), while babies from the post-term group were on average 139 g heavier than the term group babies. The percentage of babies in the ≥ 4000 g group was almost twice as high in the post-term group compared with the term group (19.0% versus 10.4%). The amount of birth defects was higher in the post-term group, 3.1% versus 2.7% observed in the term group.

## 5.2 Logistic regression

The results from univariate and multivariable analyses of binary regression analysis for each of the five outcome variables are presented in Table 2. Only the results from the multivariable analyses are presented below. Additional adjustment for mothers' age did not contribute significantly to the model (results not shown). Three outcomes were statistically significant with increased odds in the post-term group: emergency CS was 33% higher in the post-term group compared to the term group, adjusted for mothers' age, birth weight and parity (OR 1.33, 95% CI 1.16 – 1.52). Mothers who gave birth post-term had 37% higher odds of experiencing threatening intrauterine asphyxia compared to mothers who gave birth at term, adjusted for age of the mother, BMI, birth weight and parity (OR 1.37, 95% CI 1.17 – 1.61). The odds of giving birth to a baby with meconium staining were 49% higher in the post-term group compared to the term group, adjusted for birth weight (OR 1.49, 95% CI 1.32 – 1.69).

Two outcomes had increased odds in the post-term group, but were not statistically significant: The odds of PM in the post-term group was 4.0% higher compared to the term group when adjusted for birth defects, age of the mother, civil status, educational level, BMI, birth weight and parity (OR 1.04, 95% CI 0.48 – 2.23). The odds of giving birth to a baby with Apgar score below 7 (after 5 minutes) was 17% higher in the post-term group compared to the term group, adjusted for birth defects, age of the mother, civil status, educational level, BMI, birth weight and parity (OR 1.17, 95% CI 0.75 – 1.83).

Results of stratification based on interaction analysis are presented here: Stratification for the outcome PM by mother's age revealed a negative association for PM for women below 25 years (OR 0.29, 95% CI 0.04 – 2.09), and a positive association for women who were 25 years or older (OR 1.82, 95% 0.78 – 4.24), but none of the results were statistically significant. See Table 3 in Appendix 1.

Stratification for the outcome of threatening intrauterine asphyxia by BMI groups revealed a positive significant association for women with BMI < 18.5 (OR 1.33, 95% CI 1.08 – 1.64), women with BMI 18.5 – 24.9 (OR 2.17, 95% CI 1.18 – 4.00) and women with BMI 25.0 – 29.9 (OR 1.74, 95% CI 1.27 – 2.39). A negative association was found for women with BMI 30.0 – 34.9 (OR 0.45, 95% CI 0.19 – 1.04), but the result was not statistically significant. See Table 4 in Appendix 1.

**Table 1 - Demographic characteristics of women in the Murmansk County Birth Registry, 2006 - 2011 (n = 41 417).**

| | | Demographic variables | Women at term ($37^{+0}$- $41^{+6}$ weeks) | Women post term ($42^{+0}$- $45^{+0}$ weeks) | Both groups combined | Standard deviation | N (both groups combined) |
|---|---|---|---|---|---|---|---|
| | | | n= 39 522 | n= 1895 | n= 41 417 | | |
| Demographic features of the study population | Age | Mean age | 26.6 | 26.1 | 26.6 | ± 5.2 | |
| | | Age % | | | | | |
| | | < 20 | 7.0 % | 8.6 % | 7.1 % | | 2925 |
| | | 20 - 24 | 31.3 % | 34.2 % | 31.5 % | | 13013 |
| | | 25 - 29 | 33.6 % | 32.5 % | 33.6 % | | 13882 |
| | | 30 - 34 | 20.1 % | 17.8 % | 20.0 % | | 8277 |
| | | ≥35 | 7.9 % | 6.9 % | 7.9 % | | 3266 |
| | Civil Status | Civil status % | | | | | |
| | | Unmarried | 9.4 % | 10.3 % | 9.5 % | | 3916 |
| | | Married | 73.8 % | 70.6 % | 73.7 % | | 30470 |
| | | Cohabitant | 16.7 % | 18.9 % | 16.8 % | | 6931 |
| | | Other | 0.1 % | 0.2 % | 0.1 % | | 40 |
| | Education | Education % | | | | | |
| | | Secondary or less | 34.8 % | 40.7 % | 35.1 % | | 14378 |
| | | Technical school | 31.6 % | 29.6 % | 31.5 % | | 12914 |
| | | Higher education | 33.6 % | 29.7 % | 33.5 % | | 13724 |
| | Parity | Parity % | | | | | |
| | | 0 | 57.2 % | 60.2 % | 57.4 % | | 23748 |
| | | 1 | 35.7 % | 32.4 % | 35.6 % | | 14733 |
| | | 2 | 5.6 % | 5.5 % | 5.6 % | | 2323 |
| | | 3 and above | 1.4 % | 2.0 % | 1.4 % | | 590 |
| | BMI | Mean BMI | 23.3 | 23.9 | 23.3 | ± 4.2 | |
| | | BMI % | | | | | |
| | | < 18,5 | 6.5 % | 6.4 % | 6.4 % | | 2633 |
| | | 18,5 - 24,9 | 67.0 % | 61.2 % | 66.7 % | | 27252 |
| | | 25,0 - 29,9 | 19.0 % | 22.8 % | 19.2 % | | 7837 |
| | | 30,0 - 34,9 | 5.7 % | 6.5 % | 5.8 % | | 2348 |
| | | ≥ 35 | 1.8 % | 3.2 % | 1.9 % | | 762 |
| | Smoking | Smoking before | 24.5 % | 25.8 % | 24.6 % | | 10015 |
| | | Smoking during pregnancy % | 18.1 % | 20.2 % | 18.3 % | | 7432 |
| | Preeclampsia | Preeclampsia % | 8.1 % | 8.6 % | 8.1 % | | 3354 |
| | Birth weight | Mean birth weight [g] | 3429 | 3568 | 3435 | ± 451.8 | |
| | | Birth weight [g] % | | | | | |
| | | < 2500 g | 1.7 % | 1.1 % | 1.7 % | | 702 |
| | | 2500 - 2999 g | 13.6 % | 9.2 % | 13.4 % | | 5564 |
| | | 3000 - 3499 g | 40.3 % | 32.5 % | 40.0 % | | 16560 |
| | | 3500 - 3999 g | 33.9 % | 38.2 % | 34.1 % | | 14118 |
| | | ≥4000 g | 10.4 % | 19.0 % | 10.8 % | | 4469 |
| | Birth defects | Birth defects % | 2.7 % | 3.1 % | 2.7 % | | 1107 |
| Outcome variables | | Perinatal mortality [‰] | 4.0 | 6.3 | 4.1 | | 168 |
| | | Emergency caesarean section | 10.6 % | 14.6 % | 10.8 % | | 4480 |
| | | Threatening intrauterine asphyxia | 7.0 % | 9.7 % | 7.1 % | | 2955 |
| | | Meconium staining | 12.8 % | 18.3 % | 13.0 % | | 5394 |
| | | Apgar score below 7 (after 5 min) | 1.0 % | 1.4 % | 1.0 % | | 409 |

**Table 2 - Odds ratios (OR) with 95% confidence intervals (CI) of perinatal mortality, Apgar score below 7 (after 5 min), threatening intrauterine asphyxia, meconium staining and emergency caesarean section for post-term pregnancy in the Murmansk County Birth Registry, 2006 - 2011 (n = 41 417).**

| Outcome variables | Univariate analysis Post-term pregnancy | Multivariable analysis Post-term pregnancy |
|---|---|---|
| **Perinatal mortality** | 1.61 (0.89 - 2.90) | 1.04 (0.48 - 2.23)* |
| **Apgar below 7 (after 5 minutes)** | 1.42 (0.95 - 2.12) | 1.17 (0.75 - 1.83)* |
| **Threatening intrauterine asphyxia** | 1.43 (1.22 - 1.67) | 1.37 (1.17 - 1.61)† |
| **Meconium staining** | 1.53 (1.36 - 1.73) | 1.49‡ (1.32 - 1.69)‡ |
| **Emergency caesarean section** | 1.43 (1.26 - 1.63) | 1.33 (1.16 - 1.52)§ |

* Adjusted for variables mothers' age, civil status, education level, parity, BMI, birth weight and birth defects.
† Adjusted for variables mothers' age, parity, BMI and birth weight.
‡ Adjusted for variable birth weight.
§ Adjusted for variables mothers' age, parity and birth weight.

# 6. Discussion

The main findings of the study are that women giving birth post-term have statistically significant higher odds of experiencing threatening intrauterine asphyxia, meconium staining and emergency CS compared with women giving birth at term. For PM and low Apgar score, there is no difference between women giving birth post-term compared to women giving birth at term.

## 6.1 Findings of the study

### 6.1.1 Demographic findings

This study is not a comparative study between Russia and Norway, but in certain places, a comparative number from Norway was used to illustrate the situation in Murmansk County and to put the numbers into perspective. Norway is a neighbouring country with a very similar birth registry, which made it suitable for comparison.

The findings in the demographic table show that the percentage of women in the MCBR smoking both before and during pregnancy was high with 24.6% and 18.3%, respectively. In comparison, the number of women smoking before pregnancy in Norway was 9.8% and 6.4% during pregnancy (in 2010) [47]. It is well established that cigarette smoking has a detrimental effect on the foetus, increasing the risk of foetal growth restriction, placental abruption, stillbirth, and preterm labour [48]. In the MCBR, the mean weight of the babies of the mothers who smoked during pregnancy was 144 g lower compared with the women who did not smoke, confirming the association between smoking and growth restriction. The exception is foetuses affected by being SGA, a condition with several aetiological explanations.

It is further documented that cigarette smoking during pregnancy can reduce the risk for hypertensive disorders such as preeclampsia during pregnancy [48]. It is estimated that the worldwide incidence of preeclampsia is between 2 to 8% [49]. In Norway the percentage of preeclampsia is 2.6% [50]. A high percentage of smokers in the MCBR and a high percentage of preeclampsia of 8.1% do not support such an association on a population level. On the other hand, separating the smokers from the non-smokers in the MCBR revealed a prevalence of preeclampsia of 6.1% among the smokers and 8.3% among the non-smokers. This supports the hypertensive association on a personal level. One possible explanation for the high percentage of preeclampsia in the MCBR is a tendency of over-diagnosing during pregnancy as described previously, leading to hospitalisation [34, 38]. Another possible contributing factor is ethnic differences in the incidence of preeclampsia. Women in Haiti had a 18.0% incidence of preeclampsia according to a study by Small et al. [51]. It was not possible to retrieve any reliable data about national prevalence of preeclampsia in Russia.

Although a modest difference, it is interesting that there was a higher percentage of women with preeclampsia in the post-term group compared to the term group since these women should have been induced before reaching post-term. A likely explanation is that these women have not been attending regular antenatal care programs and unexpectedly appear at a delivery clinic with previously undetected preeclampsia. This explanation is further supported by the data, which show that 22.7% of the women with preeclampsia in the post-term group had not attended a previous ultrasound examination, while only 12.2% of the women without preeclampsia were missing this attendance.

The women in the post-term group were younger than in the term group. This is contrary to existing research, where higher age seems to be associated with post-term pregnancy [3]. On the other hand, there were more primiparous women in the post-term group, which can explain the younger age and why they were less educated and less are married than in the term group. The women in the post-term group had on average higher BMI than the women in the term group, which is in line with existing studies [3].

The percentage of birth defects in the MCBR as a whole was 2.7%, with 3.1% in the post-term group (in comparison, the percentage of birth defects in Norway was 4.3% in 2014 for all births after week 22 [52]). The seemingly low incidence of birth defects in the MCBR data are explained by lack of follow-up as many birth defects are diagnosed after birth, some even years later. According to a two-year follow-up study done in Murmansk County, the proportion of birth defects increased to Norwegian proportions. Interestingly, according to A. Kovalenko, even though the total incidence is more or less the same in the two countries, the type of birth defects affecting the babies are different [Personal communication, 2015 Oct 20].

The majority of post-term studies and reviews examined for this thesis compared outcomes of post-term pregnancies of women being induced at or before reaching post-term. Such a comparison was not possible in the MCBR as the induction rate was very low, only 2.8% in total with 5.2% in the post-term group, in comparison, 19.3% of all births were induced in Norway in 2012 [53]. The large difference between the two countries indicate that the medical system in Murmansk County prefer to perform planned CS instead of inductions when deemed necessary. This is further supported by the proportion of CS in Norway was 17.1% in 2010 [54], while it was 22.5% in the MCBR [44].

### 6.1.2 Perinatal mortality

The odds of the primary outcome variable, PM, were not statistically significantly higher for women giving birth post-term compared to women giving birth at term. The results of this thesis are in line with several recent studies and reviews where the pregnancies included also had the GA of the baby decided by first or second trimester ultrasound, such as the review by Wennerholm et al. [29] and Morken et al. [5]. They found that there was no difference in PM between the women who were induced when they reached post-term and those who waited for spontaneous birth, with regular monitoring of the foetus. The method used to estimate the GA is important as studies, which include pregnancies with GA decided by LMP or where the method is uncertain, can overestimate the number of post-term pregnancies, and possibly the number of deaths in the post-term group. Both the Cochrane review and the review by Hussain et al. found a statistically significant higher risk of PM in the post-term group compared to the induced group, but they have both included studies dating back to the 1960s and 1970s, before ultrasound became part of the routine examination [1, 55]. The study by Treger et al. on 36 160 accurately dated pregnancies, found no increased risk of death in the post-term group compared to the term group, and the included pregnancies were all low-risk pregnancies [24]. It is important to point out that only low-risk women should be allowed to proceed to a post-term state: post-term studies including women or foetus with known risk factors make the results prone to bias.

One such risk factor which may cause systematic error is foetuses being SGA. It was not possible to exclude SGA-babies from this study because it was not clear from the MCBR which babies had been diagnosed with this condition. It could therefore be that some of the deaths post-term are attributed to SGA. Two of the twelve deaths in the post-term group were below 2500 g, which is far below the mean and it is highly likely that they fall in this group. A study by Morken et al. compared births of both SGA and babies of normal growth born post-term, and found a statistically significant higher risk of mortality among the SGA-babies born post-term compared to the normal growth babies born at term, while there was no difference between normal growth babies born post-term compared to normal growth babies born at term. [5].

Three of the larger recent reviews on post-term pregnancies, the Cochrane review [1], Hussain et al. [55] and Wennerholm et al. [29], were all criticised in an article by Cohain [56] for considering trials and studies including high-risk pregnancies among the post term group and for including congenital malformations among the perinatal deaths. Because PM is a rare outcome, including congenital malformations can skew the study groups sufficiently to influence the analysis. In this study, birth defects have been included in the study group because in general the majority of birth defects are not severe and would therefore not influence the mortality and morbidity outcomes considered in this thesis. Exclusion would have led to an unnecessary high number of women being left out of the study group. Because women in the MCBR attended many antenatal check-ups, including several ultrasound examinations, severe and life threatening birth defects should have been diagnosed at an early stage, often leading to induced abortion or elective CS at or before term. The incidence of *severe* birth defects should therefore be lower in the post-term group compared with the term group. The demographic table shows a slightly higher frequency of birth defects in the post-term group, which we assume to be minor defects, and not related to post-term pregnancy. Birth defects were therefore not excluded, but were instead adjusted in the analyses.

The stratification analyses for PM by mother's age below and above 25 years revealed that the consequences of giving birth post-term was different for the two age groups. However, the results were not statistically significant and the confidence intervals are wide. Part of the explanation could be that even though the cohort included in the study is large, PM is a rare outcome (with only 168 cases), which makes the results difficult to interpret.

**6.1.3 Apgar score below 7 (after 5 minutes)**

The odds of Apgar score below 7 (after 5 minutes) were not higher for the post-term group compared to the term group. The finding is in line with the Caughey and the Cochrane reviews which found no significant difference between women who went into spontaneous labour post-term and women who were induced [1, 31]. Although the use of Apgar score as an assessment tool of the state of new-borns has been debated over the years, it is still in use 63 years after it was first introduced [57]. The reason could be that the scoring system does not require any machinery and gives a quick indication of the condition of the baby guiding which steps should be taken next, i.e. resuscitation or other measures. A large study of 1 029 207 deliveries in Scotland showed that the association between low Apgar score at five minutes and the risk of neonatal or infant death was very strong [58], the same association was found in a study of 25.9 million births in the United States [59].

The percentages with low Apgar score in the MCBR was 1.0% in the term group and 1.4% in the post-term group. The percentage of threatening asphyxia for the post-term group in the MCBR is 9.7% which is almost ten times the percentage of low Apgar score. Thus there is little correlation between low Apgar score and threatening intrauterine asphyxia in the study group. Part of this discrepancy can be explained by the findings of Parkhurst et al. stating that Russian doctors are rewarded for handling difficult labours [34]. Exaggerating an imminent threat during labour, leading to immediate delivery of a healthy baby can therefore be considered a success. On the other hand, several studies have pointed out that the Apgar score system was never intended to be used to predict neurological developments after asphyxia in babies, as there are several conditions, not related to asphyxia, which can result in a low Apgar score [57], for example: use of drugs, trauma, congenital anomalies and infections [59]. The MCBR lacks information on the specific progression of the condition of the babies with low Apgar score, and who survived the first seven days. Such data would have clarified whether the Apgar score is predictive for the future well-being of these children.

#### 6.1.4 Threatening intrauterine asphyxia

The odds of threatening intrauterine asphyxia were 37% higher in the post-term group compared to the term group. This outcome was widely discussed among the health personnel who were responsible for filling in data in the MCBR, because the word “threatening” can cause confusion of whether they should register imminent threat or actual threat to the baby’s life due to asphyxia. The agreement was that they should only register actual threat. Threatening intrauterine asphyxia can be caused by long-term exposure, such as smoking, or short term, such as the umbilical cord being squeezed. A challenge for health personnel is that deviating heart rate is a normal occurrence during labour and it is difficult to say which babies will progress to morbidity after birth, or worst case, death. One can confirm asphyxia by umbilical cord blood sample or scalp blood analysis, but these tests are not done in the MCBR. As placental insufficiency is believed to be one of the causes of higher mortality and morbidity post-term [24], babies being born post-term can be more vulnerable to the impact of regular contractions with reduced oxygen flow, and thereby at risk of developing threatening intrauterine asphyxia. The findings of this study do not correspond with the results found in reviews by Hussain et al., Wennerholm et al. and the Cochrane review, which conclude that there is no difference in birth asphyxia between the groups giving birth post-term and the women induced [1, 55, 29]. It should be noted that these reviews included only a few trials with this outcome in the Cochrane review and Hussain et al. (number of participants in total =757) for example.

The percentage of threatening asphyxia in the MCBR was 7.0% in the term group and 9.7% in the post-term group. As immediate delivery is the best course of action when threatening intrauterine asphyxia occurs, the percentage of emergency caesarean delivery should be on par or higher than the percentage of threatening asphyxia, which was the case in the MCBR with 10.8% emergency CS versus 7.1% threatening asphyxia. Threatening asphyxia can therefore be considered as a mediator variable in the relationship between the variable post-term and emergency CS, where the independent variable post-term influences the incidence of threatening intrauterine asphyxia, which again influences the incidence of emergency CS. It should be noted however that threatening intrauterine asphyxia does not necessarily lead to emergency CS, as other interventions could be considered, or the situation could resolve itself quickly.

The stratification analysis for threatening intrauterine asphyxia by BMI groups revealed surprising results. It was expected to find that women classified as obese (BMI ≥30) would have higher odds of experiencing threatening intrauterine asphyxia compared with women with a BMI within normal range (18.5 – 29.9), because high BMI in general is associated with higher morbidity. Instead, the highest odds with statistical significance for experiencing threatening intrauterine asphyxia was found in the group of women with normal weight (BMI 18.5 – 24.9), while for obese women the stratification results were not statistically significant. This is likely a result of misclassification of threatening intrauterine asphyxia. The issue is further elaborated in the “limitations” section.

### 6.1.5 Meconium staining

The women giving birth post-term had 49% higher odds of experiencing meconium staining compared to women at term. A study by Caughey and Musci of 45 673 women in San Francisco, found a gradual increase in meconium staining from 37 weeks and onwards, with 3% at week 37 and 18% at week 42 and later [60]. Caughey and Musci demonstrated that finding meconium in amniotic fluid is a common phenomenon, both in term and post-term pregnancies. The study population in the MCBR showed the same trend; the term group had an incidence of meconium staining of 12.8%, while the incidence in the post-term group was 18.3%.

There are two leading theories seeking to explain meconium staining; one relates it to the increased maturation of the foetus, arguing that meconium in the amniotic fluid can be seen as a normal process in a proportion of pregnancies. The second theory explains the increase as a response to an infection or chronic or acute intrauterine asphyxia [61], meaning it is a pathologic condition. The finding of this thesis supports the theory of meconium staining being a sign of maturation, but maturation can also be a confounder supporting both theories.

The study by Patel et al. found an ethnic component to the incidence of meconium staining, showing that African British and Asian British babies had a higher frequency of meconium staining compared with white British babies [7]. These results were part of a study showing that the average gestation for selected populations of African and Asian women living in Britain was a week shorter than for white British women [7].

Meconium staining can lead to meconium aspiration syndrome, which is a very rare, but potential fatal condition where the lungs of the baby become swelled and inflamed caused by aspiration of thick meconium at birth [15]. The review of Hussain et al. found a significant reduction of morbidity related to meconium aspiration for the women induced compared with the women assigned to wait for spontaneous labour post-term [55]. The same result was found in the review by Wennerholm et al. [29] and the Cochrane review [1]. Because of the higher incidence of meconium staining in the post-term group compared with the term group, we would expect to find a small, but increased incidence of meconium aspiration syndrome in the term group in the MCBR, but this variable was not registered.

#### 6.1.6 Emergency CS

Women in the post-term group had 33% higher odds of giving birth by emergency CS compared to the women who gave birth at term. This is probably the most important finding of the thesis because CS can have serious implications for mother and baby, both in the short and long term. In addition, women ending up with an emergency CS in their first pregnancy, are almost guaranteed (93.2% probability) to end up with elective CS in their future pregnancies [44].

There are several factors which can contribute to increased intervention by CS. The decision to perform an emergency CS is taken when there is an immediate threat to mother and/or foetus, such as bleeding or threatening intrauterine asphyxia, if there is a failure to progress or the position of the presenting part of the baby is incompatible with vaginal delivery. Babies born post-term will in general have higher birth weights than babies born at term [57], and the increased frequency of macrosomia (birth weight ≥4000 g) in this group (19.0% versus 10.4% in the term group) can therefore be a potential cause of failure to progress in labour [62]. The explanation can be that baby is too large for the pelvis of the mother, and will therefore not descend into the birth canal, often referred to as cephalopelvic disproportion [63].

Inductions have also been associated with a higher frequency of emergency CS compared to spontaneous birth in some reviews [28], especially for primiparous women, which are in majority in both study groups (57.4%). Other reviews such as the Cochrane review [1] and Wennerholm et al. [29] and Caughey et al. [31] dispute this finding.

### 6.2 Strengths and weaknesses of the study

The outcomes considered in the thesis: PM, threatening intrauterine asphyxia, Apgar score below 7 (after 5 minutes), meconium staining and emergency CS, are some of the most important and frequently studied outcomes in relation to post-term pregnancy and labour. The independent variables used for adjustment in the multivariable analysis have been chosen on the basis of existing literature. However, there are some considerations concerning bias, confounding and missing data that could possibly affect results, which has to be addressed separately.

The large number of births registered in the MCBR is a strength of the thesis. A large study group provides more precise results and narrower confidence intervals compared to a smaller study sample. Because the numbers are large, it was also possible to consider several outcomes in the analyses, some of them quite rare, such as PM. There is a very low percentage of missing values in the study group, most of which are random. As such, random missing values will not affect the ORs and few missing values will keep the CIs narrow. Of special interest is the smoking before and during pregnancy variable, which only has 1.4% missing values. In comparison, the Norwegian birth registry lacked this information for 14.9% of the women in 2010 [47]. The variables with most missing values: BMI and smoking before and during pregnancy, were all explored manually to see if there were any differences between the term and the post-term group, which there were not. Another strength is the completeness of the registry of 98.9% in 2006 [32], as all birth institutions in Murmansk County participated in the registry by decree, making the internal validity very high.

Ultrasound was chosen as the preferred method to estimate GA because it is the most precise method available [9]. Ultrasound is more precise than LMP on a population level because LMP is based on a person's past recollection of an event, therefore introducing random error and possibly, systematic error. For example, only 4.5% of the women in the MCBR are absolutely certain about their first day of their last menstrual period. Ultrasound estimation of GA was not adopted as the official method in Murmansk County before 2009 [32], but 97.0% of the women in the registry had an available ultrasound estimated GA. The estimate of GA by ultrasound is more reliable if performed early in the pregnancy simply because the variation in size of the foetus increases with increasing GA. Ideally the GA should be estimated at the end of the first trimester (week 10 to 14) or halfway in the second trimester [64]. The MCBR did not record when the women had their GA estimated, which is a weakness in the data. Official recommendations from the Ministry of Health have been in place since 2000 and state that all women must undergo three ultrasound scans during pregnancy, the first between week 10 to 14 [41]. It is therefore safe to assume that most women had their GA estimated during this recommended period. This assumption is further supported by the fact that 86.7% of the study population had attended their first visit to a gynaecologist by week 14 of their pregnancy.

#### 6.2.1 Confounding

Possible confounders have been adjusted for in the analyses. One potential source of confounding not adjusted for were women who progressed post-term in previous pregnancies. A study by Jukic et al. found that women who had a previous pregnancy lasting one week longer than the average pregnancy, added 2.5 days to their current pregnancy [14]. It was not possible to retrieve information about GA of previous pregnancies in the MCBR, therefore it was not included. Another source of confounding not adjusted for was women with a history of PM in previous pregnancies. Studies have found that women who experienced stillbirth in a previous pregnancy have a higher risk of experiencing it again compared with women who gave birth to a live baby [65]. This confounding factor was not included because it was not possible to obtain detailed enough information about the women with a history of PM in the MCBR.

Inclusion of mal-presentations of the foetus may have acted as a confounding factor. Births where the baby does not present itself with the back of the head first (cephalic presentation), tend to carry higher risk of mortality and morbidity [66]. Sensitivity analyses, where mal-presentations were excluded, revealed that the ORs and CIs did not change significantly. It was therefore decided to include mal-presentations in the study group, as they only constituted 1.7% in total, with 1.8% in the term group and 1.2% in the post-term group. The baby can change position right up to the time of birth, thus the higher percentage in the term group are explained by mal-presentations discovered close to term that would have lead to either induction of labour or an elective CS.

Induction of labour due to post-term was included, as these women should not have had any additional risk factors. Because induction of labour can lead to increased morbidity (especially CS) when inducing on an unripe cervix [1], all inductions, not only the ones at term, could have been excluded to avoid confounding. Other studies and reviews dispute the negative side effects of induction, and find no increased rate of emergency CS or other morbidities for the women being induced compared to the women giving birth post-term [29, 67]. In the post-term group there were 99 inductions, and none of them ended with emergency CS. It is therefore highly unlikely that inclusion of these inductions would have influenced the results of the analysis.

### 6.2.2 Bias

There is a potential bias in terms of the 539 women without an estimated GA which had to be left out of the analysis, because the outcome PM is higher in this group than in the study group. Typically, these women are individuals who are not well functioning within the society or are stigmatized because of the pregnancy. They may be teenagers, someone of very low socioeconomic status or substance abusers. Common for them all is that they often find themselves outside of the social security and health care system, only seeking skilled attendance at the very last minute or in an emergency.

13.5% of the women in the post-term group did not have the GA decided by ultrasound, instead the value of LMP was used. By using LMP, there is a risk of overestimating the GA [10], which means that some women may have been included in the post-term group, who should have been in the term group. In comparison, 5.8% of the term group did not have a GA value by ultrasound. Not having attended an ultrasound examination during the pregnancy could mean that these women did not attend the antenatal care program and therefore only came in contact with the health system late in their pregnancy or during birth. It is well established that women not attending antenatal care programmes have poorer pregnancy outcomes [68] for reasons described above. If those women who ended up in the post-term group, because they only had LMP-values, had risk factors contributing to higher mortality and morbidity compared with those women with GA decided by ultrasound, the ORs in the analyses may have been overestimated. This is a potential selection bias.

Smoking is prone to information bias because it depends on self-reported values. Being a smoker is associated with social stigma and values tend to be under-reported in any study. This under-reporting has been documented in several studies [69, 70] by validating self-reported smoking rates with blood samples. According to a study by Ford et al. [71], almost 25% of the women in their study did not report that they were smokers, and those who confirmed smoking under-reported the amount of smoking. In the MCBR, more women in the post-term group had late or no contact with the antenatal care system (according to the distribution of missing values) compared with women in the term group. As mentioned, women falling outside the system tend to have a lower socioeconomic status, which again is associated with smoking [72]. This means that there could have been more women in the post-term group under-reporting or denying that they smoked compared with the women in the term group, which, in turn, may have underestimated the number of smokers and the amount of smoking in the post-term group.

Correct registration of PM and emergency CS did not depend upon the assessment ability of the health personnel involved, and the actual numbers can therefore be trusted. For threatening intrauterine asphyxia, Apgar score below 7 (after 5 minutes) and meconium staining, the validity is subject to non-differential measurement error because diagnoses depended on the judgement and experience of the health personnel present at that particular birth. Therefore, one might find differences between birth institutions and between health personnel on how these outcomes were defined. However, this should influence the study groups at equal measure.

The results of the stratification of the outcome threatening intrauterine asphyxia by BMI groups were not as expected. A likely explanation for these results arises from how the outcome of threatening intrauterine asphyxia was classified and interpreted in the MCBR. As mentioned in “Findings of the study”, there was a discussion on how to interpret the variable. Even though it was agreed to only register actual threats of asphyxia requiring immediate intervention, it seems to have been too frequently diagnosed among the women in the cohort, with a total of 2955 cases. 66.7% of the women in the cohort had a BMI from 18.5 to 24.9, while only 7.7% had a BMI ≥30. This is a likely explanation for the high number of cases and statistically significant result of threatening intrauterine asphyxia in this group. This misclassification is a bias which can be classified as a non-differential measurement error, affecting both study groups equally. The consequence is that the results of the regression analysis lean towards the zero hypothesis. In other words, no interpretations have been made based on false positive results.

#### 6.2.3 External validity

The findings in this study can probably be extrapolated to women in North-West Russia, where the ethnic composition is similar to Murmansk County. Because ethnicity is a potential confounder related to GA, preeclampsia and meconium staining, it has to be adjusted for if the study is replicated in other parts of Russia where there is a different ethnic composition than in Murmansk County.

## 7. Conclusion

The most important finding of the thesis is that the odds of emergency CS is 33% higher in the post-term group compared with the term group (OR 1.33, 95% CI 1.16 – 1.52) . This finding is important because it is an outcome with potential serious consequences for the health care system and the individual mothers and children. Performing a CS is much more costly compared to a vaginal birth due to the need of more personnel, equipment and drugs. The cost of a CS in Russia could not be found, but for Norway the costs were 55 000 NOK for a CS compared to 22 000 NOK for a normal birth in 2008 [73]. Assuming that the difference in costs is large in the Russian system as well (even though the absolute number of women in the post-term group ending up with emergency CS is modest), the combined costs of treating them are substantial. The economic consequences are further exacerbated by the fact that 93.2% of the women in the MCBR ending up with a CS will have a repeat CS in their next pregnancy [44]. With a general trend of increasing CS rates in Murmansk County [44], the costs will continue to rise. At the individual level, an emergency CS carry several potential risks for both mother and baby, both in short and long term. For the baby, more research is surfacing linking delivery by CS and diseases later in life [18, 19], while for the mother, apart from the immediate risks of infection, blood loss and embolism, the risks of experiencing pathology in their next pregnancy are higher compared to a vaginal birth [74]. The odds of experiencing threatening intrauterine asphyxia (OR 1.37, 95% CI 1.17 – 1.61) and meconium staining (OR 1.49, 95% CI 1.32 – 1.69) are also higher for the women in the post-term group compared to the term group, which can lead to interventions such as emergency CS, where threatening intrauterine asphyxia would act as a mediator, and an affected baby. The birth institutions in Murmansk County may therefore benefit from going through their routines of how to handle post-term pregnancies and investigate why so few women were induced when they reached the post-term limit of $42^{+0}$ weeks.

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# Appendix 1

**Table 3 - Odds ratios (OR) with 95% confidence intervals (CI) of perinatal mortality for post-term pregnancy stratified by mother's age in the Murmansk County Birth Registry, 2006 – 2011 (n = 41 417).**

| Post term pregnancy | Univariate | Multivariable* |
|---|---|---|
| Mother's age < 25 yrs | 0.53 (0.13 - 2.15) | 0.29 (0.04 - 2.09) |
| Mother's age ≥ 25 yrs | 2.67 (1.38 - 5.16) | 1.82 (0.78 - 4.24) |

* Adjusted for variables civil status, birth defects, parity, birth weight, BMI and education level.

**Table 4 - Odds ratios (OR) with 95% confidence intervals (CI) of threatening intrauterine asphyxia for post-term pregnancy stratified by BMI groups in the Murmansk County Birth Registry, 2006 – 2011 (n= 41 417).**

| Post term pregnancy | Univariate | Multivariable* |
|---|---|---|
| BMI group 1 = < 18.5 | 1.37 (1.11 - 1.69) | 1.33 (1.08 - 1.64) |
| BMI group 2 = 18.5 - 24.9 | 2.04 (1.12 - 3.73) | 2.17 (1.18 - 4.00) |
| BMI group 3 = 25.0 - 29.9 | 1.74 (1.27 - 2.37) | 1.74 (1.27 - 2.39) |
| BMI group 4 = 30.0 - 34.9 | 0.54 (0.24 - 1.25) | 0.45 (0.19 - 1.04) |
| BMI group 5 = ≥35 | 1.25 (0.57 - 2.73) | 1.30 (0.58 - 2.93) |

* Adjusted for mother's age, parity and birth weight.