Preterm Births in Iceland 1997-2016:

Preterm Birth Rates by Gestational Age Groups and Type of Preterm Birth

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Thesis for the degree of Master of Public Health Sciences
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HÁSKÓLI ÍSLANDS

Fyrirburafæðingar á Íslandi 1997-2016

Tíðni fyrirburafæðinga eftir meðgöngulengd og tegund fyrirburafæðinga

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Ritgerð til meistaragráðu í Lýðheilsuvísindum

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Ágrip

Bakgrunnur

Tíðni fyrirburafæðinga í heiminum hefur farið hækkandi, aðallega vegna fjölgunar síðfyrirburafæðinga vegna inngrips (iatrogenic). Ekki er ljóst hvort tíðni fyrirburafæðinga á Íslandi hafi fylgt sama mynstri. Markmið þessarar rannsóknar var að meta tíðni fyrirburafæðinga á Íslandi frá 1997 til 2016 eftir tegundum fyrirburafæðinga.

Aðferð

Þessi rannsókn náði yfir öll lifandi fædd börn 1997-2016 úr gögnum Fæðingaskrár Embættis landlæknis. Tíðni fyrirburafæðinga var reiknuð fyrir hvert ár og lagskipt eftir meðgöngulengd og tegund fyrirburafæðingar. Hætta á fyrirburafæðingu eftir tímabilum var fengin með Poisson aðhvarfsgreiningu og leiðrétt fyrir lýðfræðilegum breytum. ICD-10 kóðar í Fæðingarskrá voru notaðir til að meta læknisfræðilegar ábendingar fyrirburafæðinga .

Niðurstöður

Heildarþýðið voru 87.076 nýburar, þar af 4.986 (5,7%) fyrirburar. Tíðni fyrirburafæðinga jókst örlítið milli 1997 og 2016, úr 5,3% í 6,1%. Tíðni síðfyrirbura (34v0d-36v6d) jókst marktækt, frá 3,7% til 4,5% af öllum fæðingum (LÁH=1,26, ÖB=1,15-1,40). Tíðni fæðinga fyrir tímann vegna inngrips (af öllum fyrirburafæðingum) tvöfaldaðist frá 20% á árunum 1997-2001 í 43% árin 2012-2016, jafnvel eftir leiðréttingu fyrir læknisfræðilegum ábendingum, (LÁH=2,40, ÖB=2,06-2,80). Tíðni fyrirburafæðinga þar sem hríðir hefjast sjálfkrafa (spontaneous) lækkaði á rannsóknartímabilinu (LRR=0,63, ÖB=0,56-0,72) og tíðni fyrirburafæðinga þar sem legvatn fer fyrir tímann áður en hríðir hefjast (PPROM) jókst smávegis (LRR=1,31, ÖB=1,11-1,54). Merki um vanda fósturs var sú ábending sem oftast fannst fyrir fyrirburafæðingum vegna inngrips (26,2%), sem minnkaði þó á rannsóknartímabilinu (32,6%-25,3%).

Ályktanir

Tíðni fyrirburafæðinga er lág á Íslandi en jókst smávegis milli 1997 og 2016, líklega vegna aukningar í síðfyrirburafæðingum af læknisfræðilegum ástæðum. Aukningin í fyrirburafæðingum vegna inngripa var marktæk þrátt fyrir að leiðrétt væri fyrir ábendingum fyrirburafæðinganna. Þetta bendir til þess að aðrir þættir en læknisfræðilegar ábendingar hafi haft áhrif á aukningu fyrirburafæðinga vegna inngripa á Íslandi.

Abstract

Introduction

The frequency of preterm births has been increasing globally, mainly due to a rise in iatrogenic late preterm births. It is not well known if the prevalence of preterm births in Iceland has been following a similar trend. The aim of this study was to assess the prevalence of preterm births in Iceland during 1997-2016 by type of preterm birth.

Methods

This study included all live-births in Iceland during 1997-2016 identified from the Icelandic Medical Birth Registry. Rates of preterm births were calculated each year and stratified by gestational age groups and type of preterm birth. Risk of preterm birth by time period was assessed with Poisson regression models adjusted for demographic variables. Indications for iatrogenic births were identified using ICD-10 codes.

Results

The study population included 87,076 infants, of which 4,986 (5.7%) were preterm. The preterm birth rate increased from 5.3 to 6.1% (ARR=1.16, CI=1.07-1.26) between 1997-2001 to 2012-2016. The rate of late preterm births (of all births, 34w0d-36w6d), increased significantly: 3.7% to 4.5% (ARR=1.26, CI=1.15-1.40). The rate of iatrogenic preterm births (of all preterm births) doubled, from 20% in 1997-2001 to 43% in 2012-2016, even after adjustment for medical indications (ARR=2.40, CI=2.06-2.80). Spontaneous preterm births decreased during the study period (ARR=0.63, CI=0.56-0.72) and PPROMs increased slightly (ARR=1.31, CI=1.11-1.54). The largest contributing indication for iatrogenic births were fetal indications (26.2%), which decreased during the study period (32.6%-25.3%).

Conclusions

Preterm birth rates are low in Iceland, however increased slightly between 1997 and 2016. This may have been due to an increase in late and iatrogenic preterm births. The increase in iatrogenic preterm births remained significant after adjusting for medical indications for iatrogenic preterm births. This suggests that other factors than medical indications are affecting the rise in iatrogenic preterm births in Iceland.

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

AOR	Adjusted Odds Ratio
ARR	Adjusted Rate Ratio
ART	Assisted Reproductive Technologies
BMI	Body Mass Index
CI	Confidence Interval
d	days (gestational age measurement)
GA	Gestational Age
HELLP	Hemolysis, Elevated Liver enzymes and Low Platelet count
ICD	The International Classification of Diseases
IUGR	Intra Uterine Growth Retardation
IQ	Intelligence quotient
LÁH	Leiðrétt áhættuhlutfall (Adjusted Rate Ratio)
NCSP	Nomesco Classification of Surgical Procedures
OR	Odds Ratio
ÖB	Öryggisbil (Confidence Interval)
PPROM	Preterm Premature Rupture of Membranes
PTB	Preterm Birth
RR	Risk Ratio
SGA	Small for Gestational Age
UK	United Kingdom
USA	United States of America
w	weeks (gestational age measurement)
WHO	World Health Organization

1 Introduction

Preterm births have been increasing globally in the last decades even though we know more regarding risk factors and contributing mechanisms causing preterm birth (1). Preterm births are the leading cause of neonatal and childhood mortality and morbidity in developed countries even though modern medicine offers new treatment and technology to increase survival and decrease morbidity (1). The frequency of preterm births spans from 5% to 18% varying by location (1). Globally, over one in ten births are preterm and it is estimated that there are 15 million preterm births every year world-wide (2). The etiology of preterm births is complex and there is not a single cause for the increase in preterm births nor a simple solution to this problem (2). Preterm birth rates are rising globally (1, 3) and in the western world this rise is mainly caused by an increase in late preterm births caused by maternal or fetal indications (iatrogenic preterm births) (1, 4, 5). However, this increase is not solely connected to an increase in maternal and fetal indications as some iatrogenic preterm births have been found to be avoidable (6) and even not medically indicated (7). This study will explore the preterm birth rate in Iceland during 1997 to 2016 by types of preterm births and gestational age groups. The rate of iatrogenic preterm births will be investigated to see if it has been increasing, and if so, whether it can be explained by rate changes in medical indications.

1.1 Preterm Births

Preterm birth is defined by The World Health Organization (WHO) as delivery before 37 week gestation (2). Preterm births are categorized by gestational age into four groups; extreme, severe, moderate and late preterm births. Preterm births are also categorized into three subtype groups based on the obstetric precursor leading to the preterm birth; spontaneous, preterm premature rupture of the membranes (PPROM) and iatrogenic (1). Multiple risk factors are connected to preterm births, and they vary between the different types of preterm births. Preterm infants have a high risk of long-term complications such as respiratory and gastrointestinal problems and neurodevelopmental impairments with increasing risk as the gestational age is lower (3).

1.1.2 Preterm Birth Categorization

1.1.2.1 Preterm births by gestational age

Preterm births are categorized by gestational age. Gestational age is usually defined in weeks (w) and days (d) measured by early ultrasound by the size of the fetus. In low resource settings the gestational age can be measured by last menstrual period of the mother, fundal height or estimated by birth weight which is not as accurate (3). Extreme preterm births are births before completed gestational week 28 (<28w0d), severe preterm births occur in weeks 28-31 (28w0d-31w6d), moderate preterm births refer to births in weeks 32-33 (32w0d-33w6d) while late preterm births are births at 34-36 weeks (34w0d-36w6d) (1). When 37 weeks gestational age has been reached, the infant is considered term, even though the definition early term is often used for 37w0d-38w6d gestational age as recent studies have shown that morbidity of early term infants is higher than for term infants (39w0d-41w6d weeks)

(8, 9). There is no official cutoff age for lowest viable gestational age but most developed countries use 22 weeks (22w0d) as cutoff age between spontaneous abortion and preterm birth (1). The age limit for viability has been lowered in recent decades with increased specialization, new treatments and equipment to save extreme premature infant's lives. In the 1970's 28 weeks was the lowest age that was considered viable (10).

Extreme preterm births are around 5% of all preterm births, severe preterm births are about 15% of preterm births while moderate preterm births include around 20% and late preterm births approximately 60% (1). The difference between these groups between countries is large since not all nations have the resources to save extreme premature infants lives and the definition of stillbirth is up to 28 weeks or less than 1000g in some less developed areas (11). Also, due to the difference in the measurement of gestational age there can be a misclassification, for example in low resource settings where intra uterine growth restriction (IUGR) is more common and gestational age is based on birth weight or fundal height, preterm infants can be misclassified into the wrong gestational age category (12). Even up to 32 weeks infants are perceived non-viable in some low-resource settings which adds to the reporting bias (11). Therefore, there are variations in the extreme and very preterm birth groups between low-, middle- and high-income countries (1, 11-13), for example, three high preterm birth rate cohorts (14-20%) from South-Asia had low proportion of extreme preterm birth rate, or 2%, while developed countries had 5.3% (12). Despite the variations in gestational age proportions between low-, middle- and high-income settings, globally the moderate and late preterm groups together are approximately 80-84% of all preterm births (11, 13).

1.1.2.2 Preterm Births by Obstetric Precursor

Preterm births are also categorized into three types based on the obstetric precursor leading to the delivery. Spontaneous preterm labor occurs when preterm deliveries start with uterine contractions with intact membranes. Preterm premature rupture of the membranes (PPROM) are preterm births when the membranes rupture at less than 37w0d gestational age at least one hour before contractions start. Iatrogenic preterm births are preterm deliveries that are induced or occur by pre-labor caesarean section due to maternal or fetal medical reasons (1).

Spontaneous and PPROM preterm births are often referred to together as spontaneous preterm births since they have many risk factors in common and the delivery starts spontaneously via mechanisms in the body (1). Iatrogenic preterm births are also sometimes called provider initiated preterm births or medically indicated, and they include preterm births of maternal and fetal indications (3).

Spontaneous preterm births are 45% of all preterm births, PPROM include around 25% while iatrogenic preterm births are approximately 30% of all preterm births (1). These percentages vary very much globally. In low income regions, where caesarean section and labor induction rates are very low, spontaneous and PPROM preterm births together are 80% of all preterm births and iatrogenic around 20% (14). In middle- and high-income countries iatrogenic preterm births have been the main cause of the increase in preterm in the last decades (1, 13). Iatrogenic preterm birth rates vary between

different parts of the world, from 19% in low-income countries (14) up to 40-50% in high-income countries (4, 15, 16).

1.2 Risk Factors for Preterm Births

Even though preterm birth is a single outcome, it is initiated by multiple mechanisms. There are various risk profiles by gestational age and for the different types of preterm births as the etiology behind them is different (1). The importance of defining risk factors is critical in the prevention of preterm births. It allows women at risk being identified and a timely intervention implemented if there is a threat of preterm delivery. Also, the risk factors can give an insight into the mechanisms leading to preterm birth and thus facilitating research in this area (1, 12).

Spontaneous and PPROM preterm births are often referred to together as spontaneous as the preterm birth starts with clinical mechanisms in the mother's body leading to rupture of the membranes or contractions of the uterus. Spontaneous and PPROM preterm births also have many risk factors in common such as infections, cervical and ischemic problems, a history of preterm birth, tobacco use and black race (17). The risk factors and precursors to spontaneous preterm birth vary by gestational age (17) and socio-economic factors (18). Even though so much is known regarding risk factors the cause of premature onset of labor is unknown in up to 50% of spontaneous preterm births (18).

Iatrogenic preterm births are often called indicated preterm births as preterm labor is induced or caesarean section is performed prematurely due to maternal or fetal indications (3). The maternal medical diseases that increase the risk for iatrogenic preterm birth are, for example, preeclampsia, hypertension and diabetes (1), whereas fetal reasons for iatrogenic preterm birth can be intrauterine growth restriction (IUGR), fetal distress, oligohydramnios and polyhydramnios (3). These maternal and fetal indications are however not solely risk factors for iatrogenic preterm births. They can also be risk factors for spontaneous preterm births as the different types also have many risk factors in common. For example, iatrogenic preterm births induced due to maternal preeclampsia or fetal intra-uterine growth retardation could have the same ischemic complications causing or proceeding a spontaneous preterm birth (19). Dividing the risk factors in two groups based on the type of preterm birth could therefore, according to Frey et al (2016), hinder the identification of relevant scientific findings in connection with these different conditions (19). The risk factors are therefore introduced here collectively for all preterm subtypes as they are risk factors for both spontaneous and iatrogenic preterm births, although at different intensity (1).

1.2.1 Previous Preterm Birth

A history of previous preterm birth increases the risk for preterm birth in later pregnancies, both spontaneous and iatrogenic (20, 21), although the mechanism behind the recurrence is different (21). The risk increases with shorter gestational age in the previous preterm birth (21). A large population study on preterm births in California USA found that the highest level of risk was connected to previous preterm birth, preexisting and gestational hypertension with preeclampsia in all types of preterm births, both with short and long gestational age (21). Previous preterm births increased the

risk for spontaneous preterm birth fivefold, whilst the risk for iatrogenic preterm birth risk was between two- and three-fold (21).

1.2.2 Short Interpregnancy Interval

A short interpregnancy interval increases the risk for preterm birth (1, 21, 22), especially early term spontaneous and PPROM (21) The mechanism for this are not fully understood, however could be connected to the fact that the maternal body wasn't ready for the next pregnancy, the uterus and cervix had not returned to normal state or are still in an inflammatory status from previous pregnancy. Nutritional depletion could also be another explanation, that pregnancy depletes maternal supplies of vitamins, minerals and amino-acids and that these nutrients aren't replenished because of the short period between pregnancies (1).

1.2.3 Socio-Economic Status and Maternal Education

Low socio-economic and educational status is also connected with increased risk of preterm birth (12, 20) as well as maternal factors that are often connected to low socio-economic status (23), such as stress, race, alcohol and tobacco use during pregnancy (19). Education is also connected with preterm birth, less than high school education has shown a 20-50% increased risk of preterm birth with the risk decreasing with higher education in a cross-country review of data from 5 countries (20). It is not fully understood how socio-economic status influences the risk for preterm birth, whether it is due to lack of health-care, absence of economic and social safety or other risk factors that could be increased in disadvantaged socio-economic surroundings (24).

1.2.4 Race

Black race is connected to higher risk of preterm birth (11, 19, 25). In USA in 2008, for example, the late preterm birth rate was 11.3% for black mothers while it was 8.2% for white mothers (25). The risk is also higher for shorter gestational age compared to other ethnicities (21).The risk for black race is double for PPROM and spontaneous preterm birth whilst black women have up to 60% increased risk of iatrogenic preterm births compared to other ethnicities (21). Globally, black women's preterm birth rate is 16-18% compared with 5-9% for white women (1). The etiology causing this difference between races, which persists even after known confounders have been accounted for, have not been fully explained. However, interaction between maternal, paternal and fetal genetics, epigenetics, microbiome and sociodemographic risk factors such as differences in health care quality and access, effects of psychosocial stress, poverty and prevalence of co-morbidities are likely underlying factors (24, 25).

1.2.5 Maternal lifestyle

Maternal lifestyle can be a risk factor, such as smoking, heavy alcohol consumption and illicit drug use during pregnancy (12). A large cross-country systematic review found that smoking increases the risk of preterm birth by 30-60% compared to non-smokers (20). Tobacco causes placental and ischemic problems as well as intra uterine growth retardation which can both lead to spontaneous and

iatrogenic preterm birth (26). Excess alcohol consumption as well as illicit drug use is also connected to an increased risk of preterm birth and other health consequences for the infant (12, 20, 27).

1.2.6 Maternal age

The age of the mother has an influence on preterm birth, both very young mothers and mothers of higher age have an increased risk of preterm birth (27). The cause for this is not fully explained, however is likely to have different explanations, connected to other risk factors linked to age, for example anemia and stress in young mothers and hypertension and ischemic problems connected to advanced age (12). A large cohort study recently found that mothers 40 year old and older had an increased risk of preterm birth, even after adjusting for confounders (27).

1.2.7 Maternal weight

Maternal weight and nutritional status is also connected to preterm birth, both underweight and overweight (12). Low body mass index is connected to an increased risk of spontaneous preterm birth (1) while high body mass index and obesity are connected to increased risk of spontaneous and iatrogenic preterm birth, but not PPROM (28).

1.2.8 Multiple gestation

Multiple gestation heightens the risk for preterm delivery with the risk increasing with each additional infant (12). More than half of all twins are born prematurely and almost all triplets and higher multiple gestations result in preterm birth (29). Multiple preterm births are more often spontaneous or PPROM, for example due to uterine overdistention causing contractions or rupture of the membranes (29). Iatrogenic preterm multiple births are connected to maternal or fetal problems, for instance preeclampsia, fetal distress or growth retardation (29). Assisted Reproductive Technologies (ART) have increased with heightened maternal age and better technologies (4, 30). ART increases the risk for all types of preterm birth but especially iatrogenic preterm birth (4). This was often due to multiple gestation especially in the first years of this new technology (30). Recent policy changes have advised against multiple embryo implantation which will hopefully turn this trend around (12).

1.2.9 Maternal Medical Conditions

Maternal underlying chronic medical conditions can be risk factors for preterm births. Diabetes more than doubles the risk for preterm delivery (20), especially spontaneous but iatrogenic as well. Reasons for this can be that diabetes increases the risk for other complications which lead to induction of labor or caesarean section, such as hypertension, preeclampsia, macrosomia and polyhydramnios (12). Hypertension has an increased risk for iatrogenic preterm birth (31) and is also connected to increased risk for preeclampsia and placental abruption which are also strongly connected to preterm birth (12). Other underlying conditions connected to preterm birth risk are thyroid disease, anemia, renal problems and preexisting infectious diseases (12). Auger et al (2011) conducted a large cohort study in Canada on the association between maternal comorbidity and preterm birth by severity and clinical subtype (31). They found several maternal comorbidities, connected to all types of preterm birth, especially at less than 32 weeks gestational age. These conditions were placental abruption,

chorioamnionitis, oligohydramnios, structural abnormality and cervical incompetence. Auger et al also found that preeclampsia and anemia increased the risk for PPROM and iatrogenic preterm birth (31).

1.2.10 Maternal Mental Conditions

Maternal psychological problems increase risk of preterm birth (1). Depression, anxiety and stress have been found to double the risk of preterm birth even after adjusting for confounders such as age, tobacco and alcohol use, and socio-economic status (32). A large systematic review on the evidence on the risk of preterm birth associated with antenatal depression, anxiety, and stress found strong evidence for increased risk for preterm birth (33). The effects of depression, anxiety and stress during pregnancy were associated with spontaneous but not with iatrogenic preterm birth (33). Violence against women is also reported to increase the risk for preterm birth as well as other physical, mental and reproductive complications (34, 35). Intimate partner violence has been found to be a significant independent risk factor for premature labor and PPROM (OR 1.30-1.62) compared to women who do not report partner violence (35).

1.2.11 Pregnancy and Reproductive Anomalies

Anomalies with the amniotic fluid, either too much (polyhydramnios) or too little (oligohydramnios) are strong risk factors for preterm birth and are often connected to maternal or fetal problems (12). Maternal problems such as a short cervix and cervical insufficiency which can be caused by surgical procedures, trauma or congenital weakness increase risk for spontaneous and PPROM preterm birth and are strongly connected to women's recurring preterm births (36) while vaginal bleeding caused by placenta previa or placental abruption increases the risk for iatrogenic preterm birth (37).

1.2.12 Infections

Infections are a strong risk factor for spontaneous and PPROM preterm births, whether they are preexisting infectious diseases such as HIV and syphilis, or not preexisting infections such as intrauterine infection, bacterial vaginosis, genital infections or even periodontal disease, pyelonephritis, appendicitis and pneumonia (38). The reasons leading to this are not fully explained, however are considered to be connected to microorganisms which initiate the inflammatory pathways stimulating prostaglandin release. This can initiate labor and other inflammatory mediators which influence changes in the membranes increasing the risk for PPROM (38).

1.2.13 Environmental, Biological and Genetic Factors

A family history of preterm birth is a risk factor for preterm birth (21). Studies on genetic associations have found connections between single-nucleotide polymorphisms in several genes and increased risk for spontaneous and PPROM preterm births (39, 40). Studies of biomarkers, for instance cytokines, chemokines and fetal fibronectin, in biological fluids (amniotic fluid, urine, vaginal secretions or blood) have improved the understanding of the mechanisms leading to preterm birth. The biomarkers have a strong relation to inflammation and an increased risk for spontaneous preterm birth (40). The mechanism behind this are not clear, but studies of a polymorphism in tumor necrosis factor-alpha, a proinflammatory cytokine, showed the most consistent increase in the risk of preterm birth

(40). Environmental factors, which activate inflammatory pathways, such as infections and stress, have been connected to preterm birth, suggesting that genetic and environmental risk factors could operate and interact through related pathways (40). There are common maternal, obstetric and serum marker risk factors between all types of preterm birth which suggest shared underlying pathways across subtypes of preterm birth (21). The serum markers have been found to be low first trimester pregnancy-associated plasma protein A, high second trimester alpha-fetoprotein and high second trimester dimeric inhibin A (21). One or more of these serum markers occurred in 52-86% of all studied pregnancies resulting in preterm birth compared to 41% resulting in term birth (21) which suggests that studying these biomarkers and genetic factors further would be important.

1.3 Prevention of Preterm Birth

Preventing preterm birth starts with a healthy mother and a healthy pregnancy (2, 41). The World Health Organization (WHO) recommends the following primary interventions to prevent preterm birth: 1) Counselling about healthy diet and nutrition and against tobacco, alcohol and drug use; 2) use of ultrasound for fetal measurements to detect number of fetuses, gestational age and anomalies; 3) regular contact with health professionals, a minimum of 8 visits during the pregnancy; 4) and finally preventing and diagnosing risk factors (2, 41). Secondary interventions include circumferential stitches for a short or structurally weak cervix, called cervical cerclage, especially if women have a previous history of preterm birth or second trimester spontaneous abortion and a diagnosis of cervical insufficiency (42). Treatment of risk factors have been found to be important secondary interventions, for instance antibiotic treatment for infections. Also, progesterone or tocolytic drugs for women with threatening preterm birth, although evidence on the effect of these treatments is not conclusive (41). Auger et al (2011) conducted a cohort study on the association between maternal comorbidity and preterm birth. They concluded that preventive strategies in reducing preterm birth should aim for the comorbidities that affect a large proportion of preterm births, especially hypertension, anemia and problems in the reproductive system (31). Jelliffe-Pawlovski et al (2016) found in their large epidemiological study that there were common risk factors, including maternal, obstetric and serum markers, that all had a role in spontaneous, PPROM and iatrogenic preterm births. This finding supports the theory that there is a shared underlying mechanism for preterm births and that preventing, monitoring and treating preterm birth risk factors is vital in the prevention of preterm birth (21).

1.4 Consequences of Preterm Birth

Preterm births are the worldwide leading cause of neonatal and childhood mortality (3) and preterm infants have a high risk of long term complications (1). Preterm infants' morbidity and mortality varies depending on gestational age, facilities and location (community prosperity) (10). In order to reduce morbidity and mortality it is beneficial to regionalize intensive care to treat premature infants in specialized tertiary care centers. That includes transporting high-risk mothers to tertiary care hospitals before delivery and also preterm infants if they are born in community hospitals/secondary care. Better outcomes are reached with maternal transport than transporting the premature neonate after birth (10).

1.4.1 Morbidity

Neonatal outcomes depend on both gestational age of the premature infant and extrinsic factors, mainly the quality of the care available. Since 1980's the morbidity in high-income countries has been decreasing and complications diminishing although prematurity to this day is the largest burden to children's health (43).

1.4.1.1 Short Term Complications

The risk for complications increases with lower gestational age as the extreme and very premature infants' skin, lungs, vascular system, brain and neurological system is more immature and less prepared for birth (3, 10). Short term complications for preterm infants are increased risk of temperature instability, respiratory difficulty such as respiratory distress syndrome and apnea, blood sugar instability, jaundice, feeding problems and brain injury (1, 10). In order to reduce complications, antenatal treatment with corticosteroid injections when preterm birth is imminent to prepare the infants' lungs for birth is recommended (44). After birth, neonatal care includes surfactant medication and ventilators to support breathing as well as kangaroo care of the preterm infant to decrease stress and prevent neurological long-term complications (10). Also, antibiotics to treat infections, incubators to prevent heat loss via the skin and feeding via tube for those who cannot feed without assistance are important (3, 10).

1.4.1.2 Long Term Complications

Long term complications for preterm infants are more common with shorter gestational age however there is no gestational age, including full term, that is fully free from long term complications (10). The prevalence of complications is inversely related to gestational age (10) and also the quality of the health care system where the premature infant is born (45).

1.4.1.2.1 Retinopathy of Prematurity

Retinopathy of prematurity is globally the main cause of a potentially avoidable childhood blindness and is defined as a visual impairment due to retinal vascular underdevelopment. This is highly connected to poorly monitored oxygen delivery to the premature infant, both hypoxia and hyperoxia (46). The risk is highest for the shortest gestational age survivors (46). Retinopathy affects nearly 16% of all preterm infants and causes long term visual impairment in 3% of all extreme and very preterm infants (46). Most cases are mild and resolve without treatment, however more severe retinopathy can progress and if untreated can result in retinal detachment and scarring of the retina, which most often leads to permanent loss of vision (46).

1.4.1.2.2 Respiratory Problems

Preterm birth is the most common cause of abnormal lung development and can lead to lifelong complications (47). Bronchopulmonary dysplasia is the most common complication of extreme prematurity (47). It is a chronic pulmonary disorder occurring in preterm infants exposed to mechanical ventilation and high oxygen concentrations following respiratory distress syndrome (47). Extreme premature infants have an increased risk of readmission to hospital up until they are 6 years old,

mainly due to respiratory infections or bronchopulmonary dysplasia which has been described in up to 40% of all very premature survivors (10). Studies on long term respiratory complications of premature bronchopulmonary dysplasia in adulthood found increased reports of emphysema, double likelihood of wheezing and triple likelihood of asthma medication compared to full-term controls (47).

1.4.1.2.3 Neurodevelopmental Impairments

Neurodevelopmental impairments include cerebral palsy, mental disorders and sensory problems, (45). Around 3% of preterm infants who survive beyond the first month develop moderate or severe neurodevelopmental impairment and additional 4.4% have mild neurodevelopmental impairment however the frequency is inversely connected with gestational age (45). The consequences of cerebral palsy vary very much, from light spasticity to quadriplegia (10). Preterm infants also have an increased risk of neuromotor dysfunction and lack of coordination (10). About 6% of extremely preterm infants develop hearing impairment and the use for hearing aid at the age of 6 years (48).

Many preterm children have long term specific learning or behavioral impairments or dysfunction in the cognitive area such as attention deficit with or without hyperactivity, anxiety, dyslexia or other specific learning impairment (45). These sequalae are not limited to short gestational age as late preterm birth has been associated with lower IQ and behavioral problems at the age of 6, independent of maternal IQ, residency, and socio-demographic factors (49).

1.4.2 Mortality

There are large variations in mortality rates following preterm birth between countries, within countries, between hospitals, secondary and tertiary care, gestational age and even social groups (10, 50). The difference in preterm birth survival between high and low income regions is dramatic (12), there is a so-called 10:90 survival gap, due to the fact that over 90% of extreme preterm births in low-income settings end in death during the first few days of life while less than 10% of extreme preterm births result in neonatal death in high-income regions (12). A prospective cohort study in Europe on the survival of extreme premature infants in 12 regions in 5 countries (Belgium, France, Italy, Portugal and the UK) in 2010-2012 showed a great variability in outcome (50). Survival at 23 weeks was 0-25% whilst survival at 24 weeks was 21-50% reflecting on the treatments provided (50). All centers had 0% of infants born at 22 weeks survive to discharge though (50). In high-income settings the survival of preterm infants in weeks 28-32 is at 95%, whereas it is 30% in low-income settings (11). Neonatal deaths because of prematurity in Afghanistan and Somalia are 16 per 1000 whilst in Japan, Sweden and Norway they are less than 0.5 per 1000 (11).

1.5 Epidemiology of Preterm Birth

The frequency of preterm birth varies, but the global burden of prematurity is increasing as the frequency of preterm births is rising in most countries (1).

1.5.1 Global variations

According to WHO, the global estimation on the preterm birth rate for 2014 is 10.6%, which is the same as in 2010 but higher than in 2000 when it was 9.8% (51). The preterm birth rate is higher in low and middle income countries than in the more developed countries, ranging from 5% in some Northern European countries up to 19.1% in Bangladesh (51) and 18% in sub-Saharan African Countries (3), for example 16.6% in Tanzania, 12.0% in Ethiopia, 11.4% in Nigeria (51) and 18.1% in Malawi (11). The preterm birth rate in USA is 12%, it is nearly 15% in Cyprus and around 11% in Austria and Singapore (52). In the Nordic countries it is 5-7%; 5.5% in Finland, 5.9% in Sweden, 6.7% in Norway (5) and 5% in Denmark (53). A systematic analysis on preterm birth rates from 1990 to 2010 in 65 countries (developed, Latin America and Caribbean region) showed a rise in 48 countries, 14 were stable while only three countries (Croatia, Ecuador and Estonia) had reduced preterm birth rates during the study period (13). In the developed regions the study found a 19.4% increase in the preterm birth rate over the 20 years period, while the increase in Latin-America was 9.1% and in the Caribbean 25.8% (13).

The majority of preterm births occur in low- and middle-income countries (51). Over 60% of preterm births occur in South-Asia and in sub-Saharan Africa (13). In the lower-income countries, on average, 12% of births are preterm compared with 9% in higher-income countries (3). Additionally, within countries, poorer families are at higher risk than families that are more privileged (3).

1.5.2 Increase in Late Iatrogenic Preterm Births in High- and Middle-income Countries

Globally, the proportions between the types of preterm birth vary (4). The proportion of spontaneous and PPROM preterm births is higher in low income countries than in high- and middle-income countries where iatrogenic preterm birth have been increasing in the last decades, especially late preterm births (4, 15, 16). In USA, for example, iatrogenic preterm births increased from around 30% in 1989 to 40-50% of all preterm births in 2000 (54). This increase has also been seen in middle-income countries like Brazil where iatrogenic preterm birth rate has increased to over 35% in a multicenter study in Brazil in 2011-2012 (55), and has been seen up to 61% in private hospitals in Brazil (56). In Europe, many countries also have had an increase in the iatrogenic preterm birth rate (5). In a study on the preterm birth trends in European countries from 1996 to 2008 iatrogenic singleton preterm births increased in 5 of 19, Belgium (1.5-2.0% of all life births), Czech Republic (1.1-1.9%), France (1.5-2.6%), Norway (1.6-2.1%) and Slovenia (0.7-1.3%) (5). This increase in iatrogenic preterm births is however not as evident in Europe as in USA and Brazil, possibly due to lower preterm birth and caesarian section rates. For example the overall preterm birth rate was 5.1-5.2% from 1987 to 2005 in Finland and even though iatrogenic preterm births increased during the study period, the relative risk remained unchanged probably as the caesarean section rates declined even though labor induction increased (57).

The gestational age group that has been increasing the most in the last decades is the late preterm group (1, 4, 5). In USA it has increased by 33% from the 1990's and until 2008 (25). The late preterm birth rate in high-income countries is now well over 70% as shown in a recent study conducted by

Richards et al (2016) of temporal trends in late preterm birth rates in Norway, Denmark, Sweden, USA, Canada and Finland 2006-2014 (8). The increase in iatrogenic late preterm birth seems to have plateaued in the last few years, as the late preterm birth rate decreased during the study period in two countries, USA (annual decrease of 1.6%) and Norway (annual decrease of 2.9%) (8). This plateau may be due to an increased focus on late preterm births in the preterm academic community (25, 58). Priorities in research and guidelines in optimizing care were published in 2007 and 2011 from the National Center for Health Statistics, Eunice Kennedy Schriver National Institute and Child Health and Human development and Society for Maternal and Fetal Medicine (59). The term late preterm was introduced instead of the previously used near term which was a misnomer. Using near term for preterm birth in weeks 34 to 36 implied that it was safe (58), but the fact is that the mortality and morbidity of late preterm infants is higher than in term infants (9, 58, 60). The redefinition of the term emphasized that preterm births are a global burden and that late and iatrogenic preterm births should be avoided if possible as well as early term births (before 39 weeks of gestation) (58). Studies agree on that not one recorded indication is the single cause of this increase in iatrogenic preterm births (15), they are heterogenous (61) and there is a complex process behind each iatrogenic preterm birth which should be analyzed in detail to improve preventive strategies based on the latest evidence (55).

Iatrogenic preterm births are also called medically indicated preterm births and have been thought to be rising due to a rise in the medical indications that precede them (3, 62). The leading indications for iatrogenic preterm births are preeclampsia, IUGR, multiple pregnancies, placental insufficiency (63), hypertensive disorders and diabetes (55). There has been an increase in obesity and maternal age which has increased risk for diabetes, hypertension and preeclampsia which are all risk factors for preterm birth and known indications for iatrogenic preterm birth (12). Also, caesarean sections, induced deliveries (62) and assisted fertility treatments have increased (1, 11, 52). These indications do however not sufficiently explain the increase in iatrogenic preterm births as some iatrogenic late preterm births have been found to be avoidable (6) and even non evidence based and that evidence based guidelines were needed (7, 64). Morais et al (2013) conducted a retrospective cohort study at two tertiary referral centers in a nationalized healthcare system in Canada 2010-2011 to determine the proportion, characteristics, and predictors of late preterm birth in relation to evidence-based and non-evidence based indications (64). They followed Holland et al (2009) who reported that 17% of late preterm births could have been avoided (6) and Gyamfi-Bannerman et al (2011) who reported that 18% of all late preterm births and over half on iatrogenic late preterm births were non-evidence based (7). Morais et al found that 25.2% of all late preterm births did not have guidelines or randomized control trial evidence as a basis for the delivery (64). Logistic regression included gestation at birth, delivery provider, previous stillbirth, previous caesarean section, corticosteroid administration, and previous preterm birth as predictors for non-evidence based late preterm birth (64). These findings emphasize the need to evaluate the indications for late preterm induction or caesarean section especially considering the increased morbidity of late preterm birth compared to term (9, 58, 60).

Some studies on the trends on preterm birth have focused on possible opportunities in the reduction of the preterm birth rate in the world (52). Chang et al (2013) examined trends in preterm births in 39 developed countries with very high human development index in order to find a rate

reduction target (52). They analyzed drivers for preterm birth rate increase in USA from 1989 to 2004 and trend analysis, target population and intervention efficacy analysis for each country (52). They concluded that there was a way to decrease the preterm birth rate in these countries by 5% in total by working on smoking cessation, not inserting multiple embryos in fertility treatments, using cervical cerclage and progesterone supplementation and most importantly reducing iatrogenic labor induction or caesarean delivery without medical indication (52). In USA there was an estimated potential for 8% decrease (52). However, there was less room for improvement in Sweden, only 2% as there were fewer iatrogenic preterm births (52). Chang et al emphasized that although the focus should be on stopping non-indicated preterm births there will continue to be incidences where preterm births are indicated, and total prevention of preterm births could not be achieved without preventive therapies which eradicate all fetal, obstetric and maternal complications (52).

1.6 Preterm births in Iceland

The preterm birth rate in Iceland was 4.8% in 1972-1981 (65) and 5.4% in 2011 (66). In Iceland reports from the Icelandic Medical Birth Registry have been published since 1972 for all birthing centers in Iceland including Landspítali, Iceland´s only tertiary birthing hospital, where approximately 75% of all births in Iceland occur and over 90% of all preterm births (67). In Landspitali, the preterm birth rate has been stable at around 6-7% in the last few years (67) which is an increase from around 2000 when it was stable around 5% (68).

The labor induction rate in Iceland has been increasing over the last decades, from around 14% in 2000 (68), 18.4% in 2011 (69) and up to 28% in 2016 (67). The caesarean section rate has been slowly declining during the last decade after a steady increase up to 18% in the beginning of this century (68). The caesarean rate is currently around 17% (67). Elective caesarean rate is 6.5% in Iceland (67) while it was 5.6% in 2011 (69). Although preterm birth rate, induction of labor and elective caesarean rate are rising in Iceland, these obstetric parameters are among the few lowest in Europe (70). Births after assisted reproductive techniques have remained stable. However, maternal age has been increasing in Iceland as well as obesity, diabetes and other risk factors that can influence maternal and fetal complications (67, 71).

Little data is available on the proportions between the three types of preterm births, spontaneous, PPROM and iatrogenic in Iceland. It is also not well known how the rates of the preterm birth subtypes and gestational age groups have changed in the past decades.

2 Specific aims

In this study, we will explore the preterm birth rate in Iceland during 1997 to 2016 for the whole country overall and for all three types of preterm births as well for gestational age groups. We will investigate if the rate of iatrogenic births has been increasing, and if so, whether it is explained by rate changes in medical indications. There is limited information published on the obstetric precursor leading to preterm births in Iceland, therefore little is known whether iatrogenic preterm births are increasing in Iceland as in other countries. Therefore, in this study, we aim to assess the epidemiology of preterm births in Iceland during 1997-2016. More specifically we aim to assess the trend in the rate of preterm birth in Iceland from 1997-2016, overall and separately for the three types of preterm birth (PPROM, spontaneous, iatrogenic), estimate the trend in the rate of preterm birth according to gestational age, overall and for the three types of preterm birth and assess the relative contribution of each indication to the rate of iatrogenic preterm birth.

References

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet (London, England). 2008;371(9606):75-84.
2. Preterm Birth https://www.who.int/news-room/fact-sheets/detail/preterm-birth: WHO; 2018 [Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth. Accessed Feb 15 2019.
3. Harrison MS, Goldenberg RL. Global burden of prematurity. Seminars in fetal & neonatal medicine. 2016;21(2):74-9.
4. Henderson JJ, McWilliam OA, Newnham JP, Pennell CE. Preterm birth aetiology 2004-2008. Maternal factors associated with three phenotypes: spontaneous preterm labour, preterm pre-labour rupture of membranes and medically indicated preterm birth. 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 Obstet. 2012;25(6):642-7.
5. Zeitlin J, Szamotulska K, Drewniak N, Mohangoo AD, Chalmers J, Sakkeus L, et al. Preterm birth time trends in Europe: a study of 19 countries. BJOG : an international journal of obstetrics and gynaecology. 2013;120(11):1356-65.
6. Holland MG, Refuerzo JS, Ramin SM, Saade GR, Blackwell SC. Late preterm birth: how often is it avoidable? American journal of obstetrics and gynecology. 2009;201(4):404.e1-4.
7. Gyamfi-Bannerman C, Fuchs KM, Young OM, Hoffman MK. Nonspontaneous late preterm birth: etiology and outcomes. American journal of obstetrics and gynecology. 2011;205(5):456.e1-6.
8. Richards JL, Kramer MS, Deb-Rinker P, Rouleau J, Mortensen L, Gissler M, et al. Temporal Trends in Late Preterm and Early Term Birth Rates in 6 High-Income Countries in North America and Europe and Association With Clinician-Initiated Obstetric Interventions. Jama. 2016;316(4):410-9.
9. Bulut C, Gursoy T, Ovali F. Short-Term Outcomes and Mortality of Late Preterm Infants. Balkan medical journal. 2016;33(2):198-203.
10. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet (London, England). 2008;371(9608):261-9.
11. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller AB, et al. Born too soon: the global epidemiology of 15 million preterm births. Reproductive health. 2013;10 Suppl 1:S2.
12. March of Dimes, PMNCH, Save the Children, WHO. Born Too Soon: The Global Action Report on Preterm Birth. Geneva: World Health Organization; 2012. Accessed Mar 22 2019.
13. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet (London, England). 2012;379(9832):2162-72.
14. Morisaki N, Togoobaatar G, Vogel JP, Souza JP, Rowland Hogue CJ, Jayaratne K, et al. Risk factors for spontaneous and provider-initiated preterm delivery in high and low Human Development Index countries: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG : an international journal of obstetrics and gynaecology. 2014;121 Suppl 1:101-9.
15. Yang X, Zeng W. Clinical analysis of 828 cases of iatrogenic preterm births. The journal of obstetrics and gynaecology research. 2011;37(8):1048-53.
16. Ada ML, Hacker MR, Golen TH, Haviland MJ, Shainker SA, Burris HH. Trends in provider-initiated versus spontaneous preterm deliveries, 2004-2013. Journal of perinatology : official journal of the California Perinatal Association. 2017;37(11):1187-91.
17. Steer P. The epidemiology of preterm labour. BJOG : an international journal of obstetrics and gynaecology. 2005;112 Suppl 1:1-3.
18. Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and racial disparity. Acta obstetricia et gynecologica Scandinavica. 2008;87(6):590-600.

19. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. Seminars in fetal & neonatal medicine. 2016;21(2):68-73.

20. Ferrero DM, Larson J, Jacobsson B, Di Renzo GC, Norman JE, Martin JN, Jr., et al. Cross-Country Individual Participant Analysis of 4.1 Million Singleton Births in 5 Countries with Very High Human Development Index Confirms Known Associations but Provides No Biologic Explanation for 2/3 of All Preterm Births. PloS one. 2016;11(9):e0162506.

21. Jelliffe-Pawlowski LL, Baer RJ, Blumenfeld YJ, Ryckman KK, O'Brodovich HM, Gould JB, et al. Maternal characteristics and mid-pregnancy serum biomarkers as risk factors for subtypes of preterm birth. BJOG : an international journal of obstetrics and gynaecology. 2015;122(11):1484-93.

22. Muglia LJ, Katz M. The enigma of spontaneous preterm birth. The New England journal of medicine. 2010;362(6):529-35.

23. Joseph KS, Fahey J, Shankardass K, Allen VM, O'Campo P, Dodds L, et al. Effects of socioeconomic position and clinical risk factors on spontaneous and iatrogenic preterm birth. BMC pregnancy and childbirth. 2014;14:117.

24. Manuck TA. Racial and ethnic differences in preterm birth: A complex, multifactorial problem. Seminars in perinatology. 2017;41(8):511-8.

25. Shapiro-Mendoza CK, Lackritz EM. Epidemiology of late and moderate preterm birth. Seminars in fetal & neonatal medicine. 2012;17(3):120-5.

26. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2004;6 Suppl 2:S125-40.

27. Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F. Effect of maternal age on the risk of preterm birth: A large cohort study. PloS one. 2018;13(1):e0191002.

28. Torloni MR, Betran AP, Daher S, Widmer M, Dolan SM, Menon R, et al. Maternal BMI and preterm birth: a systematic review of the literature with meta-analysis. 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 Obstet. 2009;22(11):957-70.

29. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. BJOG : an international journal of obstetrics and gynaecology. 2006;113 Suppl 3:17-42.

30. Blondel B, Kaminski M. Trends in the occurrence, determinants, and consequences of multiple births. Seminars in perinatology. 2002;26(4):239-49.

31. Auger N, Le TU, Park AL, Luo ZC. Association between maternal comorbidity and preterm birth by severity and clinical subtype: retrospective cohort study. BMC pregnancy and childbirth. 2011;11:67.

32. Baer RJ, Chambers CD, Bandoli G, Jelliffe-Pawlowski LL. Risk of preterm birth by subtype among Medi-Cal participants with mental illness. American journal of obstetrics and gynecology. 2016;215(4):519.e1-9.

33. Staneva A, Bogossian F, Pritchard M, Wittkowski A. The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: A systematic review. Women and birth : journal of the Australian College of Midwives. 2015;28(3):179-93.

34. Krug EG, Mercy JA, Dahlberg LL, Zwi AB. The world report on violence and health. Lancet (London, England). 2002;360(9339):1083-8.

35. Sharps PW, Laughon K, Giangrande SK. Intimate partner violence and the childbearing year: maternal and infant health consequences. Trauma, violence & abuse. 2007;8(2):105-16.

36. Ville Y, Rozenberg P. Predictors of preterm birth. Best practice & research Clinical obstetrics & gynaecology. 2018;52:23-32.

37. Krupa FG, Faltin D, Cecatti JG, Surita FG, Souza JP. Predictors of preterm birth. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2006;94(1):5-11.

38. Gravett MG, Rubens CE, Nunes TM. Global report on preterm birth and stillbirth (2 of 7): discovery science. BMC pregnancy and childbirth. 2010;10 Suppl 1:S2.

39. Engel SA, Erichsen HC, Savitz DA, Thorp J, Chanock SJ, Olshan AF. Risk of spontaneous preterm birth is associated with common proinflammatory cytokine polymorphisms. Epidemiology (Cambridge, Mass). 2005;16(4):469-77.

40. Crider KS, Whitehead N, Buus RM. Genetic variation associated with preterm birth: a HuGE review. Genetics in medicine : official journal of the American College of Medical Genetics. 2005;7(9):593-604.

41. Iams JD, Romero R, Culhane JF, Goldenberg RL. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet (London, England). 2008;371(9607):164-75.

42. Berghella V, Odibo AO, To MS, Rust OA, Althuisius SM. Cerclage for short cervix on ultrasonography: meta-analysis of trials using individual patient-level data. Obstetrics and gynecology. 2005;106(1):181-9.

43. Blencowe H, Vos T, Lee AC, Philips R, Lozano R, Alvarado MR, et al. Estimates of neonatal morbidities and disabilities at regional and global levels for 2010: introduction, methods overview, and relevant findings from the Global Burden of Disease study. Pediatric research. 2013;74 Suppl 1:4-16.

44. Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. Jama. 1995;273(5):413-8.

45. Blencowe H, Lee AC, Cousens S, Bahalim A, Narwal R, Zhong N, et al. Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. Pediatric research. 2013;74 Suppl 1:17-34.

46. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatric research. 2013;74 Suppl 1:35-49.

47. Islam JY, Keller RL, Aschner JL, Hartert TV, Moore PE. Understanding the Short- and Long-Term Respiratory Outcomes of Prematurity and Bronchopulmonary Dysplasia. American journal of respiratory and critical care medicine. 2015;192(2):134-56.

48. Marlow N, Wolke D, Bracewell MA, Samara M. Neurologic and developmental disability at six years of age after extremely preterm birth. The New England journal of medicine. 2005;352(1):9-19.

49. Talge NM, Holzman C, Wang J, Lucia V, Gardiner J, Breslau N. Late-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. Pediatrics. 2010;126(6):1124-31.

50. Smith LK, Blondel B, Van Reempts P, Draper ES, Manktelow BN, Barros H, et al. Variability in the management and outcomes of extremely preterm births across five European countries: a population-based cohort study. Archives of disease in childhood Fetal and neonatal edition. 2017;102(5):F400-f8.

51. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. The Lancet Global health. 2019;7(1):e37-e46.

52. Chang HH, Larson J, Blencowe H, Spong CY, Howson CP, Cairns-Smith S, et al. Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. Lancet (London, England). 2013;381(9862):223-34.

53. Auger N, Hansen AV, Mortensen L. Contribution of maternal age to preterm birth rates in Denmark and Quebec, 1981-2008. American journal of public health. 2013;103(10):e33-8.

54. Ananth CV, Joseph KS, Oyelese Y, Demissie K, Vintzileos AM. Trends in preterm birth and perinatal mortality among singletons: United States, 1989 through 2000. Obstetrics and gynecology. 2005;105(5 Pt 1):1084-91.

55. Souza RT, Cecatti JG, Passini R, Jr., Tedesco RP, Lajos GJ, Nomura ML, et al. The Burden of Provider-Initiated Preterm Birth and Associated Factors: Evidence from the Brazilian Multicenter Study on Preterm Birth (EMIP). PloS one. 2016;11(2):e0148244.

56. Leal Mdo C, Esteves-Pereira AP, Nakamura-Pereira M, Torres JA, Domingues RM, Dias MA, et al. Provider-Initiated Late Preterm Births in Brazil: Differences between Public and Private Health Services. PloS one. 2016;11(5):e0155511.

57. Jakobsson M, Gissler M, Paavonen J, Tapper AM. The incidence of preterm deliveries decreases in Finland. BJOG : an international journal of obstetrics and gynaecology. 2008;115(1):38-43.

58. Raju T. The "Late Preterm" Birth-Ten Years Later. Pediatrics. 2017;139(3).

59. Raju TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics. 2006;118(3):1207-14.

60. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet (London, England). 2016;388(10063):3027-35.

61. Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Maternal, fetal, and placental conditions associated with medically indicated late preterm and early term delivery: a retrospective study. BJOG : an international journal of obstetrics and gynaecology. 2016;123(5):763-70.

62. Zhang X, Kramer MS. The rise in singleton preterm births in the USA: the impact of labour induction. BJOG : an international journal of obstetrics and gynaecology. 2012;119(11):1309-15.

63. Xue Q, Shen F, Gao Y, Tong M, Zhao M, Chen Q. An analysis of the medical indications for preterm birth in an obstetrics and gynaecology teaching hospital in Shanghai, China. Midwifery. 2016;35:17-21.

64. Morais M, Mehta C, Murphy K, Shah PS, Giglia L, Smith PA, et al. How often are late preterm births the result of non-evidence based practices: analysis from a retrospective cohort study at two tertiary referral centres in a nationalised healthcare system. BJOG : an international journal of obstetrics and gynaecology. 2013;120(12):1508-14.

65. Snædal G, Biering G, Sigvaldason H, Ragnarsson J. Fæðingar á Íslandi 1972-1981, 9.grein: Lengd meðgöngu. Læknablaðið. 1983;69(9):303-5.

66. Delnord M, Blondel B, Zeitlin J. What contributes to disparities in the preterm birth rate in European countries? Current opinion in obstetrics & gynecology. 2015;27(2):133-42.

67. Jónasdóttir E, Eiríksdóttir VH. Skýrsla frá fæðingaskráningunni fyrir árið 2016 [Available from: https://www.landspitali.is/library/Sameiginlegar-skrar/Gagnasafn/Rit-og-skyrslur/Faedingaskraningar/faedingarskraning_skyrsla_2016.pdf. Accessed 8 Jan 2018.

68. Geirsson RT, Garðarsdóttir G, Pálsson G, Bjarnadóttir RI. Skýrsla frá Fæðingaskránni fyrir árið 2003. Landspítali - Háskólasjúkrahús; 2004.

69. Langhoff-Roos J, Krebs L, Klungsoyr K, Bjarnadottir RI, Kallen K, Tapper AM, et al. The Nordic medical birth registers--a potential goldmine for clinical research. Acta obstetricia et gynecologica Scandinavica. 2014;93(2):132-7.

70. Zeitlin J, Mohangoo AD, Delnord M. EUROPEAN PERINATAL HEALTH REPORT Health and Care of Pregnant Women and Babies in Europe in 2010. EURO-PERISTAT project; 2013. [Available from https://www.europeristat.com/images/doc/EPHR2010_w_disclaimer.pdf. Accessed Mar 27 2019.

71. Olafsdottir AS, Skuladottir GV, Thorsdottir I, Hauksson A, Steingrimsdottir L. Maternal diet in early and late pregnancy in relation to weight gain. International journal of obesity (2005). 2006;30(3):492-9.

Article Manuscript

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Preterm births in Iceland 1997-2016:

Preterm birth rates by gestational age groups and type of preterm birth

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Abstract

Introduction

The frequency of preterm births has been increasing globally, mainly due to a rise in iatrogenic late preterm births. It is not well known if the prevalence of preterm births in Iceland has been following a similar trend. The aim of this study was to assess the prevalence of preterm births in Iceland during 1997-2016 by type of preterm birth.

Methods

This study included all live-births in Iceland during 1997-2016 identified from the Icelandic Medical Birth Registry. Rates of preterm births were calculated each year and stratified by gestational age groups and type of preterm birth. Risk of preterm birth by time period was assessed with Poisson regression models adjusted for demographic variables. Indications for iatrogenic births were identified using ICD-10 codes.

Results

The study population included 87,076 infants, of which 4,986 (5.7%) were preterm. The preterm birth rate increased from 5.3 to 6.1% (ARR=1.16, CI=1.07-1.26) between 1997-2001 to 2012-2016. The rate of late preterm births (of all births, 34w0d-36w6d), increased significantly: 3.7% to 4.5% (ARR=1.26, CI=1.15-1.40). The rate of iatrogenic preterm births (of all preterm births) doubled, from 20% in 1997-2001 to 43% in 2012-2016, even after adjustment for medical indications (ARR=2.40, CI=2.06-2.80). Spontaneous preterm births decreased during the study period (ARR=0.63, CI=0.56-0.72) and PPROMs increased slightly (ARR=1.31, CI=1.11-1.54). The largest contributing indication for iatrogenic births were fetal indications (26.2%), which decreased during the study period (32.6%-25.3%).

Conclusions

Preterm birth rates are low in Iceland, however increased slightly between 1997 and 2016. This may have been due to an increase in late and iatrogenic preterm births. The increase in iatrogenic preterm births remained significant after adjusting for medical indications for iatrogenic preterm births. This suggests that other factors than medical indications are affecting the rise in iatrogenic preterm births in Iceland.

Introduction

Preterm births are the worldwide leading cause of neonatal and childhood mortality and morbidity (1, 2). Preterm infants have a high risk of long-term complications such as respiratory and gastrointestinal problems (3) with increasing risk for complications with lower gestational age (1). Preterm births have various etiologies, different risk factors and maternal characteristics (3, 4) and are categorized according to the obstetric precursor leading to the delivery. Spontaneous preterm births (deliveries that start with uterine contractions with intact membranes before completed 37 gestational weeks) are approximately 40-45% of preterm births (3). Preterm premature rupture of the membranes or PPROM (ruptured membranes at less than 37 weeks of gestational age at least one hour before contractions start), are about 25-30% of all preterm births and iatrogenic births (induced delivery or pre-labor caesarean section due to maternal or fetal medical reasons) are around 30-35%% of all preterm births (3).

The total preterm birth rate in the world is 11% (5). The rate varies however between different parts of the world, being around 5% in several Northern European countries (5) (such as 5,5% in Finland and 5,9% in Sweden, Ireland and Lithuania (6)) while in the USA it has been around 12% (5). The highest rates are seen in sub-Saharan African countries or up to 18% (1, 5). The global burden of prematurity has been increasing as studies have shown that the preterm birth rates are rising globally (1, 3). For example, a systematic analysis on preterm birth rates 1990-2010 in 65 countries showed a rise in all but 17 countries, 14 countries had a stable preterm birth rate while only three countries (Croatia, Ecuador and Estonia) had reduced preterm birth rates during the study period (5). In the western world, this rise in preterm birth rate is mainly due to an increase in iatrogenic preterm births at late preterm gestational age (3, 4, 6). Iatrogenic preterm births are also sometimes called provider initiated or medically indicated preterm births as they require an early delivery due to maternal or fetal indications, (1, 7, 8). However, these indications may not explain the increase in iatrogenic preterm births as some of them have been found to be avoidable (9) and even not medically indicated (10, 11).

The preterm birth rate in Iceland was 4.8% in 1972-1981 (12) and 5.4% in 2010 (13). In Landspitali University Hospital, (Iceland´s only tertiary hospital with 75% of all births and over 90% of all preterm births) the preterm birth rate had been stable around 6,7% in the previous years, however it increased to 7,9% in 2016 (14). In this study, we will explore the preterm birth rate in Iceland during 1997 to 2016 for the whole country overall and for all three types of preterm births as well for gestational age groups. We will investigate if the rate of iatrogenic births has been increasing, and if so, whether it is explained by rate changes in medical indications.

Methods

Data sources and study population

This retrospective descriptive population-based cohort study is based on individual data on all births in Iceland from January 1st1997 to December 31st 2016 identified from the Icelandic Medical Birth Registry.

The Icelandic Medical Birth Registry includes information on all births in Iceland after 22 gestational weeks, both live-births and stillbirths. This registration began in 1972 and has been electronic since 1981. The Medical Birth Registry is held by the Directorate of Health and processed by Landspitali University Hospital which has published an annual report from the registry since 1995. Data for both home and hospital births in Iceland is sent to the database from all birthing centers in Iceland. Information regarding pregnancy, delivery, delivery complications, interventions, and the infant is registered. Among other things measured is information regarding place of birth, time of birth, gestational age, previous births, delivery type, treatment during delivery, as well as weight and length of the baby and maternal characteristics (15).

In this study, all live births were included. Initial data included all births, live and dead (n=87,386), 310 were excluded because of stillbirth, 97 of which were term and 213 were preterm. The majority of these stillbirths (306) occurred in utero, while 6 died during the delivery. Births at term and post-term (37w0d-45w0d) and preterm births (22w0d-36w6d) were identified using the variable gestational age in weeks measured with early ultrasound. Preterm births were categorized into four groups, extreme preterm birth (<28w0d), severe preterm birth (28w0d-31w6d weeks), moderate preterm birth (32w0d-33w6d weeks) and late preterm (34w0d-36w6d weeks). Preterm births were also categorized as spontaneous, preterm premature rupture of the membranes (PPROM) or iatrogenic using the variable onset of labor as well as the registered International Classification of Diseases and Health Related Problems, 10th revision (ICD-10) codes for the preterm births that were missing an onset of labor registration. PPROM births were identified by the ICD-10 codes for premature rupture of the membranes (ICD-10 codes O42.0, O42.1, O42.2 and O42.9) for preterm births only. Iatrogenic preterm births were identified when the onset of labor was induced (O83.8), when there was an elective caesarean section (O82.0), for preterm birth without spontaneous labor (O60.3) or for induction of labor identified with NOMESCO Classification of Surgical Procedures (NCSP) for prostaglandin induction of labor (MAXC02). Preterm births were identified as spontaneous when the onset of labor was registered spontaneous or if they had the ICD-10 code for spontaneous preterm birth (O60.1).

In order to adjust for iatrogenic preterm birth indication in the preterm subgroup analysis, all births were categorized into groups based on their ICD-10 diagnosis codes (Table 1). The groups identified were considered particularly important as indications for iatrogenic preterm births. They were: placental abruption (placenta praevia with haemorrhage, placental abruption, other premature separation of placenta), severe preeclampsia (severe preeclampsia, HELLP syndrome, eclampsia), chorioamnionitis, fetal indication (suspected placental insufficiency: IUGR, oligohydramnios, abnormal Doppler), red cell immunization (maternal care for rhesus and other isoimmunization), obstetric cholestasis, hypertensive disorders (essential hypertension, preeclampsia superimposed and pregnancy induced preeclampsia), diabetes mellitus (type 1 and 2 and pre-existing type 1 and 2 diabetes mellitus), maternal illness, multiple gestation and unclear. The group maternal illness was chosen if no other group applied but there was a disease or disorder diagnosis that could affect the pregnancy. These diagnoses were for instance gall and kidney stones, thrombosis, idiopathic thrombocytopenic purpura, heart failure, hydronephrosis, subluxation of symphysis pubis in

pregnancy, exhaustion and supraventricular tachycardia. Many preterm births had more than one diagnosis. We designated an order of importance to the diagnosis groups, with the first group being the most likely to cause iatrogenic preterm birth and thus overriding all others (Table 1).

For example, if the mother had diabetes, twins and severe preeclampsia the iatrogenic cause was registered as severe preeclampsia. When none of the previously mentioned diagnoses were registered, nor any ICD-10 code that could explain preterm induction of labor or elective caesarean section the preterm birth was categorized as unclear which became the 11th indication group.

This study was approved by the National Bioethics Committee in Iceland (VSNb2017050009/03.03) and performed in accordance with the Declaration of Helsinki.

Statistical analysis

Rates of preterm births were calculated for each birth year from 1997 to 2016 as well as for four periods, 1997-2001, 2002-2006, 2007-2011 and 2012-2016.

Preterm birth was modelled as the dependent variable in a Poisson regression model, using birth year period (four five-year periods) as the independent variable to estimate the rate ratio and 95% confidence interval for the risk of preterm birth for each time period relative to the first period. This was done overall and for each gestational week group and subtype group. All Poisson regression models were adjusted for demographic variables (maternal age (continuous), marital status (married/cohabiting, single/divorced/widowed), residential area (Metropolitan area, other), country of origin (Iceland, other), parity (primipara, multipara), multiple gestation (yes, no) and employment status (employed, student, unemployed, homemaker, pension/disability/other)). The Poisson regression model for iatrogenic preterm births was also adjusted for the iatrogenic indication groups (placental abruption, severe preeclampsia, chorioamnionitis, fetal indication, red cell immunization, obstetric cholestasis, hypertensive disorders, diabetes mellitus, maternal illness, multiple gestation and unclear). Test for linear and non-linear trend over time periods was performed using orthogonal polynomial contrasts. Relative contributing indications for iatrogenic preterm births in Iceland 1997-2016 based on ICD-10 codes were calculated as the number of iatrogenic preterm births for each indication divided by all iatrogenic preterm births.

Results

Total number of live infants born during the study period from 1997-2016 was 87,076. Total preterm births (22w0d-36w6d) during the study period were 4,986 (5.7%). The demographic characteristics of all preterm births in Iceland during the study period are shown in Table 2. Extreme (<28w0d) and severe preterm births (28w0d-31w6d) decreased during the study period while moderate (32w0d-33w6d) and late preterm births (34w0d-36w6d) increased ($p<0.001$). Spontaneous preterm births decreased during the study period from 56% of all preterm births to 29%, while PPROM increased slightly from 24% to 28% and iatrogenic preterm births doubled from 20% to 43% of all preterm births ($p<0.001$). The proportion of young mothers under 20 years decreased during the study period and the proportion of mothers over 41 years increased ($p<0.001$). Similarly, the proportion of primiparas

increased, while the proportion of multiparas decreased (p<0.001). Multiple pregnancies, twins and triplets, increased slightly during the study period while the proportion of singletons decreased (p<0.001). The proportion of single, divorced or widowed mothers and student or unemployed mothers increased during the study period while the proportion of homemakers or mothers on pension decreased (p<0.001). Mothers of foreign origin increased in proportion during the study period and the proportion of mothers living outside the capital area decreased (p<0.001).

Preterm birth rates overall and according to gestational age and subgroup are shown in Figure 1 with associated unadjusted and adjusted relative risks for five-year birth year periods shown in Table 3. The preterm birth rate increased from 1997-2001 to 2012-2016: 5.3–6.1% (RR 1.15, 95% 1.06-1.25; ARR 1.16, 95% CI 1.07-1.26), however the increase was not consistent (p<0.01 for non-linearity). The rates by gestational age changed moderately during the study period. Extreme preterm births decreased significantly from 1997-2001 to 2007-2011 (ARR 0.65, 95% CI 0.45-0.94) as well as severe preterm births from 1997-2001 to 2012-2016 (ARR 0.70, 95% CI 0.54-0.91). There was a significant increase in moderate preterm births compared to 1997-2001 (2012-2016: ARR 1.29, 95% CI 1.02-1.69) and the rate of late preterm births increased significantly in all 5-year periods compared to 1997-2001: 3.7%-4.5% (2012-2016: ARR 1.26, 95% CI 1.15-1.40).

Figure 1 and Table 3 show that spontaneous preterm births decreased during the study period from 3.0%-1.8% which was significant for the two latter time periods compared to 1997-2001 (2012-2016: ARR 0.63, 95% CI 0.56-0.72). PPROMs increased moderately from 1.3% to 1.7% with a significant increase in all study periods compared to 1997-2001 (2012-2016: ARR 1.31, 95% CI 1.11-1.54). The rate of iatrogenic preterm births doubled, from 1.1% to 2.6%, a significant increase for the latter two time periods compared to 1997-2001 (2012-2016: ARR 2.37, 95% CI 2.02-2.78). When we additionally adjusted the iatrogenic births for the iatrogenic indication groups (placental abruption, severe preeclampsia, chorioamnionitis, fetal indication, red cell immunization, obstetric cholestasis, hypertensive disorders, diabetes mellitus, maternal illness and multiple gestation) the relative risks did not change considerably (2012-2016: ARR 2.40, 95% CI 2.06-2.80).

When we looked at the proportions of preterm births by gestational age and type simultaneously, spontaneous preterm births were decreasing in all gestational age subgroups with the largest decrease for moderate and late preterm births, from 56-57% to 28% (Figure 2). Similarly, iatrogenic preterm births increased in all gestational age groups, but mostly in moderate and late preterm births from 22-23% to 43-44% (Figure 2).

We also examined the relative contributing indications for iatrogenic preterm births in Iceland during the study period based on ICD-10 codes (Figure 3). The largest contributing indication for iatrogenic births was fetal indication (26.2%), which decreased during the study period (32.6%-25.3%). Hypertensive disorders were the second largest contributing indication (18.2%) and severe preeclampsia came third (16.9%). Both remained relatively stable during the study period. The indications that increased in contribution were obstetric cholestasis, placental abruption and diabetes mellitus (Figure 3).

Discussion

Main findings

This study of all live births in Iceland shows the rate of preterm births from January 1st 1997 to December 31st 2016. Our results showed that preterm births in Iceland increased slightly between 1997 and 2016. This may have been due to an increase in moderate, late and iatrogenic preterm births while extreme, severe and spontaneous preterm births decreased. The increase in iatrogenic preterm births remained significant after adjusting for medical indications for iatrogenic preterm births. This suggests that other factors than medical indications are affecting the rise in iatrogenic preterm births in Iceland.

Strengths and limitations

The main strength of this study is the population-based design. We used individual data from the Icelandic Medical Birth Registry which is a standardized database that includes high quality data on all births in Iceland (16). In addition to all information regarding each birth, gestational age, parity, ICD-10 codes etc. we obtained additional information regarding maternal characteristics. Some information that could be connected to preterm births was missing however. For instance, maternal ethnicity, smoking and substance abuse was not listed in the data and mother's body mass index (BMI) was only available for a short period of time. These factors are strongly related to socio-economic status (17). Therefore, we were able to work around this limitation by adjusting our regression models for maternal characteristics that are also strong predictors of socio-economic status, namely marital status, occupation, residency and nationality which were available in our data (18). Also, the variable onset of labor was missing for many preterm births which led us to use ICD-10 codes to distinguish between iatrogenic, PPROM and spontaneous preterm births. Using these codes was found to be a reliable identification of elective caesarean section, induction of labor and preterm rupture of membranes and gave us a more precise description on the onset of labor. Another limitation is the fact that the ICD-10 diagnoses used to identify medical indications for the preterm births may not have been the direct indications for the births. Even though the ICD-10 diagnoses were registered, it was not clear whether they were the cause of the preterm birth. However, after an analysis of the ICD-10 diagnoses the most likely indication for the preterm birth was chosen by consulting obstetricians and we therefore feel confident with our analysis.

Interpretation

The changes in the preterm birth rates in high income countries have been similar to what we found in our study in Iceland: An increase in the preterm birth rate, mainly due to late and iatrogenic preterm births (3, 8, 19). Even though the preterm birth rate in Iceland was increasing during the study period, from 5.3% to 6.1%, it was relatively low compared to the global preterm birth rate of 11% (5). Iceland's rate was similar to the rate in the northern European countries around Iceland (Finland, Sweden and Ireland with rates of 5.5%-5.9%) (6). However, it was much lower than for instance the rates in Brazil and USA (12%) (7, 19). Many high income countries such as Denmark, France and Poland have slightly higher preterm birth rates than Iceland (6.7%), while Switzerland, Spain, Australia, Canada,

UK and The Netherlands have even higher rates (7.4-8.0%) (19). This could partly be due to the different population structures in these countries as rates have been found to differ between ethnic groups as black mothers have higher rates of preterm birth (20), from 16.2% in 2003 to 12.8% in 2013 compared to 12.3% to 11.2% among white women in the same time period. The difference between races diminished over time, perhaps with increased awareness (21).

The gestational age group that increased the most in size in our study was the late preterm group, from 69% of all preterm births in years 1997-2001 to 74% in 2012-2016. This is a similar trend to what other studies have found (3, 4, 6). The late preterm group has been increasing more than the other gestational age groups globally and is over 70% of all preterm births in Norway, Denmark, Sweden, USA, Canada and Finland (71-76%) (22). This increase in preterm births at 34w0d-36w6d seems to have plateaued in the last few years after an increased focus on late preterm births in the preterm academic community (20, 23). Priorities in research and guidelines in optimizing care were published in 2007 and 2011 from the National Centre for Health Statistics, Eunice Kennedy Shriver National Institute and Child Health and Human Development and Society for Maternal and Fetal Medicine (24). The term late preterm was introduced instead of the previously used near term which was a misnomer. Using near term for premature infants born after 34w0d-36w6d implied that it was safe (23), but the fact is that the mortality and morbidity of late preterm is much higher than in term infants (2, 23, 25). The redefinition of the term emphasized that preterm births is a global burden and that late preterm (and iatrogenic preterm) births should be avoided if possible as well as early term births (before 39 weeks of gestation) (23). Recent studies show that after this guideline change the late preterm birth rate dropped in USA (22, 23) and Norway (22).

The largest increase in the preterm birth rate in our study was for iatrogenic preterm births, which more than doubled (up to 43% of all preterm births). A similar trend was evident in previous studies from many different parts of the world. The rate of iatrogenic preterm births has been increasing significantly over the last decades in Europe (3, 6, 19, 26) as well as in USA (3, 19, 26), where it was 48.3% in 2003 (21). In Brazil the rate of iatrogenic preterm births was 32-61% overall during 2011-2012 based on whether it was a public or private health care facility (7, 27) and in Shanghai, China it was 47.2% in 2004 and 51.1% in 2007 (28). A study from Australia found an increase in iatrogenic preterm births from 39.5% in 2004 to 44% in 2008 (4). Despite the worldwide increase in iatrogenic preterm births a recent study from USA found a decrease in the overall preterm birth rate due to a decrease in the iatrogenic preterm births following the guideline changes in 2007 and 2011 (21). The rate of preterm births in USA decreased from 12.3% to 11.2% from 2003 to 2013 and the proportion of iatrogenic preterm births decreased from 48.3% to 41.8% (21).

The increase of iatrogenic preterm births in our study was significant even after adjusting our regression models for the identified medical indications (placental abruption, severe preeclampsia, chorioamnionitis, fetal indication, red cell immunization, obstetric cholestasis, hypertensive disorders, diabetes mellitus, maternal illness and multiple gestation) (1, 3). This suggests that there are other factors than these indications that are the cause of this increase in iatrogenic preterm births in Iceland. Zhang et al published in 2012 that in USA there was a strong connection between the increase in the preterm birth rate and labor induction (29). In Iceland, the labor induction rate has been increasing

over the last decades (14, 34) which could be a contributing factor. Previous research is however in agreement that not one recorded indication is the single cause for this increase in iatrogenic preterm births (28), they are heterogenous (30) and that there is a complex process behind each iatrogenic preterm birth which should be analyzed in detail to improve preventive strategies based on the latest evidence (7).

A known risk factor for preterm birth include: age (teen pregnancy or maternal advanced age), short interpregnancy interval, multiple pregnancy, assisted reproductive treatment, previous preterm birth, substance abuse and tobacco use during pregnancy. Also, low socio-economic status, black race and clinical factors such as infections, periodontal disease or vaginal bacteriosis, malnutrition and poor weight gain during pregnancy (1). These risk factors vary between the types of preterm birth. Infection or cervical malfunction are risk factors for spontaneous preterm births (3). The fact that spontaneous preterm births were decreasing in our study could be because obstetric practices have become better equipped to deal with these risk factors. Advanced mother's age however, influences the risk for both spontaneous and iatrogenic preterm births (17, 31). In our study, maternal age was increasing during the study period. We adjusted our regression models for maternal age and despite that, the increase in the preterm birth rate and iatrogenic preterm birth rate was significant as well as the decrease in the spontaneous preterm birth rate.

The largest contributing medical indication in our study was fetal indication (suspected placental insufficiency) as it was the contributing indication in about a third of the iatrogenic preterm births. The contribution was however decreasing during the study period at the same time as iatrogenic preterm births were increasing which is an interesting find. The contributing indications that were rising in the study were placental abruption, diabetes mellitus, obstetric cholestasis, and maternal illnesses. Diabetes mellitus has been connected with increased risk of iatrogenic preterm births (7, 32) as well as placental abruption (3, 20) and obstetric cholestasis (28) even though they are not the most discussed in the related studies. Together they contributed to about a fifth of iatrogenic preterm births and not enough to be the cause of this extreme rise in iatrogenic preterm births in Iceland. Swift et al (34) found an increase in labor induction in Iceland from 1995-2014. This increase was however more evident for women without a diabetes mellitus or hypertensive disorders diagnoses, and the increase could not be explained by advanced maternal age (34) which is an interesting find.

The fact that the increase in late preterm births has been turned in USA and Norway as mentioned earlier shows that it is possible to change the trend following a change in clinical guidelines. Chang et al (19) suggested that there was a way to decrease the preterm birth rate in 39 countries with very high human development index by 5% in total by working on smoking cessation, not inserting multiple embryos in artificial insemination, using cervical cerclage and progesterone supplementation with the most important being reducing iatrogenic labor induction or caesarean delivery without medical indication. In USA they estimated a potential for an 8% decrease but they found less room for improvement, only 2%, in Sweden as there were fewer medically indicated iatrogenic preterm births (19). Sweden and Iceland have a similar preterm birth rate (6) and good health care systems (33) which leads us to assume that there might be a potential for a similar reduction in the preterm birth rate in Iceland as in Sweden. Chang et al emphasize that although the focus should be on stopping

non-indicated preterm births there will continue to be incidences where preterm births are indicated, and total prevention of preterm births will not be achieved without preventive treatments which eliminate all fetal, obstetric and maternal complications (19).

In conclusion, our study shows that despite a low preterm birth rate compared to the global preterm birth rate, it may be increasing in Iceland and the epidemiology of preterm births is changing. Iatrogenic, PPROM, moderate and late preterm births are increasing, while spontaneous, extremely and very preterm births are decreasing. The increase of the iatrogenic preterm births was not explained by the known maternal and medically contributing factors we were able to include in our study. These findings emphasize the need for further studies on the causes of preterm births, especially iatrogenic preterm births.

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References

1. Harrison MS, Goldenberg RL. Global burden of prematurity. Seminars in fetal & neonatal medicine. 2016;21(2):74-9.
2. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet (London, England). 2016;388(10063):3027-35.
3. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet (London, England). 2008;371(9606):75-84.
4. Henderson JJ, McWilliam OA, Newnham JP, Pennell CE. Preterm birth aetiology 2004-2008. Maternal factors associated with three phenotypes: spontaneous preterm labour, preterm pre-labour rupture of membranes and medically indicated preterm birth. 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 Obstet. 2012;25(6):642-7.
5. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet (London, England). 2012;379(9832):2162-72.
6. Zeitlin J, Szamotulska K, Drewniak N, Mohangoo AD, Chalmers J, Sakkeus L, et al. Preterm birth time trends in Europe: a study of 19 countries. BJOG : an international journal of obstetrics and gynaecology. 2013;120(11):1356-65.
7. Souza RT, Cecatti JG, Passini R, Jr., Tedesco RP, Lajos GJ, Nomura ML, et al. The Burden of Provider-Initiated Preterm Birth and Associated Factors: Evidence from the Brazilian Multicenter Study on Preterm Birth (EMIP). PloS one. 2016;11(2):e0148244.
8. Xue Q, Shen F, Gao Y, Tong M, Zhao M, Chen Q. An analysis of the medical indications for preterm birth in an obstetrics and gynaecology teaching hospital in Shanghai, China. Midwifery. 2016;35:17-21.
9. Holland MG, Refuerzo JS, Ramin SM, Saade GR, Blackwell SC. Late preterm birth: how often is it avoidable? American journal of obstetrics and gynecology. 2009;201(4):404.e1-4.
10. Gyamfi-Bannerman C, Fuchs KM, Young OM, Hoffman MK. Nonspontaneous late preterm birth: etiology and outcomes. American journal of obstetrics and gynecology. 2011;205(5):456.e1-6.
11. Morais M, Mehta C, Murphy K, Shah PS, Giglia L, Smith PA, et al. How often are late preterm births the result of non-evidence based practices: analysis from a retrospective cohort study at two tertiary referral centres in a nationalised healthcare system. BJOG : an international journal of obstetrics and gynaecology. 2013;120(12):1508-14.
12. Snædal G, Biering G, Sigvaldason H, Ragnarsson J. Fæðingar á Íslandi 1972-1981, 9.grein: Lengd meðgöngu. Læknablaðið. 1983;69(9):303-5.
13. Delnord M, Blondel B, Zeitlin J. What contributes to disparities in the preterm birth rate in European countries? Current opinion in obstetrics & gynecology. 2015;27(2):133-42.
14. Jónasdóttir E, Eiríksdóttir VH. Skýrsla frá fæðingaskráningunni fyrir árið 2016 [Available from: https://www.landspitali.is/library/Sameiginlegar-skrar/Gagnasafn/Rit-og-skyrslur/Faedingaskraningar/faedingarskraning_skyrsla_2016.pdf. Accessed 8 January 2019.
15. Landlæknir. Fæðingarskrá [Available from: https://www.landlaeknir.is/tolfraedi-og-rannsoknir/gagnasofn/gagnasafn/item12340/Faedingaskra. Accessed 22 Sept 2018.
16. Langhoff-Roos J, Krebs L, Klungsoyr K, Bjarnadottir RI, Kallen K, Tapper AM, et al. The Nordic medical birth registers--a potential goldmine for clinical research. Acta obstetricia et gynecologica Scandinavica. 2014;93(2):132-7.

17. Joseph KS, Fahey J, Shankardass K, Allen VM, O'Campo P, Dodds L, et al. Effects of socioeconomic position and clinical risk factors on spontaneous and iatrogenic preterm birth. BMC pregnancy and childbirth. 2014;14:117.

18. Adler NE, Ostrove JM. Socioeconomic status and health: what we know and what we don't. Annals of the New York Academy of Sciences. 1999;896:3-15.

19. Chang HH, Larson J, Blencowe H, Spong CY, Howson CP, Cairns-Smith S, et al. Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. Lancet (London, England). 2013;381(9862):223-34.

20. Shapiro-Mendoza CK, Lackritz EM. Epidemiology of late and moderate preterm birth. Seminars in fetal & neonatal medicine. 2012;17(3):120-5.

21. Ada ML, Hacker MR, Golen TH, Haviland MJ, Shainker SA, Burris HH. Trends in provider-initiated versus spontaneous preterm deliveries, 2004-2013. Journal of perinatology : official journal of the California Perinatal Association. 2017;37(11):1187-91.

22. Richards JL, Kramer MS, Deb-Rinker P, Rouleau J, Mortensen L, Gissler M, et al. Temporal Trends in Late Preterm and Early Term Birth Rates in 6 High-Income Countries in North America and Europe and Association With Clinician-Initiated Obstetric Interventions. Jama. 2016;316(4):410-9.

23. Raju T. The "Late Preterm" Birth-Ten Years Later. Pediatrics. 2017;139(3).

24. Raju TN, Higgins RD, Stark AR, Leveno KJ. Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development. Pediatrics. 2006;118(3):1207-14.

25. Bulut C, Gursoy T, Ovali F. Short-Term Outcomes and Mortality of Late Preterm Infants. Balkan medical journal. 2016;33(2):198-203.

26. Morisaki N, Togoobaatar G, Vogel JP, Souza JP, Rowland Hogue CJ, Jayaratne K, et al. Risk factors for spontaneous and provider-initiated preterm delivery in high and low Human Development Index countries: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG: an international journal of obstetrics and gynaecology. 2014;121 Suppl 1:101-9.

27. Leal Mdo C, Esteves-Pereira AP, Nakamura-Pereira M, Torres JA, Domingues RM, Dias MA, et al. Provider-Initiated Late Preterm Births in Brazil: Differences between Public and Private Health Services. PloS one. 2016;11(5):e0155511.

28. Yang X, Zeng W. Clinical analysis of 828 cases of iatrogenic preterm births. The journal of obstetrics and gynaecology research. 2011;37(8):1048-53.

29. Zhang X, Kramer MS. The rise in singleton preterm births in the USA: the impact of labour induction. BJOG: an international journal of obstetrics and gynecology. 2012;119(11):1309-15.

30. Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Maternal, fetal, and placental conditions associated with medically indicated late preterm and early term delivery: a retrospective study. BJOG: an international journal of obstetrics and gynaecology. 2016;123(5):763-70.

31. Trilla CC, Medina MC, Ginovart G, Betancourt J, Armengol JA, Calaf J. Maternal risk factors and obstetric complications in late preterm prematurity. European journal of obstetrics, gynecology, and reproductive biology. 2014;179:105-9.

32. Jelliffe-Pawlowski LL, Baer RJ, Blumenfeld YJ, Ryckman KK, O'Brodovich HM, Gould JB, et al. Maternal characteristics and mid-pregnancy serum biomarkers as risk factors for subtypes of preterm birth. BJOG: an international journal of obstetrics and gynaecology. 2015;122(11):1484-93.

33. Björnberg A. Euro Health Consumer Index - 2017 Report [Available from: https://healthpowerhouse.com/media/EHCI-2017/EHCI-2017-report.pdf. Accessed 29 Nov, 2018.

34. Swift EM, Tomasson G, Gottfreethsdottir H, Einarsdottir K, Zoega H. Obstetric interventions, trends, and drivers of change: A 20-year population-based study from Iceland. Birth (Berkeley, Calif). 2018;45(4):368-76.

Tables and Figures

Table 1. **Iatrogenic preterm births' indications according to registered ICD-10 diagnoses.**

no	Indication group	ICD-10 codes
1	Abruptio placentae	O44.1, O45.0, O45.8
2	Severe preeclampsia	O14.1, O14,9, O15.0, O15.1
3	Chorioamnionitis	O41.1
4	Fetal indication	O36.3, O36.5, O41.0, O68.0
5	Red cell immunization	O36.0, O36,1
6	Cholestasis	O26.6
7	Hypertensive disorders	O10.0, O11, O13, O14.0
8	Diabetes Mellitus	O24.0, O24.1, O24.4, O24.9
9	Maternal illness	K80.2, I82, D69.3, I50.9, N13, O26.7, D69.6, O26.8, Z94.0
10	Multiple gestation	O30.0, O30.1, O43.0

Table 2. **Characteristics of all preterm births in Iceland from January 1st 1997 to December 31st 2016 according to birth year period.**

Birth year period	1997-2001		2002-2006		2007-2011		2012-2016		
All Preterm Births	1111		1265		1307		1303		**p-value***
Gestational age n (%)									**0.001**
<28w0d	74	(6.7)	55	(4.3)	54	(4.1)	56	(4.3)	
28w0d-31w6d	142	(12.8)	130	(10.3)	129	(9.9)	105	(8.1)	
32w0d-33w6d	130	(11.7)	163	(12.9)	185	(14.2)	179	(13.7)	
34w0d-36w6d	765	(68.9)	917	(72.5)	939	(71.8)	963	(73.9)	
Type of preterm birth n (%)									**<0.001**
Spontaneous	621	(55.9)	682	(53.9)	517	(39.6)	380	(29.2)	
PPROM	263	(23.7)	323	(25.5)	390	(29.8)	369	(28.3)	
Iatrogenic	227	(20.4)	260	(20.6)	400	(30.6)	554	(42.5)	
Maternal age n (%)									**<0.001**
≤20years	70	(6.3)	54	(4.3)	64	(4.9)	28	(2.1)	
21-25years	196	(17.6)	226	(17.9)	225	(17.2)	217	(16.7)	
26-30years	342	(30.8)	407	(32.2)	419	(32.1)	369	(28.3)	
31-35years	286	(25.7)	343	(27.1)	356	(27.2)	374	(28.7)	
36-40years	189	(17.0)	197	(15.6)	186	(14.2)	237	(18.2)	
41years+	28	(2.5)	38	(3.0)	57	(4.4)	78	(6.0)	
Parity n (%)									**<0.001**
Primipara	446	(40.1)	502	(39.7)	645	(49.3)	654	(50.4)	
Multipara	665	(59.9)	765	(60.3)	662	(50.7)	649	(49.8)	
Multiple gestation n (%)									**<0.001**
Singletons	780	(70.2)	855	(67.6)	998	(76.4)	894	(68.6)	
Multiples	331	(29.8)	410	(32.4)	309	(23.6)	409	(31.4)	
Marital status n (%)									**<0.001**
Married/Cohabiting	964	(86.8)	1052	(83.2)	1305	(79.2)	1027	(78.8)	
Single/Divorced/Widowed	144	(13.0)	209	(16.5)	256	(19.6)	225	(17.3)	
Missing	3	(0.3)	4	(0.3)	16	(1.2)	51	(3.9)	
Employment status n (%)									**<0.001**
Employed	774	(69.7)	926	(73.2)	932	(71.3)	966	(74.1)	
Student	141	(12.7)	154	(12.2)	185	(14.2)	181	(13.9)	
Unemployed	0	(0.0)	4	(0.3)	47	(3.6)	53	(4.1)	
Homemaker	147	(13.2)	98	(7.7)	79	(6.0)	42	(3.2)	
Pension/Disability/Other	49	(4.4)	80	(6.3)	33	(2.5)	29	(2.2)	
Missing	0	(0.0)	3	(0.2)	31	(2.4)	32	(2.5)	
Country of origin n (%)									**<0.001**
Icelandic	1068	(96.1)	1176	(93.0)	1147	(87.8)	1136	(87.2)	
Not Icelandic	43	(3.9)	89	(7.0)	160	(12.2)	167	(12.8)	
Residential area n (%)									**<0.001**
Capital area	627	(56.4)	808	(63.9)	849	(65.0)	857	(65.8)	
Rural area	484	(43.6)	457	(36.1)	458	(35.0)	446	(34.2)	

*Chi-square test

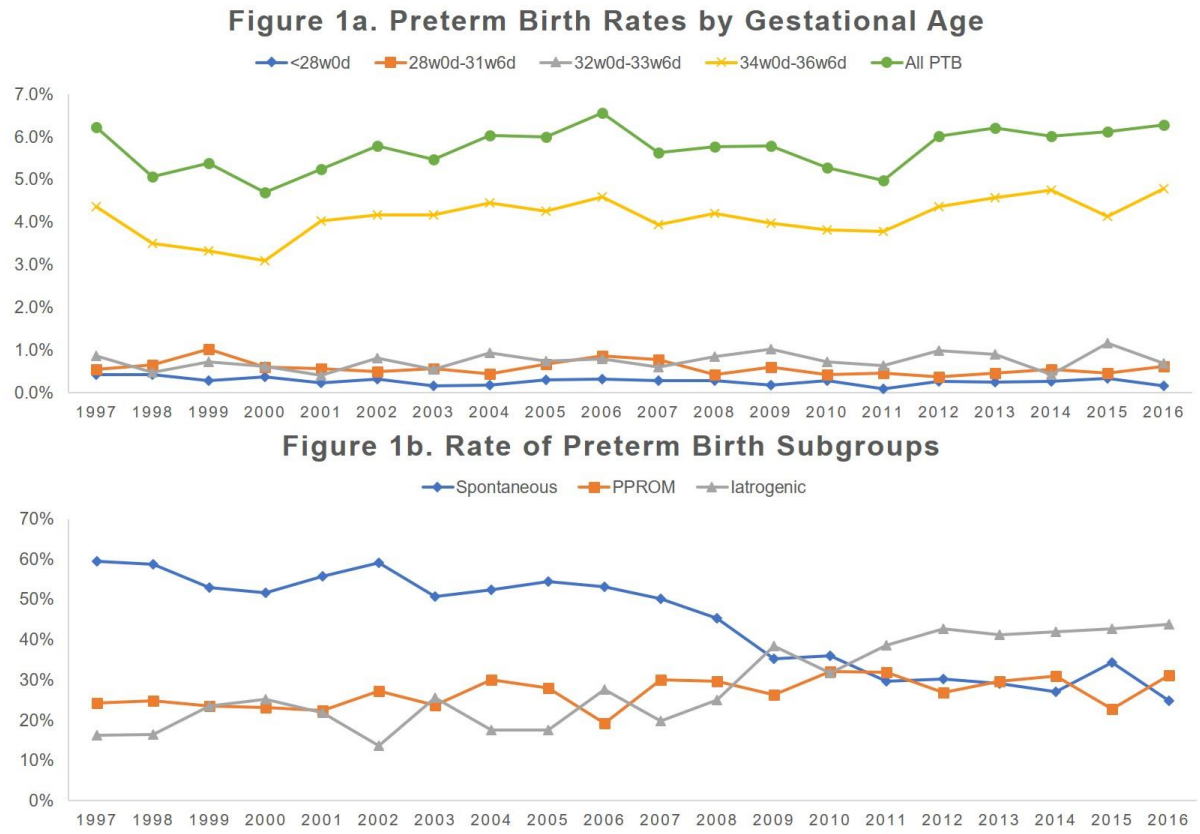

Figure 1. **Preterm Birth Rates (%) in Iceland 1997-2016.**

Figure 1a. Rate of preterm birth by gestational age of all births: all preterm births, and subgroups by gestational age (<28w0d, 28w0d-31w6d, 32w0d-33w6d and 34w0d-36w6d).

Figure 1b. Rate of preterm birth subgroup of all births: spontaneous, PPROM and iatrogenic.

PPROM=Preterm premature rupture of the membranes

Table 3. **Rate ratios and 95% confidence intervals for the risk of preterm birth according to birth year period for all births (n=87,076) in Iceland during 1997-2016, overall and by gestational week group and preterm birth subgroup.**

Birth year period	1997-2001	2002-2006	2007-2011	2012-2016
All preterm births *n (%)*	*1111 (5.3%)*	*1265 (6.0%)*	*1307 (5.5%)*	*1303 (6.1%)*
RR (95%CI)	Ref	**1.12 (1.04-1.22)**	1.03 (0.95-1.12)	**1.15 (1.06-1.25)**
ARR (95%CI) *	Ref	**1.12 (1.03-1.21)**	1.07 (0.99-1.16)	**1.16 (1.07-1.26)**
Gestational week group				
34w0d-36w6d*n (%)*	*765 (3.7%)*	*917 (4.3%)*	*939 (4.0%)*	*963 (4.5%)*
RR (95%CI)	Ref	**1.18 (1.08-1.30)**	1.08 (0.98-1.19)	**1.24 (1.12-1.36)**
ARR (95% CI) *	Ref	**1.19 (1.08-1.31)**	**1.13 (1.02-1.24)**	**1.26 (1.15-1.40)**
32w0d-33w6d*n (%)*	*130 (0.6%)*	*163 (0.8%)*	*185 (0.8%)*	*179 (0.8%)*
RR (95%CI)	ref	1.24 (0.98-1.56)	**1.25 (1.00-1.57)**	**1.35 (1.08-1.70)**
ARR (95% CI) *	ref	1.20 (0.95-1.51)	**1.27 (1.01-1.59)**	**1.29 (1.02-1.63)**
28w0d-31w6d *n (%)*	*142 (0.7%)*	*130 (0.6%)*	*129 (0.5%)*	*105 (0.5%)*
RR (95%CI)	ref	0.90 (0.71-1.15)	0.80 (0.63-1.01)	**0.73 (0.56-0.94)**
ARR (95% CI) *	ref	0.87 (0.68-1.10)	0.79 (0.62-1.02)	**0.70 (0.54-0.91)**
<28w0d *n (%)*	*74 (0.4%)*	*55 (0.3%)*	*54 (0.2%)*	*56 (0.3%)*
RR (95%CI)	ref	0.73 (0.52-1.04)	**0.64 (0.45-0.91)**	0.74 (0.53-1.05)
ARR (95% CI) *	ref	0.72 (0.51-1.03)	**0.65 (0.45-0.94)**	0.73 (0.50-1.05)
Type of preterm birth				
Spontaneous *n (%)*	*621 (3.0%)*	*682 (3.2%)*	*517 (2.2%)*	*380 (1.8%)*
RR (95%CI)	ref	1.08 (0.97-1.21)	**0.73 (0.65-0.82)**	**0.60 (0.53-0.68)**
ARR (95% CI) *	ref	1.09 (0.98-1.22)	**0.78 (0.69-0.88)**	**0.63 (0.56-0.72)**
PPROM *n (%)*	*263 (1.3%)*	*323 (1.5%)*	*390 (1.6%)*	*369 (1.7%)*
RR (95%CI)	ref	**1.21 (1.03-1.43)**	**1.30 (1.12-1.52)**	**1.38 (1.18-1.61)**
ARR (95% CI) *	ref	**1.19 (1.01-1.40)**	**1.29 (1.10-1.51)**	**1.31 (1.11-1.54)**
Iatrogenic *n (%)*	*227 (1.1%)*	*260 (1.2%)*	*400 (1.7%)*	*554 (2.6%)*
RR (95%CI)	ref	1.13 (0.95-1.35)	**1.55 (1.32-1.82)**	**2,40 (2.05-2.80)**
ARR (95% CI) *	ref	1.11 (0.93-1.33)	**1.61 (1.36-1.90)**	**2.37 (2.02-2.78)**
ARR (95% CI) **	ref	1.13 (0.95-1.35)	**1.55 (1.32-1.82)**	**2.40 (2.06-2.80)**

*Adjusted for maternal age, marital status, residential area, country of origin, parity, multiple gestation and employment status.

**Adjusted for iatrogenic indication groups: placental abruption, severe preeclampsia, chorioamnionitis, fetal indication, red cell immunization, cholestasis, hypertensive disorders, diabetes mellitus, maternal illness and multiple gestation.

RR=rate ratio

ARR=adjusted rate ratio

PPROM=Preterm premature rupture of the membranes

Figure 2. Proportion of Preterm Birth Subgroups

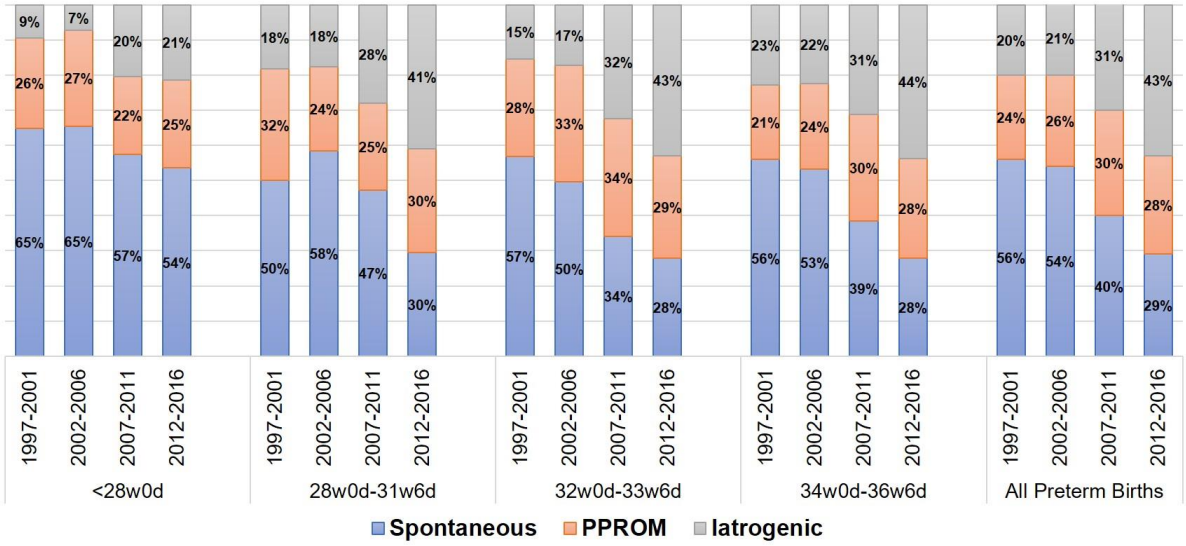

Figure 2. Proportion of preterm birth subgroup (spontaneous, PPROM and iatrogenic) for all preterm births in Iceland from 1997 to 2016 according to gestational age group in weeks (<28w0d, 28w0d-31w6d, 32w0d-33w6d and 34w0d-36w6d).

PPROM=Preterm premature rupture of the membranes

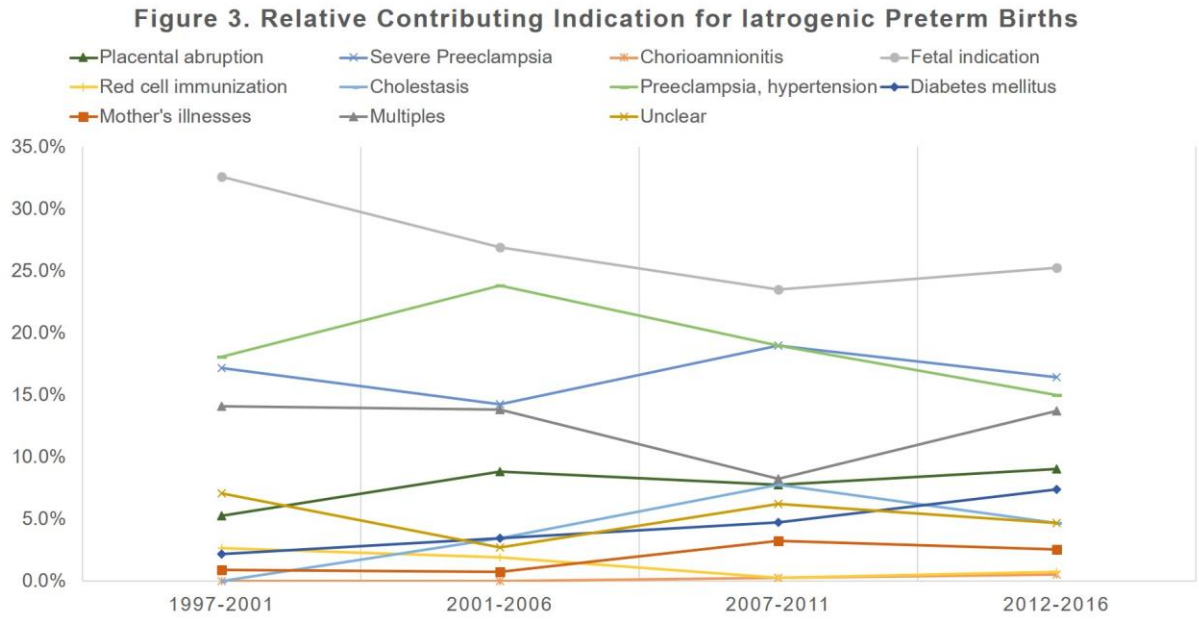

Figure 3. **Relative contributing indications for iatrogenic preterm births in Iceland 1997-2016 based on ICD-10 codes (calculated as n iatrogenic preterm births for each indication / all iatrogenic preterm births).**