Multiple births in Iceland during 1997-2018

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Abstract

Introduction

Multiple birth rates have been increasing globally since the 1980s and until the 2000s when regulations limited multiple embryo transfers during IVF treatments. Iceland passed similar regulations in 2009 and it is unknown whether these changes affected rates of multiple births in Iceland. The aim of the study was to assess the rates of multiple births and obstetrical interventions for multiples in Iceland during 1997-2018.

Methods

This study included multiple live births in Iceland during 1997-2018 identified from the Icelandic Medical Birth Registry. Multiple birth rates were calculated by birth year period overall and by grouped maternal age. Rates of cesarean delivery and induction of labor for multiples were calculated by birth year period. Logistic regression models were used to assess the risk of multiple birth and the risk of obstetrical intervention for multiple births according to birth year period.

Results

The study included 95 405 live births, of which 3314 (3.5%) were multiples. Multiple births rates decreased during the study period with the largest decrease from 2006 to 2009. The risk of multiple birth decreased in 2009-2013 (AOR=0.76, 95% CI=0.69-0.84) compared to 1997-2002 and was further decreased for maternal age 35+ (AOR=0.58, 95% CI=0.48-0.69). Induction of labor rates increased from 25% in 1997-2002 to 55% in 2009-2013 (AOR=4.25, 95% CI=3.40-5.33) whereas elective (AOR=0.62, 95% CI=0.48-0.80) and emergency cesarean (AOR=0.81, 95% CI=0.64-1.01) rates declined.

Conclusion

Multiple live births decreased during the study period with the largest decrease from 2006-2009 and for mothers aged 35+ years. These results indicate that international embryo transfer regulations published before the Icelandic regulations in 2009 may have had the largest effect on multiple birth rates in Iceland, but that the Icelandic policy introduced in 2009 may have had some effect on further reducing these rates, particularly for older mothers.

Ágrip

Bakgrunnur

Tíðni fjölburafæðinga hefur verið að aukast á heimsvísu síðan á níunda áratugnum og þangað til upp úr aldamótum þegar breytingar á reglugerðum takmörkuðu fjölda fósturvísa í tæknifrjóvgun og mælt var með einnar fósturvísis frjóvgun. Á Íslandi komu svipaðar reglugerðir um 2009 sem takmörkuðu fjölda fósturvísa í tæknifrjóvgun fyrir konur undir 36 ára við einn fósturvísi og það er ennþá óljóst hvort þessar reglugerðir hafa haft áhrif á tíðni fjölburafæðinga á Íslandi. Markmið rannsóknarinnar var því að meta tíðni fjölburafæðinga á Íslandi á árunum 1997-2018 og rannsaka tíðni inngripa í fjölburafæðingum.

Aðferð

Þessi rannsókn náði yfir alla lifandi fædda fjölbura á Íslandi á árunum 1997-2018 úr gögnum Fæðingarskrár Embættis Landlæknis. Tíðni fjölburafæðinga var reiknuð fyrir hvert tímabil fyrir sig og samkvæmt aldurshópum mæðranna. Tíðni keisarafæðinga og framkallaðra fæðinga fyrir fjölbura var einnig reiknað eftir aldurshópum. Mat á hættu á fjölburafæðingum og hættu á inngripum við fjölburafæðingar var fengin með logistískri aðhvarfsgreiningu fyrir hvert tímabil.

Niðurstöður

Heildarþýðið voru 95 405 nýburar, þar af 3314 (3.5%) fjölburar. Tíðni fjölburafæðinga lækkaði yfir rannsóknartímabilið með mestu lækkun á árunum 2006-2009. Hættan á fjölburafæðingum lækkaði á árunum 2009-2013 (AOR=0.76, 95% CI=0.69-0.84) samanborið við 1997-2002 og var enn lægri í aldurshópnum 35+ (AOR=0.58, 95% CI=0.48-0.69). Tíðni framkallaðra fæðinga jukust frá 25% á árunum 1997-2002 til 55% á árunum 2009-2013 (AOR=4.25, 95% CI=3.40-5.33) þar sem tíðni valkeisaraskurðar (AOR=0.62, 95% CI = 0.48 - 0.80) og bráðakeisaraskurðar (AOR=0.81, 95% CI=0.64-1.01) lækkaði.

Ályktanir

Fjölburafæðingum fækkaði yfir rannsóknartímabilið og mesta lækkunin var frá 2006 til 2009 og hjá mæðrum aldurshópnum 35+. Þessar niðurstöður gefa til kynna að alþjóðlegar reglugerðir sem voru birtar fyrir 2009 gætu hafa haft mest áhrif á tíðni fjölburafæðinga á Íslandi, en íslensku reglugerðirnar sem tóku gildi árið 2009 gætu hafa haft einhver áhrif á lægri tíðni fjölburafæðinga á Íslandi, sérstaklega hjá eldri mæðrum.

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Abbreviations

AOR: Adjusted odds ratio

ART: Assisted reproductive technology

CDC: Centre for Disease Control and Prevention

DC/DA: Dichorionic/diamniotic

ESHRE: European Society of Human Reproduction and Embryology

EIM: European IVF Monitoring

HFEA: Human Fertilisation and Embryo Authority

HOM: Higher order multiple

ICD-10: International Classification of Diseases and Health Related Problems 10th revision

IUGR: Intrauterine growth restriction

IVF: In vitro fertilization

MAR: Medically assisted reproduction

MC/DA: Monochorionic/diamniotic

MC/MA: Monochorionic/monoamniotic

MZT: Monozygotic

NCSP: NOMESCO Classification of Surgical Procedures

NCHS: National Centre for Health Statistics

NICE: National Institute for Clinical Excellence

NICU: Neonatal intensive care unit

NPIC: National Perinatal Information Center

NOMESCO: Nordic Medico-Statistical Committee

OECD: Organization for Economic Co-operation and Development

OR: Odds ratio

PPH: Post-partum hemorrhage

RDS: Respiratory distress syndrome

SET: Single embryo transfer

TAMBA: Twin and Multiple Birth Association

TTTS: Twin-to-twin transfusion syndrome

WHO: World Health Organization

1 Introduction

Throughout many countries in the world, the number of multiple births as a proportion of all births has been increasing (Heino et al., 2016; Monden et al., 2021). Medically assisted reproduction (MAR) became more widely used after the 1980s and has contributed to an increased incidence of multiple births over the decades since (D'Alton & Breslin, 2020). A growing number of women are choosing to delay childbearing and increased maternal age has been shown to increase the risk of spontaneous multiple pregnancy (Heino et al., 2016). Neonates resulting from multiple pregnancies have increased morbidity and mortality rates when compared to singletons, largely due to complications arising from preterm birth (Heino et al., 2016). Neonates born preterm have a higher risk of physical and cognitive developmental delays and higher risk for developing chronic diseases later in life (Heino et al., 2016). Multiple pregnancies also carry increased risk of morbidity and mortality for mothers (Monden et al., 2021). Maternal risk for complications during pregnancy such as hyperemesis gravidarum and anemia, is increased for multiple pregnancies, as well as more serious complications resulting from gestational diabetes and hypertensive diseases (D'Alton & Breslin, 2020). Multiple birth rates have increased in several parts of the world over the decades since the 1980s until embryo transfer guidelines and policy changes were made in the early 2000s where the rates then began to peak and level off (Monden et al., 2021). Icelandic regulations for embryo transfers were passed in 2009 and we aimed to investigate how trends in multiple birth rates may have changed in relation to the regulatory changes. We also aimed to investigate obstetrical intervention rates for multiples during the same time-period.

2 Epidemiology of multiple births

Since the 1980s, the world has seen unprecedented levels of multiple births. A recent study comparing global twinning rates in 2010-2015 to 1980-1985 found that global twinning rates increased substantially and to varying degrees in many countries in Europe, North America, and Asia, ranging from a 32% increase in Asia to 71% increase in North America (Monden et al., 2021). Global twinning rates increased from 9.1 to 12 twin deliveries per 1000 deliveries and have peaked to over 15 per 1000 in almost all African countries, as well as in Canada, many countries in the European Union, the USA, Israel, Korea, and Taiwan (Monden et al., 2021). Twinning rates below 10 per 1000 during the 2010-2015 period were only found in poorer countries in Latin America, South and South-East Asia (Monden et al., 2021). When comparing the two time periods, global birth rates rose by only 8%, while global twin deliveries increased by 42%, and by 2010-2015 1.6 million sets of twins were being born worldwide each year (Monden et al., 2021). The highest twinning rates continue to be found in Africa and 80% of the world´s twin deliveries occur in Africa and Asia (Monden et al., 2021).

In 2010, the median twinning rate in Europe was 16.8 per 1000, calculated as the number of women with multiple gestation pregnancy and delivering live or stillbirths (Heino et al., 2016). This rate was found to vary widely throughout Europe largely due to differing cultures, legislation, and funding for infertility treatment between countries (Heino et al., 2016). Iceland had one of the lowest multiple birth rates in Europe in 2010, with less than 15 per 1000 (Heino et al., 2016).

3 Reasons for multiple births

Medically assisted reproduction (MAR) has been a driving force for increased multiple birth rates in several countries around the world (Monden et al., 2021). Additionally, many societies have shifted toward a more modern norm of delayed childbearing (Mills et al., 2011). Delayed childbearing has resulted in increased incidence of advanced maternal age and higher birth orders which are associated with increased rates of multiple birth (Monden et al., 2021). The effect of MAR on multiple birth rates is said to be on average three times than that of delayed childbearing, with large variations between countries (Pison et al., 2015).

3.1 Medically assisted reproduction

MAR refers to treatments or techniques that are used to treat infertility and establish a pregnancy (Monden et al., 2021). The term includes more complex assisted reproductive technology (ART) methods as well as less complicated ovarian stimulation and artificial insemination techniques (Monden et al., 2021). In vitro fertilization (IVF) and ovarian stimulation are associated with increased multiple births and are main contributors for increased multiple birth rates (Dudenhausen & Maier, 2010; Monden et al., 2021). Ovarian stimulation involves pharmacological stimulation of the ovaries to induce the development of ovarian follicles, resulting in 5 to 10 mature eggs rather than only one mature egg which typically results from a normal menstrual cycle (Bosch et al., 2020). Ovarian stimulation can be used for fertilization with timed intercourse or insemination, as well as for retrieval of multiple mature eggs for use in IVF (Bosch et al., 2020). IVF involves the fertilization outside of the woman's body, with retrieved eggs and sperm in a laboratory setting, and subsequent implantation of the resulting fertilized embryo, or multiple embryos, into the woman's uterus (Bosch et al., 2020). The use of MAR became widely used in the 1970s in countries with higher economic status and gained momentum in the 1980s and 1990s in countries in Asia, Latin American and South Asia where emerging economies allowed for greater access and availability (Monden et al., 2021). It was not until around 2000 before MAR became used on a larger scale in Asia and in some wealthier of the African countries (Monden et al., 2021).

3.2 Delayed childbearing

Delayed childbearing refers to first pregnancies occurring in women aged 35 and older and is a well-known risk factor for spontaneous, non-identical, multiple birth (Adashi & Gutman, 2018). The risk of dizygotic twins, pregnancies resulting from the fertilization of 2 eggs, increases with maternal age up to age 39, after which the risk begins to decrease (Dudenhausen & Maier, 2010). Advancements and increased availability of contraception methods in the 1960s provided women with more control over their own reproduction and allowed women to pursue educational and career opportunities outside of the home (Mills et al., 2011). A study out of the USA examined Centre for Disease Control and Prevention (CDC) data from 1949-1966 to assess the risk of unassisted multiple birth before the adoption of MAR and found a three-fold risk for women between 35-39 years when compared to women aged 15-19 years (Adashi & Gutman, 2018). In addition, the study found that the risk was also race-dependent and further increased for black women compared to white women (Adashi & Gutman, 2018).

The average age of mothers in OECD countries at first delivery has increased by about 1 year for every decade since the 1970s (Mills et al., 2011). This number has further increased to about 4 years for every decade in Europe and Japan where the average maternal age at first birth increased from 25 years in 1970 to 29 years in 2008 (Mills et al., 2011). On average, women in Iceland delay childbearing for the highest number of years among OECD countries, with the average maternal age at first birth increasing by over 5 years from 1970-2008, while the least amount of change was seen in the USA where the average age increased by only 1.5 years during the same period (Mills et al., 2011). Large variations in proportion of women giving birth aged 35 and older are found between countries throughout Europe, from 10% in Romania to 34.7% in Italy (Heino et al., 2016). In 2010 in Iceland, the percentage of women giving birth aged 35 and older was 19.1% (Heino et al., 2016).

4 Embryo transfer policy

4.1 Global variations

The risk of multiple birth following IVF is directly associated with the number of embryos transferred per cycle (Medical Advisory Secretariat, 2006). In the earlier days of IVF when embryo quality and implantation rates were lower, multiple embryo transfer was used to improve implantation success rates and reduce the number of required cycles (Medical Advisory Secretariat, 2006). As multiple birth rates began to rapidly increase along with the increasingly widespread use of MAR, the health risks and associated complications of multiple births also became a growing public health concern among medical communities and policy makers alike (Monden et al., 2021). In the 2000s, many countries began to make changes to clinical practice guidelines, policy and legislation that limited the number of embryos transferred with a shifting focus toward successful, singleton births (Monden et al., 2021). While there is considerable variation to embryo transfer guidelines between countries, in the early 2000s, the average number of embryos transferred was lower in Europe compared to North America (Medical Advisory Secretariat, 2006).

Finland became the first country to implement elective single embryo transfer guidelines in 1997, which became standard practice in that country in 2000 (Medical Advisory Secretariat, 2006). Sweden implemented similar single embryo transfer guidelines after policy changes were passed in 2002 (Medical Advisory Secretariat, 2006). Both countries later reported a decrease in multiple births resulting from IVF with stable overall delivery rates (Medical Advisory Secretariat, 2006). Finland´s multiple birth rate decreased from 25% to 7% between 1997 to 2003, while Sweden reported multiple birth rates below 10% in 2004 (Medical Advisory Secretariat, 2006). The UK followed suit in 2004 when the National Institute for Clinical Excellence (NICE) published guidelines suggesting limits to embryo transfers (Fields et al., 2013) and in 2006 the UK Human Fertilisation and Embryo Authority (HFEA) declared full-term singleton births with normal birth weight as the definition of success for assisted reproduction technologies (Miller et al., 2016). A population-based cohort study examining cumulative live birth rates after IVF in the UK during 1992-2007 was published in 2016 (McLernon et al., 2016). This study compared two time periods, 1992-1998 and 1999-2007, and found that multiple pregnancy rates decreased from 31.9% to 26.2% and later decreased to 16.4% in 2013 as reported by the HFEA (McLernon et al., 2016). Australia and New Zealand later experienced a self-regulated shift toward elective single embryo transfer (SET) and multiple births resulting from IVF reduced between 2009 to 2013 from 8.2% to 5.6% respectively (Miller et al., 2016).

The European Society of Human Reproduction and Embryology (ESHRE) 2016 report analyzed by the European IVF Monitoring (EIM) Consortium indicated that 51.9% of transfer cycles involved two embryos, however, the proportion of single transfers increased and the proportion of three or more decreased when compared to 2015 (Gliozheni et al., 2020). As a result, the proportion of twin and triplet deliveries continued to decline because of decreasing numbers of embryos per transfer (Gliozheni et al., 2020).

4.2 Embryo transfer regulations in Iceland

In 2009, Iceland regulations for assisted reproduction were passed that limited the number of embryos for women under 36 years old to a single embryo transfer (*Reglugerð Um Tæknifrjóvgun.* | *Heilbrigðisráðuneyti* | *Reglugerðasafn*, 2009)). Transfer of two or more embryos were permitted under two circumstances i) the woman is at the upper limit of the fertile period or has reduced potential for implantation and ii) it is not considered likely that the remaining embryos can be frozen for later use (*Reglugerð Um Tæknifrjóvgun.* | *Heilbrigðisráðuneyti* | *Reglugerðasafn*, 2009).

5 Health Implications of multiple births

In multiple pregnancies the mothers are more likely to experience complications during their pregnancies compared to singleton pregnancies. These are complications like gestational diabetes, gestational hypertension and pre-eclampsia (D'Alton & Breslin, 2020). Multiple births are also associated with higher risk for complications during delivery for both mother and child (D'Alton & Breslin, 2020), such as increased risk of cesarean delivery (Barrett et al., 2013) and severe post-partum hemorrhage (PPH) (Knight et al., 2009). Multiples are also more likely to be born prematurely and to have lower birth weight. In addition, stillbirth and neonatal mortality rates are higher among multiples (Monden et al., 2021). Current evidence suggests that multiple births have 3-7 times greater neonatal morbidity and mortality rates when compared to singletons and these rates are often associated with timing and mode of delivery (Félix Martins Santana et al., 2019). Neonatal morbidity and mortality rates for multiple births are primarily affected by preterm birth and intrauterine growth restriction (Garite et al., 2004). More serious complications with increased associated risk of perinatal illness and mortality can arise in monochorionic multiple pregnancies in which a single placenta is shared (Bolch et al., 2018).

5.1 Maternal complications

5.1.1 Gestational diabetes

Gestational diabetes mellitus (GDM) is diabetes with first onset during pregnancy and is associated with increased risk for adverse pregnancy outcomes (Egan et al., 2020). Mothers with GDM are at higher risk for pre-eclampsia and cesarean delivery, while their infants are at higher risk for being large for gestational age and hypoglycemia after birth (Egan et al., 2020). A study out of Ontario, Canada comparing the incidence and risk factors for GDM between women with twin and singleton pregnancies found that women pregnant with twins were at a significantly higher risk for GDM, an increase that was largely due to an increased risk of mild, diet treated GDM (Hiersch et al., 2018). The effect of known risk factors for GDM was similar between the singleton and twin groups (Hiersch et al., 2018). However, a study conducted in Australia comparing pregnancy outcomes for women pregnant with singletons with GDM, women pregnant with twins with GDM, and women pregnant with twins without GDM found that the women pregnant with twins with GDM had the highest rates of adverse pregnancy outcomes (Ooi & Wong, 2018).

5.1.2 Hypertensive diseases

Hypertensive diseases are among the most common pregnancy complications affecting both maternal and fetal morbidity and mortality worldwide (Laine et al., 2019; WHO, 2011). Multiple pregnancy is a risk factor for hypertensive diseases such as pre-eclampsia (Laine et al., 2019). This increased risk may be associated with larger placental mass found in multiple pregnancies (D'Alton & Breslin, 2020; Laine et al., 2019). Hypertensive diseases occur 2 to 3 times more frequently in multiples when compared to singletons (Hayes-Ryan et al., 2020). Incidence of pre-eclampsia is also increased in multiple pregnancies and is more likely to occur earlier and can be more severe (D'Alton & Breslin, 2020). Pre-eclampsia is new onset hypertension occurring in pregnancy that is characterized by damage to organ systems that is only definitively treated by termination of the pregnancy or delivery (WHO, 2011). Mothers of twin pregnancies have 3 to 4 times greater risk of developing pre-eclampsia when compared to singleton mothers (Laine et al., 2019).

5.1.3 Cesarean delivery

Multiples are most frequently delivered by mode of cesarean (Barrett et al., 2013; Santana et al., 2016). Global rates of elective cesarean delivery for twins have increased over the past decades (Barrett et al., 2013; Lee et al., 2011). Maternal complications due to cesarean delivery include surgical site infection, venous thromboembolism, and PPH (Burke & Allen, 2020). Cesarean delivery imposes the highest maternal risk of PPH when compared to vaginal delivery (Burke & Allen, 2020).

5.1.4 Post-partum hemorrhage

PPH is a leading cause of maternal mortality and morbidity worldwide (Knight et al., 2009). Complications arising from excessive bleeding and blood loss in PPH include fatigue, anemia, cardiac ischemia and death (Evensen & Anderson, 2017). Multiple pregnancy is a risk factor for PPH (Evensen & Anderson, 2017). Severe maternal outcomes, maternal near miss and death, are more frequently associated with multiple pregnancies (Santana et al., 2016).

5.2 Neonatal complications

5.2.1 Chorionicity

Monozygotic (MZT) twins result from a single fertilized egg, or zygote, that splits into two embryos and are commonly referred to as identical (Bolch et al., 2018). Monozygotic triplets are very rare (Bolch et al., 2018). Monozygotic multiples are at increased risk of preterm birth, with 63% of MZT twins and all MZT triplets born before 37 weeks gestation (Bolch et al., 2018). MZT twins can be further categorized according to chorionicity and amnionicity into monochorionic-monoamniotic (MC/MA), monochorionic-diamniotic (MC/DA), and dichorionic-diamniotic (DC/DA) (Song et al., 2017). Monochorionic (MC) twins share a single placenta and occur in 75% of MZT pregnancies (Bolch et al., 2018). MC/DA twins account for the highest proportion of MC twins with MC/MA twins accounting for only 2% (Cordero et al., 2006). MC twins have 9 times the risk of perinatal mortality than twins who do not share a placenta (Bolch et al., 2018). A very serious complication called twin-to-twin transfusion syndrome (TTTS) occurs in 10-15% of MC pregnancies where there is unequal blood flow from the placenta and transfusion of blood from a donor twin to the recipient twin. TTTS may lead to anemia, growth restriction, and decreased urine output for the donor twin and conversely blood volume overload, and excess urine output for the recipient twin (Bolch et al., 2018). Left untreated, these infants are at extreme risk of cardiac failure with 70-100% mortality rates (Bolch et al., 2018). In addition to the risk of preterm birth and TTTS, MC/MA are at further risk of complication due to umbilical cord entanglement and congenital malformation (Cordero et al., 2006). Spontaneous MZT twins occur 1 in 250 pregnancies and current evidence suggests that MZT twins occur at higher rates among twins conceived with ART (Song et al., 2017).

5.2.2 Gestational age of multiples

Spontaneous delivery is more likely to start earlier in multiple pregnancies than in singleton pregnancies (Dudenhausen & Maier, 2010). Delivery guidelines pertaining to multiple births are complex, can vary greatly between different medical societies, and are largely based on chorionicity, amnionicity and other factors including presentation, fetal weight and various complications (D'Alton & Breslin, 2020; Félix Martins Santana et al., 2019). The average gestational age at delivery is shorter in multiple than singleton pregnancies. (Dudenhausen & Maier, 2010). The average duration of pregnancies for twins is 36 weeks and for triplets is 32 weeks, compared to 39 weeks for singletons (Dudenhausen & Maier, 2010). A study conducted in Korea reviewed 94 170 multiple deliveries to examine the risk of stillbirth and neonatal mortality associated with each additional week of expectant management among twins and triplets compared to planned delivery by induction of labor or cesarean (Ko et al., 2018). The risk of stillbirth significantly increased between gestational age 34 and 35 weeks and between 37 and 38 weeks for twins and between 34 and 37 weeks for triplets (Ko et al., 2018). The risk of stillbirth and neonatal mortality associated with expectant management for twins at 37 weeks gestation was increased compared to planned delivery (Ko et al., 2018). The risks associated with expectant management for triplets could not be estimated because of too few neonatal deaths among this group. According to NICE guidelines, planned birth should be offered at 37 weeks for DC/DA twin pregnancies, at 36 weeks for MC/DA twin pregnancies, between 32 and 33+6 for MC/MA twin pregnancies, and at 35 weeks for uncomplicated triplet pregnancies (NICE, 2019).

5.2.3 Preterm birth

According to the World Health Organization (WHO), preterm birth is defined as live births that occur before 37 weeks of completed gestation (WHO, 2018). Preterm birth is further defined by sub-categories of gestational age into extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), and moderate to late preterm (32 to 37 weeks) (WHO, 2018). The risk of morbidity and mortality as a consequence of preterm birth increases with decreasing gestational age (Harrison & Goldenberg, 2016).

The risk of infant mortality is most significant during the neonatal period, or first 28 days after delivery, when global neonatal mortality rates due to preterm birth are said to be up to 35% (Walani, 2020). A study assessing the risk of neonatal mortality for multiples was conducted in Iran in 2009 and found an overall neonatal mortality rate of 155 per 1000 live births of multiple gestations (Nasseri & Azhir, 2009). The study further concluded that neonatal outcomes for multiples was associated with gestational age rather than plurality (Nasseri & Azhir, 2009).

Preterm birth accounts for an estimated 1 million child deaths per year and prematurity and complication due to preterm birth is the leading cause of child mortality under the age of 5 worldwide (WHO, 2018). Since infants born preterm are born with immature organ systems, they are at higher risk of developing serious health complications and long-term adverse outcomes (Ward & Beachy, 2003). Preterm infants are at higher risk for health complications of central nervous system, gastrointestinal and pulmonary systems (Ward & Beachy, 2003) as well as visual and hearing problems and lifelong disability (WHO, 2018) .

Preterm birth occurs spontaneously or by iatrogenic early delivery (WHO, 2018). The global rate of preterm birth in 2014 was 10.6% and is increasing in frequency largely due to increasing rates of iatrogenic late preterm birth by induction of labor and elective caesarean delivery (Grétarsdóttir et al., 2019). Spontaneous preterm birth and premature rupture of membranes (PROM) is more likely to occur in multiple pregnancies (Quinn et al., 2016). Preterm birth is a main contributing factor to the increased mortality rate among multiples and about one-third of preterm multiple births are medically indicated (Murray et al., 2018). Iatrogenic preterm delivery by induction of labor or cesarean is more likely to occur in multiples as indicated by complications arising from pre-eclampsia (Quinn et al., 2016).

In Scotland, the rate of preterm birth before 37 weeks gestation for multiples is 50% and is even higher in the US at 56% (Murray et al., 2018). In Iceland, the overall preterm birth rate increased from 5.3% to 6.1% between 1997 to 2001 and 2012 to 2016 and was only evident in multiples (Grétarsdóttir et al., 2019).

5.2.4 Intrauterine growth restriction

Intrauterine growth restriction (IUGR) is defined by a rate of neonatal growth that is less than the expected neonatal growth potential (Sharma et al., 2016). Clinically, the term is used to describe infants who are born showing signs of in-utero growth restriction or malnutrition, regardless of birth weight percentile and should not be confused with lower birth weight, which solely refers to infants with birth weight less than 2500 g (Sharma et al., 2016). Several factors can contribute to intrauterine growth restriction in multiple pregnancies including reduced uterine blood flow, umbilical cord abnormalities, placental positioning, the mother´s nutritional status as well as blood flow disorders related monochorionic pregnancies with a shared placenta (Dudenhausen & Maier, 2010). The results can cause both short-term and long-term complications such as poor growth outcomes and neurological development complications for the neonate as well as growth failure, cognitive and behavioural problems and learning disabilities in childhood (Sharma et al., 2016). Various health problems and diseases have been seen in adulthood of infants who were born with IUGR including, but not limited to, social problems and poor cognitive function, type 2 diabetes, obesity, ischemic heart disease and stroke (Sharma et al., 2016).

6 Healthcare costs

Multiple births are associated with substantially increased inpatient hospital costs, primarily during the birth and neonatal period, but also extending into the first year of life (Chambers et al., 2014). A study conducted by the National Perinatal Information Centre (NPIC) out of the United States found that twins accounted for nearly 15% of all NICU admissions (NIPC, 2011) while accounting for only 3% of all live births (Murray et al., 2018). In the UK, a survey conducted by the Twin and Multiple Birth Association (TAMBA) found that 44% of mothers of multiples reported that at least one of the multiples required NICU care (Murray et al., 2018). A retrospective population cohort study conducted out of Western Australia examined the hospital costs of multiple-birth and singleton-birth children during the first 5 years of life and found that the mean hospital costs of singleton, twin, and higher order multiples (HOM) were $2730, $8993, and $24 411 USD respectively (Chambers et al., 2014). The mean length of stay following delivery was 5 days for singletons, 14 days for twins, and 34 days for HOMs (Chambers et al., 2014). Furthermore, twins were 66% more likely, and HOMs 243% more likely, to be readmitted to hospital in the first year of life and 13% and 62% more likely respectively to be readmitted to hospital in the second year of life, when compared to singletons (Chambers et al., 2014). Large cost differences between the pluralities mainly occurred during the perinatal period as a result of preterm birth and low birth weight where excess costs observed were during initial birth admissions (Chambers et al., 2014).

7 Obstetrical interventions in multiple births

Obstetrical intervention rates have been increasing in middle- and high-income countries over the past 30 years with wide variation between countries (Swift et al., 2018). Multiple births are at an increased risk for obstetrical intervention (Murray et al., 2018). There is little debate that the optimal mode of delivery for triplets continues to be planned cesarean delivery since the probability of successful vaginal delivery in this group is very low (Lappen et al., 2016). However, there is conflicting evidence regarding optimal mode of delivery for twins. Despite a lack of evidence to support that planned cesarean delivery results in improved outcomes, planned cesarean delivery rates for twins have increased worldwide, up to 75% in the US in 2008 and 45% in France in 2010 (Schmitz et al., 2017). The Twin Birth Study, a randomized control trial of planned caesarean or vaginal delivery (by induction of labor) for twin pregnancy, enrolled 2804 women from 25 different countries from 106 centres between 2003 to 2011. The results of the study indicated that for twins of gestational age 32+0 to 38+6 with the first twin in cephalic presentation, planned cesarean delivery did not significantly increase or decrease the risk of neonatal morbidity or mortality compared to planned vaginal delivery (Barrett et al., 2013).

8 Obstetrical intervention rates in Iceland

In 2018, a 20-year population-based study examining obstetrical intervention rates and trends in Iceland was conducted for all births during 1995-2014. The study found a considerable increase in induction of labor rates overall with relatively stable rates of cesarean delivery and instrumental delivery for all births (Swift et al., 2018). When the results were stratified for multiple birth, the study found decreasing emergency cesarean rates, increasing induction of labor rates and stable, relatively low rates of instrumental delivery for the group (Swift et al., 2018). During 1997-2015, the overall cesarean rate for multiples was 45.9% (Einarsdóttir, K, Sigurðardóttir, H, Bjarnadóttir, RI, 2019).

9 Significance

There is an absence of studies to date which examine the effect of changes to multiple birth rates in Iceland. The results produced by this study are clinically relevant to obstetric care and may contribute to knowledge for improvements in evidence-based practice. Monitoring the rates of obstetrical intervention for multiple births allows for the examination of changes in trends that need further study as well as the capture of patterns and changes that can occur quickly in small populations such as Iceland. Furthermore, this study may provide an estimate for the likelihood of delivery without major interventions for multiple births, information that is highly relevant to mothers during antenatal care. This type of monitoring also allows for the evaluation of the effectiveness of implemented protocols such as the embryo transfer policy in 2009. Monitoring obstetrical intervention rates has already had a positive impact on clinical practice in Iceland. For example, the implementation of Robson classification allowed for comparison of cesarean section rates between countries and helped to offer explanations for varying rates with differing prenatal care systems (Einarsdóttir, K, Sigurðardóttir, H, Bjarnadóttir, RI, 2019). We aimed to contribute additional knowledge pertaining specifically to multiple births.

10 Specific aims

In this study we examined multiple birth rates in Iceland overall and according to maternal age group during 1997-2018. We examined the trends in multiple birth rates with special interest in changes occurring since the regulations for embryo transfer were passed in Iceland in 2009. We also aimed to study the rate of obstetrical interventions for multiple births in Iceland during the same period.

References

Adashi, E. Y., & Gutman, R. (2018). Delayed childbearing as a growing, previously unrecognized contributor to the national plural birth excess. *Obstetrics and Gynecology*, *132*(4), 999–1006. https://doi.org/10.1097/AOG.0000000000002853

Barrett, J. F. R., Ch, B., Hannah, M. E. C. M., Hutton, E. K., Willan, A. R., Allen, A. C. C. M., Armson, B. A., Gafni, A., Joseph, K. S., Mason, D., Ohlsson, A., Ross, S., Sanchez, J. J., Asztalos, E. v, Cology, G., & Killam Health, I. W. (2013). A Randomized Trial of Planned Cesarean or Vaginal Delivery for Twin Pregnancy. *N Engl j Med*, *14*(3), 1295–1305. https://doi.org/10.1056/NEJMoa1214939

Bolch, C., Fahey, M., Reddihough, D., Williams, K., Reid, S., Guzys, A., Cole, S., Edwards, A., Fung, A., Hodges, R., Palma-Dias, R., Teoh, M., & Walker, S. (2018). Twin-to-twin transfusion syndrome neurodevelopmental follow-up study (neurodevelopmental outcomes for children whose twin-to-twin transfusion syndrome was treated with placental laser photocoagulation). *BMC Pediatrics*, *18*(1), 256. https://doi.org/10.1186/s12887-018-1230-8

Bosch, E., Broer, S., Griesinger, G., Grynberg, M., Humaidan, P., Kolibianakis, E., Kunicki, M., la Marca, A., Lainas, G., le Clef, N., Massin, N., Mastenbroek, S., Polyzos, N., Sunkara, S. K., Timeva, T., Töyli, M., Urbancsek, J., Vermeulen, N., & Broekmans, F. (2020). ESHRE guideline: ovarian stimulation for IVF/ICSI†. *Human Reproduction Open*, *2020*(2), 1–13. https://doi.org/10.1093/hropen/hoaa009

Burke, C., & Allen, R. (2020). Complications of Cesarean Birth. *MCN: The American Journal of Maternal/Child Nursing*, *45*(2), 92–99. https://doi.org/10.1097/NMC.0000000000000598

Chambers, G. M., van Hoang, P., Lee, E., Hansen, M., Sullivan, E. A., Bower, C., & Chapman, M. (2014). Hospital costs of multiple-birth and singleton-birth children during the first 5 years of life and the role of assisted reproductive technology. *JAMA Pediatrics*, *168*(11), 1045–1053. https://doi.org/10.1001/jamapediatrics.2014.1357

Cordero, L., Franco, A., & Joy, S. D. (2006). Monochorionic monoamniotic twins: Neonatal outcome. *Journal of Perinatology*, *26*(3), 170–175. https://doi.org/10.1038/sj.jp.7211457

D'Alton, M., & Breslin, N. (2020). Management of multiple gestations. *International Journal of Gynecology and Obstetrics*, *150*(1), 3–9. https://doi.org/10.1002/ijgo.13168

Dudenhausen, J. W., & Maier, R. F. (2010). M E D I C I N E Perinatal Problems in Multiple Births. *Deutsches Ärzteblatt International*, *107*(38), 663–668. https://doi.org/10.3238/arztebl.2010.0663

Egan, A. M., Bogdanet, D., Griffin, T. P., Kgosidialwa, O., Cervar-Zivkovic, M., Dempsey, E., Allotey, J., Alvarado, F., de Valk, H. W., Galjaard, S., Loeken, M. R., Michael, &, Maresh, J. A., Napoli, A., Crowther, C., Biesty, L. M., Devane, D., Fidelma, &, & Dunne, P. (2020). *A core outcome set for studies of gestational diabetes mellitus prevention and treatment*. https://doi.org/10.1007/s00125-020-05123-6

Einarsdóttir, K, Sigurðardóttir, H, Bjarnadóttir, RI, et. al. (2019). The Robson 10-group classification in Iceland: Obstetric interventions and outcomes. *Birth Issues in Perinatal Care*, *46*(2), 270–278. https://doi.org/doi.org/10.1111/birt.12415

Evensen, A., & Anderson, J. M. (2017). Postpartum Hemorrhage: Prevention and Treatment. In *American Family Physician* (Vol. 95, Issue 7). http://online.lexi.com/action/home

Félix Martins Santana, E., Melo Corrêa, V., Bottura, I., & Pedro Parise Filho, J. (2019). Time and Mode of Delivery in Twin Pregnancies. In *Multiple Pregnancy - New Challenges*. IntechOpen. https://doi.org/10.5772/intechopen.80092

Fields, E., Chard, J., James, D., & Treasure, T. (2013). Fertility (update): Summary of nice guidance. In *BMJ (Online)* (Vol. 346, Issue 7896). British Medical Journal Publishing Group. https://doi.org/10.1136/bmj.f650

Garite, T. J., Clark, R. H., Elliott, J. P., & Thorp, J. A. (2004). Twins and triplets: The effect of plurality and growth on neonatal outcome compared with singleton infants. *American Journal of Obstetrics and Gynecology*, *191*(3), 700–707. https://doi.org/10.1016/j.ajog.2004.03.040

Gliozheni, O., Hambartsoumian, E., Strohmer, H., Petrovskaya, E., Tishkevich, O., Bogaerts, K., Wyns, C., Balic, D., Antonova, I., Pelekanos, M., Rezabek, K., Markova, J., Lemmen, J., Sõritsa, D., Gissler, M., Pelkonen, S., Pessione, F., de Mouzon, J., Tandler, A., … Goossens, V. (2020). ART in Europe, 2016: results generated from European registries by ESHRE†. *Human Reproduction Open*, *2020*(3). https://doi.org/10.1093/hropen/hoaa032

Grétarsdóttir, Á. S., Aspelund, T., Steingrímsdóttir, Þ., Bjarnadóttir, R. I., & Einarsdóttir, K. (2019). Preterm births in Iceland 1997-2016: Preterm birth rates by gestational age groups and type of preterm birth. *Birth*. https://doi.org/10.1111/birt.12467

Harrison, M. S., & Goldenberg, R. L. (2016). Global burden of prematurity. In *Seminars in Fetal and Neonatal Medicine* (Vol. 21, Issue 2, pp. 74–79). W.B. Saunders Ltd. https://doi.org/10.1016/j.siny.2015.12.007

Hayes-Ryan, D., Meaney, S., Hodnett, A., Geisler, M., & O'Donoghue, K. (2020). The maternal and perinatal implications of hypertensive disorders of pregnancy in a multiple pregnancy cohort. *Acta Obstetricia et Gynecologica Scandinavica*, *99*(4), 525–536. https://doi.org/10.1111/aogs.13774

Heino, A., Gissler, M., Hindori-Mohangoo, A. D., Blondel, B., Klungsøyr, K., Verdenik, I., Mierzejewska, E., Velebil, P., Ólafsdóttir, H. S., Macfarlane, A., Zeitlin, J., Haidinger, G., Alexander, S., Pavlou, P., Mortensen, L., Sakkeus, L., Lack, N., Antsaklis, A., Berbik, I., … McComb, N. (2016). Variations in multiple birth rates and impact on perinatal outcomes in Europe. *PLoS ONE*, *11*(3). https://doi.org/10.1371/journal.pone.0149252

Hiersch, L., Berger, H., Okby, R., Ray, J. G., Geary, M., Mcdonald, S. D., Murry-Davis, B., Riddell, C., Halperin, I., Hasan, H., Barrett, J., & Melamed, N. (2018). Incidence and risk factors for gestational diabetes mellitus in twin versus singleton pregnancies. *Archives of Gynecology and Obstetrics*, *298*(3), 579–587. https://doi.org/10.1007/s00404-018-4847-9

Jonsson, M. (2015). Induction of twin pregnancy and the risk of caesarean delivery: a cohort study. *BMC Pregnancy and Childbirth*, *15*(1), 1–7. https://doi.org/10.1186/s12884-015-0566-4

Knight, M., Callaghan, W. M., Berg, C., Alexander, S., Bouvier-Colle, M. H., Ford, J. B., Joseph, K. S., Lewis, G., Liston, R. M., Roberts, C. L., Oats, J., & Walker, J. (2009). Trends in postpartum hemorrhage in high resource countries: A review and recommendations from the international postpartum hemorrhage collaborative group. *BMC Pregnancy and Childbirth*, *9*. https://doi.org/10.1186/1471-2393-9-55

Ko, J. S., Chung, J., & Kim, G. (2018). *Optimal Timing of Delivery Based on the RIsk of Stillbirth and Infant Death Associated with Each Additional Week of Expectant Management in MUltiple Prenancies: a National Cohort Study of Koreans*. *33*(25), 1–11.

Laine, K., Murzakanova, G., Sole, K. B., Pay, A. D., Heradstveit, S., & Raïsänen, S. (2019). Prevalence and risk of pre-eclampsia and gestational hypertension in twin pregnancies: A population-based register study. *BMJ Open*, *9*(7), e029908. https://doi.org/10.1136/bmjopen-2019-029908

Langhoff-Roos, J., Krebs, L., Klungsøyr, K., Bjarnadottir, R. I., Källén, K., Tapper, A. M., Jakobsson, M., Børdahl, P. E., Lindqvist, P. G., Gottvall, K., Colmorn, L. B., & Gissler, M. (2014). The Nordic medical birth registers - A potential goldmine for clinical research. *Acta Obstetricia et Gynecologica Scandinavica*, *93*(2), 132–137. https://doi.org/10.1111/aogs.12302

Lappen, J. R., Hackney, D. N., & Bailit, J. L. (2016). Maternal and neonatal outcomes of attempted vaginal compared with planned cesarean delivery in triplet gestations. *American Journal of Obstetrics and Gynecology*, *215*(4), 493.e1-493.e6. https://doi.org/10.1016/j.ajog.2016.04.054

Lee, H. C., Gould, J. B., Boscardin, W. J., El-Sayed, Y. Y., & Blumenfeld, Y. J. (2011). Trends in cesarean delivery for twin births in the united states: 1995-2008. *Obstetrics and Gynecology*, *118*(5), 1095–1101. https://doi.org/10.1097/AOG.0b013e3182318651

McLernon, D. J., Maheshwari, A., Lee, A. J., & Bhattacharya, S. (2016). Cumulative live birth rates after one or more complete cycles of IVF: A population-based study of linked cycle data from 178 898 women. *Human Reproduction*, *31*(3), 572–581. https://doi.org/10.1093/humrep/dev336

Medical Advisory Secretariat. (2006). In vitro fertilization and multiple pregnancies: an evidence-based analysis. *Ontario Health Technology Assessment Series*, *6*(18), 1–63. http://www.ncbi.nlm.nih.gov/pubmed/23074488

Miller, L. M., Hodgson, R., Wong, T. Y., Merrilees, M., Norman, R. J., & Johnson, N. P. (2016). Single embryo transfer for all? *Australian and New Zealand Journal of Obstetrics and Gynaecology*, *56*(5), 514–517. https://doi.org/10.1111/ajo.12478

Mills, M., Rindfuss, R. R., McDonald, P., & te Velde, E. (2011). Why do people postpone parenthood? Reasons and social policy incentives. *Human Reproduction Update*, *17*(6), 848–860. https://doi.org/10.1093/humupd/dmr026

Monden, C., Pison, G., & Smits, J. (2021). Twin Peaks: more twinning in humans than ever before. *Human Reproduction*, *00*(0), 1–8. https://doi.org/10.1093/humrep/deab029

Murray, S. R., Stock, S. J., Cowan, S., Cooper, E. S., & Norman, J. E. (2018). Spontaneous preterm birth prevention in multiple pregnancy. *The Obstetrician & Gynaecologist*, *20*(1), 57–63. https://doi.org/10.1111/tog.12460

Nasseri, F., & Azhir, A. (2009). The neonatal outcome in twin versus triplet and quadruplet pregnancies. *Journal of Research in Medical Sciences*, *14*(1), 7–12. /pmc/articles/PMC3129073/

NICE. (2019). *Recommendations | Twin and triplet pregnancy | Guidance | NICE*. NICE Guideline [NG137]. https://www.nice.org.uk/guidance/ng137/chapter/Recommendations#timing-of-birth

NIPC. (2011). Special Care Nursery Admissions Background. *National Perinatal Information System/Quality Analytic Services*, 39–41. https://www.marchofdimes.org/peristats/pdfdocs/nicu_summary_final.pdf

Ooi, S., & Wong, V. W. (2018). Twin pregnancy with gestational diabetes mellitus: A double whammy? In *Diabetes Care* (Vol. 41, Issue 2, pp. e15–e16). American Diabetes Association Inc. https://doi.org/10.2337/dc17-2227

Pison, G., Monden, C., & Smits, J. (2015). Twinning Rates in Developed Countries: Trends and Explanations. *Population and Development Review*, *41*(4), 629–649. https://doi.org/10.1111/j.1728-4457.2015.00088.x

Pyykönen, A., Gissler, M., Løkkegaard, E., Bergholt, T., Rasmussen, S. C., Smárason, A., Bjarnadóttir, R. I., Másdóttir, B. B., Källén, K., Klungsoyr, K., Albrechtsen, S., Skjeldestad, F. E., & Tapper, A. M. (2017). Cesarean section trends in the Nordic Countries – a comparative analysis with the Robson classification. *Acta Obstetricia et Gynecologica Scandinavica*, *96*(5), 607–616. https://doi.org/10.1111/aogs.13108

Quinn, J. A., Munoz, F. M., Gonik, B., Frau, L., Cutland, C., Mallett-Moore, T., Kissou, A., Wittke, F., Das, M., Nunes, T., Pye, S., Watson, W., Ramos, A. M. A., Cordero, J. F., Huang, W. T., Kochhar, S., & Buttery, J. (2016). Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine*, *34*(49), 6047–6056. https://doi.org/10.1016/j.vaccine.2016.03.045

Reglugerð um tæknifrjóvgun. | Heilbrigðisráðuneyti | Reglugerðasafn. (2009). Reglugerðasafn. https://www.reglugerd.is/reglugerdir/eftir-raduneytum/heilbrigdis/nr/10797

Santana, D. S., Cecatti, J. G., Surita, F. G., Silveira, C., Costa, M. L., Souza, J. P., Mazhar, S. B., Jayaratne, K., Qureshi, Z., Sousa, M. H., & Vogel, J. P. (2016). Twin Pregnancy and Severe Maternal Outcomes. *Obstetrics & Gynecology*, *127*(4), 631–641. https://doi.org/10.1097/AOG.0000000000001338

Schmitz, T., Prunet, C., Azria, E., Bohec, C., Bongain, A., Chabanier, P., D'Ercole, C., Deruelle, P., de Tayrac, R., Dreyfus, M., Dupont, C., Gondry, J., Graesslin, O., Kayem, G., Langer, B., Marpeau, L., Morel, O., Parant, O., Perrotin, F., … Goffinet, F. (2017). Association between Planned Cesarean Delivery and Neonatal Mortality and Morbidity in Twin Pregnancies. *Obstetrics and Gynecology*, *129*(6), 986–995. https://doi.org/10.1097/AOG.0000000000002048

Sharma, D., Shastri, S., & Sharma, P. (2016). Intrauterine Growth Restriction: Antenatal and Postnatal Aspects. *Clinical Medicine Insights: Pediatrics*, *10*, CMPed.S40070. https://doi.org/10.4137/cmped.s40070

Song, B., Wei, Z.-L., Xu, X.-F., Wang, X., He, X.-J., Wu, H., Zhou, P., & Cao, Y.-X. (2017). Prevalence and risk factors of monochorionic diamniotic twinning after assisted reproduction: A six-year experience base on a large cohort of pregnancies. *PLOS ONE*, *12*(11), e0186813. https://doi.org/10.1371/journal.pone.0186813

Swift, E. M., Tomasson, G., Gottfreðsdóttir, H., Einarsdóttir, K., & Zoega, H. (2018). Obstetric interventions, trends, and drivers of change: A 20-year population-based study from Iceland. *Birth*, *45*(4), 368–376. https://doi.org/10.1111/birt.12353

Tal, A., Zafran, N., Peretz, H., Garmi, G., Romano, S., & Salim, R. (2019). Trend in cesarean delivery rate among twin pregnancies over a 20 years epoch and the accompanied maternal and perinatal outcomes. *European Journal of Obstetrics and Gynecology and Reproductive Biology: X*, *3*, 100023. https://doi.org/10.1016/j.eurox.2019.100023

Walani, S. R. (2020). Global burden of preterm birth. *International Journal of Gynecology and Obstetrics*, *150*(1), 31–33. https://doi.org/10.1002/ijgo.13195

Ward, R. M., & Beachy, J. C. (2003). Neonatal complications following preterm birth. *BJOG: An International Journal of Obstetrics & Gynaecology*, *110*, 8–16. https://doi.org/10.1046/j.1471-0528.2003.00012.x

WHO. (2011). *WHO recommendations for Prevention and treatment of pre-eclampsia and eclampsia*. https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/

WHO. (2018). *Preterm birth*. Key Facts. https://www.who.int/news-room/fact-sheets/detail/preterm-birth

Article Manuscript

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Multiple births in Iceland 1997-2018

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Abstract

Introduction

Multiple birth rates have been increasing globally since the 1980s and until the 2000s when regulations limited multiple embryo transfers during IVF treatments. Iceland passed similar regulations in 2009 and it is unknown whether these changes affected rates of multiple births in Iceland. The aim of the study was to assess the rates of multiple births and obstetrical interventions for multiples in Iceland during 1997-2018.

Methods

This study included multiple live births in Iceland during 1997-2018 identified from the Icelandic Medical Birth Registry. Multiple birth rates were calculated by birth year period overall and by grouped maternal age. Rates of cesarean delivery and induction of labor for multiples were calculated by birth year period. Logistic regression models were used to assess the risk of multiple birth and the risk of obstetrical intervention for multiple births according to birth year period.

Results

The study included 95 405 live births, of which 3314 (3.5%) were multiples. Multiple births rates decreased during the study period with the largest decrease from 2006 to 2009. The risk of multiple birth decreased in 2009-2013 (AOR=0.76, 95% CI=0.69-0.84) compared to 1997-2002 and was further decreased for maternal age 35+ (AOR=0.58, 95% CI=0.48-0.69). Induction of labor rates increased from 25% in 1997-2002 to 55% in 2009-2013 (AOR=4.25, 95% CI=3.40-5.33) whereas elective (AOR=0.62, 95% CI=0.48-0.80) and emergency cesarean (AOR=0.81, 95% CI=0.64-1.01) rates declined.

Conclusion

Multiple live births decreased during the study period with the largest decrease from 2006-2009 and for mothers aged 35+ years. These results indicate that international embryo transfer regulations published before the Icelandic regulations in 2009 may have had the largest effect on multiple birth rates in Iceland, but that the Icelandic policy introduced in 2009 may have had some effect on further reducing these rates, particularly for older mothers.

Introduction

Multiple birth rates have been increasing globally since the 1980s and especially among wealthier nations within Europe, North America, and Asia (Monden et al., 2021). Delayed childbearing, higher birth orders, and advancements to medically assisted reproduction are widely accepted as associations for the increasing rates (Monden et al., 2021). Multiple births are more likely to have complications at delivery and to be born prematurely (Félix Martins Santana et al., 2019; Jonsson, 2015; Monden et al., 2021). Additionally, multiple births pose a significantly higher risk for maternal complications, both antenatal and post-partum (Félix Martins Santana et al., 2019; Jonsson, 2015; Monden et al., 2021).

In the 1990s, rising multiple birth rates associated with MAR and the risks associated with multiple births for both mother and child, sparked concern among medical and public health communities (Monden et al., 2021). Guidelines in many developed countries changed around 2000 that limited the number of transferred embryos and changed the approach toward lower-risk singleton live births (Monden et al., 2021). In 2009, regulations were passed in Iceland that shifted toward this approach and limited multiple embryo transfers during IVF treatments for women under 36 years old. However, an analysis of multiple birth rates in Iceland and an estimate of the effect of the guideline change on multiple birth rates in Iceland is yet to be conducted.

Increased obstetrical intervention rates have been seen for multiples. An overall increase in rates of cesarean delivery before labor for multiples has been seen worldwide (Jonsson, 2015). Induction of labor is often indicated in multiple pregnancies and induction of labor has been associated with an increased risk for cesarean delivery (Jonsson, 2015). It is unknown whether Iceland follows these same trends for multiples.

In Iceland, overall cesarean delivery rates over the past two decades have remained relatively low and stable while induction of labor rates have significantly increased (Swift et al., 2018). Furthermore, preterm delivery rates for multiple births have been increasing in Iceland (Grétarsdóttir et al., 2019). To date, studies that examine the overall obstetrical intervention rates for multiple births in Iceland are missing in the literature.

With this in mind, we firstly aimed to study multiple birth rates in Iceland during 1997-2018, overall and according to maternal age, with special interest in examining the trends for changes occurring since the change to the multiple embryo transfer regulations were implemented in Iceland in 2009. We also aimed to study the rate of obstetrical interventions for multiple births in Iceland during the same period.

Methods

Data sources and study population

This retrospective descriptive population-based cohort study is based on data collected from the Icelandic Medical Birth Registry from 1997 through 2018. This nationwide centralized registry contains registered information which includes complete coverage of all live births and stillbirths in Iceland as well as maternal sociodemographic characteristics. This database includes live births and stillbirths for infants weighing >500 g or having gestational age >22 weeks. The initial data included all births, singleton and multiple both live and dead (n = 95 733), but 328 were excluded because of stillbirth, 288 of which were singleton and 40 multiples resulting in the sample size (n = 95 405) that was used for calculation of multiple live birth rates. Sets of multiples were not determined from the data and therefore multiple live birth counts in the numerator represent individual live births that occurred from multiple deliveries. Multiple birth calculations are shown as a ratio rather than a percent, multiplied by 1000 rather than 100, consistent with NCHS procedures (March of Dimes, 2021). We then excluded singleton data for assessment of obstetrical intervention rates as this study was restricted to multiple live births (n = 3314). The multiple live births included twins (n = 3201) and triplets (n =113) and there were no higher order live births identified during the study period. Birth year period and maternal age groups were specifically categorized to allow for the assessment of trends occurring after embryo transfer regulations were passed in Iceland in 2009. Birth year period was categorized into 4 groups (1997-2002, 2003-2008, 2009-2013, 2014-2018) and maternal age was categorized into 3 groups using the variable maternal age at delivery (≤24, 25-34, ≥35 years). Gestational age was identified using the variable gestational age in weeks measured with ultrasound and was categorized into 4 groups for characteristics analysis only (preterm <37, early term 37+0 to 38+6, term 39+0 to 40+6, post term ≥41+0).

The outcome for obstetrical intervention was categorized into elective cesarean, induction of labor, instrumental birth, and emergency cesarean and were captured using the registered International Classification of Diseases and Health Related Problems 10th revision (ICD-10) codes and NOMESCO Classification of Surgical Procedures codes. Elective cesarean was identified using ICD-10 code “O82.0”. Induction of labor was identified using ICD-10 code “O83.8” and NCSP codes “MASC00, MAXC00, MAXC02, MAXC09”. Instrumental birth included deliveries where vacuum, forceps or a combination of the methods were used and was identified using ICD-10 codes “O81.0, O81.1, O81.2, O81.4, O81.5” and NCSP codes “MASF00, MASF10, MASF20, MASF96, MASG03, MASG13”. Emergency cesarean included deliveries where cesarean was performed after the onset of delivery and was identified using ICD-10 code “O82.1”. Multiple delivery ICD-10 codes “O84.0, O84.1, O84.2, O84.8” were used to identify and categorize variables in the absence of or in combination with the previously indicated ICD-10 codes.

Statistical analysis

Multiple live birth rates and obstetrical intervention rates in multiples were calculated for each birth year from 1997-2018 and for four time periods, 1997-2002, 2003-2008, 2009-2013, 2014-2018. Multiple birth was then modeled as the dependent variable in a logistic regression model, using birth year period as the independent variable. Additional models were conducted for obstetrical intervention rates (elective cesarean, induction of labor, instrumental birth, and emergency cesarean) as the dependent variables. The models estimated the odds ratio and 95% confidence interval for the risk of multiple birth or obstetrical intervention for each birth year period with the first birth year period, 1997-2002, as the reference. This was done overall and for each maternal age group (multiple births). The logistic regression models were all adjusted for demographic variables: marital status (married/cohabiting, single/divorced/widowed, unknown), residential area (capital area, outside capital area), country of origin (Icelandic, non-Icelandic), employment status (employed, student, unemployed, homemaker, pension/disability/other). In addition, the logistic regression model for risk of obstetrical intervention for multiple live births was adjusted for maternal age (continuous).

Results

In this study of multiple live births in Iceland during 1997-2018 were 95 405 total live births and 3314 (3.5%) multiples. Table 1 shows the demographics of multiple births according to birth year. Multiple births were most commonly delivered at preterm and early term gestational age, 47.6% and 40.6% respectively. Term gestational age at delivery decreased during the study period from 18.3% to 3.4% and preterm gestational age at delivery increased during the study period from 41.4% to 54.3%. Multiparous mothers accounted for 69.6% of the multiple births. The proportion of multiparas decreased from 81.1% to 60.2% whereas the proportion of primiparas increased from 18.9% to 39.8%. A total of 3201 (96.6%) multiple births were twins and 113 (3.4%) were triplets. There were no documented higher order births during the study period. The proportion of triplets decreased during the study period from 5.8% to 1.8% whereas the proportion of twins increased from 94.2% to 98.2%. Mothers of foreign origin increased in proportion and the proportion of mothers living within the capital area increased during the study period. The proportion of married or cohabitating mothers decreased during the study period as well as the proportion of homemakers. The proportion of spontaneous onset of delivery decreased during the study period from 55.6% to 23.5%, whereas induction of labor substantially increased from 14.2% to 52.6%. Mode of delivery remained relatively stable with a decrease in the proportion of elective cesarean after birth year period 1997-2002.

Multiple live births decreased during the study period, with the largest decrease from 2006 to 2009, after which the rate leveled off. Figure 1 shows the multiple live birth rates per 1000 live births and indicates a downward trend after 2006. Mothers aged 35+ had the highest rate of multiple birth by proportion for every birth year period (Figure 2). This rate decreased significantly during the study period until 2009-2013. Rates in the <25 and 25-34 age groups remained relatively constant throughout the study period by comparison and mothers aged <25 consistently had the lowest rates of multiple births throughout all birth year periods (Figure 2).

The risk of multiple birth decreased in 2009-2013 (AOR 0.76, 95% 0.69 - 0.84) and in 2014-2018 (AOR 0.82 0.74 - 0.91) compared to 1997-2002 (Table 2). When the results were stratified according to maternal age group, the risk of multiple birth was further decreased for maternal age 35+ in 2009-2013 (AOR 0.58 95% 0.48 - 0.69) and 2014-2018 (AOR 0.58 95% 0.48 - 0.70) compared to 1997-2002 (Table 2).

We examined the risk of obstetrical intervention for multiple births in Iceland during the study period (Figure 3 and Table 3). The odds ratios for induction of labor increased for every birth year period when compared to 1997-2002, and most notably in birth year period 2009-2013 (AOR 4.25 95% 3.40- 5.33) (Table 3). Proportionate induction of labor rates increased from 25% in 1997-2002 to 55% in 2009-2013 (Figure 3).

The odds ratios for instrumental birth increased for every birth year period when compared to 1997-2002, but the increase was not statistically significant after adjustment (Table 3). Proportionate instrumental birth rates remained low, however increased from 4.8% in birth year period 1997-2002 to 8.2% in birth year period 2014-2018 (Figure 3). Elective cesarean and emergency cesarean rates declined throughout the study period, 24% to 17% for elective cesarean and 29% to 22% for emergency cesarean (Figure 3). The odds ratios for elective cesarean decreased similarly in all time periods when compared to 1997-2002 with the decrease in 2014-2018 being (AOR 0.64, 95% 0.49-0.83). The odds ratios for emergency cesarean decreased only in 2014-2018 (AOR 0.63, 95% 0.49-0.80) when compared to 1997-2002.

Discussion

In this study we found that multiple live births rates decreased during the study period with the largest decrease from 2006 to 2009, after which the rate leveled off. The risk of multiple birth also decreased in all birth year periods compared to 1997-2002 and the largest decrease was observed in the strata of maternal age 35+ years. Obstetrical intervention rates for elective cesarean and emergency cesarean declined while induction of labor rates increased considerably throughout the study period. The risk for both elective and emergency cesarean decreased while the risk for induction of labor increased.

Previous studies of multiple birth rates have found considerable increases in multiple birth rates in many European countries, North America, and East Asia when compared to the 1980s (Monden et al., 2021). Although these countries had significant increases in multiple birth rates, in some cases increasing two-fold or more, the rates leveled off in the early 2000s after changes to regulations and clinical practice guidelines implemented strategies to limit embryo transfer and shift the focus toward successful singleton live birth (Monden et al., 2021).

A previous study examining trends in twinning rates in developed countries found that countries in Europe including Czech Republic, Denmark, Finland, Hungary, Iceland, Netherlands, Norway, Scotland, and Sweden and non-European OECD countries including Australia, Japan, and New Zealand experienced a peak and subsequent decline in twinning rates (Pison et al., 2015). Apart from Finland, which peaked in 1998, and Sweden, which peaked in 1999, these countries experienced a peak in twinning rates after 2000 (Pison et al., 2015). Iceland was found to have peaked between 1997-2006, with the small population size making exact dating for Iceland more difficult (Pison et al., 2015). The Icelandic regulations for embryo transfer were passed in 2009, however our study found that multiple birth rates began to decrease before this time. It appears likely that Iceland began changes to clinical practice as a reflection of other international policies and regulations which had been published earlier. In 2004 the original fertility guideline by the National Institute for Clinical Excellence (NICE) was first published in the UK (Fields et al., 2013), suggesting limits to the number of embryos transferred, and in 2006 the UK Human Fertilisation and Embryo Authority (HFEA) declared full-term singleton births with normal birth weight as the definition of success for assisted reproduction technologies (Miller et al., 2016).

A study published in 2016 examining variations in multiple birth rates and the impact on perinatal outcomes in Europe found that Iceland was in the group with the lowest multiple birth rates with less than 15 per 1000 in 2010 (Heino et al., 2016). This study calculated multiple birth rates as the number of women with multiple pregnancies per 1000 women delivering live birth or stillbirth. Our study found a similar result when adjusted for calculation method differences. This study concluded that Europe showed wide variation in multiple birth rates and trends with no obvious pattern between geographical areas during the study period (Heino et al., 2016). While changes in multiple birth rates for Iceland were not calculated in this study´s comparison of 2004 to 2010, results indicated decreased rates for Demark, the Netherlands, and Norway but increased rates for all other participating countries, with the largest increase seen in the Brussels Region of Belgium, Luxembourg, and Malta (Heino et al., 2016).

Previous studies of obstetrical intervention rates in Iceland found that cesarean rates decreased between 1997-2015 for multiples with an overall cesarean rate of 45.9% for the group (Einarsdóttir, K, Sigurðardóttir, H, Bjarnadóttir, RI, 2019). Our study found the same overall cesarean rate for multiple births when elective and emergency rates were combined. Another study examining obstetrical interventions in Iceland during 1995-2014, found decreasing emergency cesarean rates for multiples, increasing induction of labor rates with stable, relatively low rates of instrumental delivery (Swift et al., 2018). These results are also in line with our findings.

A study examining cesarean trends in Nordic countries using Robson classification found decreasing cesarean rates for Robson groups 8-10 (Robson group 8 is multiples) in Finland, Iceland, Norway, and Sweden (Pyykönen et al., 2017). In contrast, increased cesarean delivery rates for multiples in Israel and the United States have been observed (Tal et al., 2019). A significantly increased rate of cesarean delivery for twin pregnancies was found from 43.4% in 1995 to 66.0% in 2015 in Israel (Tal et al., 2019). While in the United States, cesarean delivery rates for twins increased from 53.4% to 75% between 1995-2008 (Lee et al., 2011).

Strengths and limitations

A notable strength of our study is the use of data from the nationwide centralized Icelandic Birth Registry which includes complete coverage of all live births and stillbirths in Iceland over the 22-year study period. Nordic countries, including Iceland, have kept compulsory birth registers that provide basic information of the mother, neonate, and father with additional medical and social characteristics data for decades (Langhoff-Roos et al., 2014). The high-quality data obtained from this database and population-based study design is the main strength of this study. However, there was some data that was missing that left us unable to fully categorize characteristics for a small number of the multiples. Additionally, missing ICD-10 codes used to categorize onset of labor and mode of delivery rendered some data incomplete. To account for this limitation, we chose to specify obstetrical interventions for cesarean delivery as either elective or emergency to ensure all multiples were counted in the rate calculations.

Conclusion

Multiple live births decreased during the study period with the largest decrease in the birth year period 2009-2013 compared to 1997-2002 and for mothers aged 35+ years. These results indicate that the limited multiple embryo policy introduced in 2009 may have had some effect on reducing multiple birth rates in Iceland, particularly for older mothers, although the main decrease may have happened earlier in response to international guidelines. Both elective and emergency cesarean rates for multiple births decreased during the study period while induction of labor rates increased considerably.

References

Einarsdóttir, K, Sigurðardóttir, H, Bjarnadóttir, RI, et. al. (2019). The Robson 10-group classification in Iceland: Obstetric interventions and outcomes. *Birth Issues in Perinatal Care*, *46*(2), 270–278. https://doi.org/doi.org/10.1111/birt.12415

Félix Martins Santana, E., Melo Corrêa, V., Bottura, I., & Pedro Parise Filho, J. (2019). Time and Mode of Delivery in Twin Pregnancies. In *Multiple Pregnancy - New Challenges*. IntechOpen. https://doi.org/10.5772/intechopen.80092

Fields, E., Chard, J., James, D., & Treasure, T. (2013). Fertility (update): Summary of nice guidance. In *BMJ (Online)* (Vol. 346, Issue 7896). British Medical Journal Publishing Group. https://doi.org/10.1136/bmj.f650

Grétarsdóttir, Á. S., Aspelund, T., Steingrímsdóttir, Þ., Bjarnadóttir, R. I., & Einarsdóttir, K. (2019). Preterm births in Iceland 1997-2016: Preterm birth rates by gestational age groups and type of preterm birth. *Birth*. https://doi.org/10.1111/birt.12467

Heino, A., Gissler, M., Hindori-Mohangoo, A. D., Blondel, B., Klungsøyr, K., Verdenik, I., Mierzejewska, E., Velebil, P., Ólafsdóttir, H. S., Macfarlane, A., Zeitlin, J., Haidinger, G., Alexander, S., Pavlou, P., Mortensen, L., Sakkeus, L., Lack, N., Antsaklis, A., Berbik, I., … McComb, N. (2016). Variations in multiple birth rates and impact on perinatal outcomes in Europe. *PLoS ONE*, *11*(3). https://doi.org/10.1371/journal.pone.0149252

Jonsson, M. (2015). Induction of twin pregnancy and the risk of caesarean delivery: a cohort study. *BMC Pregnancy and Childbirth*, *15*(1), 1–7. https://doi.org/10.1186/s12884-015-0566-4

Langhoff-Roos, J., Krebs, L., Klungsøyr, K., Bjarnadottir, R. I., Källén, K., Tapper, A. M., Jakobsson, M., Børdahl, P. E., Lindqvist, P. G., Gottvall, K., Colmorn, L. B., & Gissler, M. (2014). The Nordic medical birth registers - A potential goldmine for clinical research. *Acta Obstetricia et Gynecologica Scandinavica*, *93*(2), 132–137. https://doi.org/10.1111/aogs.12302

Lee, H. C., Gould, J. B., Boscardin, W. J., El-Sayed, Y. Y., & Blumenfeld, Y. J. (2011). Trends in cesarean delivery for twin births in the united states: 1995-2008. *Obstetrics and Gynecology*, *118*(5), 1095–1101. https://doi.org/10.1097/AOG.0b013e3182318651

March of Dimes. (2021). *Peristats | March of Dimes*. Peristats. https://www.marchofdimes.org/peristats/calculations.aspx?reg=&top=&id=19

Miller, L. M., Hodgson, R., Wong, T. Y., Merrilees, M., Norman, R. J., & Johnson, N. P. (2016). Single embryo transfer for all? *Australian and New Zealand Journal of Obstetrics and Gynaecology*, *56*(5), 514–517. https://doi.org/10.1111/ajo.12478

Monden, C., Pison, G., & Smits, J. (2021). Twin Peaks: more twinning in humans than ever before. *Human Reproduction*, *00*(0), 1–8. https://doi.org/10.1093/humrep/deab029

Pison, G., Monden, C., & Smits, J. (2015). Twinning Rates in Developed Countries: Trends and Explanations. *Population and Development Review*, *41*(4), 629–649. https://doi.org/10.1111/j.1728-4457.2015.00088.x

Pyykönen, A., Gissler, M., Løkkegaard, E., Bergholt, T., Rasmussen, S. C., Smárason, A., Bjarnadóttir, R. I., Másdóttir, B. B., Källén, K., Klungsoyr, K., Albrechtsen, S., Skjeldestad, F. E., & Tapper, A. M. (2017). Cesarean section trends in the Nordic Countries – a comparative analysis with the Robson classification. *Acta Obstetricia et Gynecologica Scandinavica*, *96*(5), 607–616. https://doi.org/10.1111/aogs.13108

Swift, E. M., Tomasson, G., Gottfreðsdóttir, H., Einarsdóttir, K., & Zoega, H. (2018). Obstetric interventions, trends, and drivers of change: A 20-year population-based study from Iceland. *Birth*, *45*(4), 368–376. https://doi.org/10.1111/birt.12353

Tal, A., Zafran, N., Peretz, H., Garmi, G., Romano, S., & Salim, R. (2019). Trend in cesarean delivery rate among twin pregnancies over a 20 years epoch and the accompanied maternal and perinatal outcomes. *European Journal of Obstetrics and Gynecology and Reproductive Biology: X*, *3*, 100023. https://doi.org/10.1016/j.eurox.2019.100023

Tables and figures

Table 1 Characteristics of multiple live births according to birth year period, Iceland, 1997-2018

	1997-2002 (N=990)	2003-2008 (N=961)	2009-2013 (N=694)	2014-2018 (N=669)	Overall (N=3314)
Gestational age					
Preterm	410 (41.4%)	457 (47.6%)	346 (49.9%)	363 (54.3%)	1576 (47.6%)
Early term	388 (39.2%)	392 (40.8%)	288 (41.5%)	278 (41.6%)	1346 (40.6%)
Term	181 (18.3%)	112 (11.7%)	50 (7.2%)	23 (3.4%)	366 (11.0%)
Post term	4 (0.4%)	0 (0%)	7 (1.0%)	4 (0.6%)	15 (0.5%)
Missing	7 (0.7%)	0 (0%)	3 (0.4%)	1 (0.1%)	11 (0.3%)
Maternal age					
<25	88 (8.9%)	93 (9.7%)	71 (10.2%)	37 (5.5%)	289 (8.7%)
25-34	571 (57.7%)	586 (61.0%)	409 (58.9%)	426 (63.7%)	1992 (60.1%)
35+	331 (33.4%)	282 (29.3%)	214 (30.8%)	206 (30.8%)	1033 (31.2%)
Parity					
Multipara	803 (81.1%)	686 (71.4%)	426 (61.4%)	403 (60.2%)	2318 (69.9%)
Primipara	187 (18.9%)	275 (28.6%)	268 (38.6%)	266 (39.8%)	996 (30.1%)
Multiple					
Triplets	57 (5.8%)	32 (3.3%)	12 (1.7%)	12 (1.8%)	113 (3.4%)
Twins	933 (94.2%)	929 (96.7%)	682 (98.3%)	657 (98.2%)	3201 (96.6%)
Country of origin					
Icelandic	954 (96.4%)	886 (92.2%)	640 (92.2%)	587 (87.7%)	3067 (92.5%)
Non-Icelandic	36 (3.6%)	75 (7.8%)	54 (7.8%)	82 (12.3%)	247 (7.5%)
Residential area					
Capital area	565 (57.1%)	579 (60.2%)	461 (66.4%)	449 (67.1%)	2054 (62.0%)
Outside capital area	425 (42.9%)	382 (39.8%)	233 (33.6%)	220 (32.9%)	1260 (38.0%)
Marital status					
Married/cohabiting	921 (93.0%)	877 (91.3%)	593 (85.4%)	558 (83.4%)	2949 (89.0%)
Single/divorced/widowed	63 (6.4%)	83 (8.6%)	89 (12.8%)	86 (12.9%)	321 (9.7%)
Unknown	6 (0.6%)	1 (0.1%)	12 (1.7%)	25 (3.7%)	44 (1.3%)
Employment status					
Employed	771 (77.9%)	768 (79.9%)	526 (75.8%)	542 (81.0%)	2607 (78.7%)
Student	65 (6.6%)	103 (10.7%)	97 (14.0%)	68 (10.2%)	333 (10.0%)
Unemployed	0 (0%)	2 (0.2%)	18 (2.6%)	18 (2.7%)	38 (1.1%)
Homemaker	127 (12.8%)	60 (6.2%)	30 (4.3%)	14 (2.1%)	231 (7.0%)
Pension/disability/other	27 (2.7%)	24 (2.5%)	12 (1.7%)	13 (1.9%)	76 (2.3%)
Missing	0 (0%)	4 (0.4%)	11 (1.6%)	14 (2.1%)	29 (0.9%)
Onset of labor					
Spontant	550 (55.6%)	486 (50.6%)	150 (21.6%)	157 (23.5%)	1343 (40.5%)
Induction of labor	141 (14.2%)	207 (21.5%)	384 (55.3%)	352 (52.6%)	1084 (32.7%)
Cesarean	299 (30.2%)	257 (26.7%)	160 (23.1%)	160 (23.9%)	876 (26.4%)
Other	0 (0%)	11 (1.1%)	0 (0%)	0 (0%)	11 (0.3%)

Mode of delivery					
Normal delivery	414 (41.8%)	426 (44.3%)	348 (50.1%)	330 (49.3%)	1518 (45.8%)
Instrumental	48 (4.8%)	73 (7.6%)	46 (6.6%)	55 (8.2%)	222 (6.7%)
Elective cesarean	235 (23.7%)	162 (16.9%)	112 (16.1%)	115 (17.2%)	624 (18.8%)
Emergency cesarean	286 (28.9%)	278 (28.9%)	182 (26.2%)	150 (22.4%)	896 (27.0%)
Other	7 (0.7%)	22 (2.3%)	6 (0.9%)	19 (2.8%)	54 (1.6%)

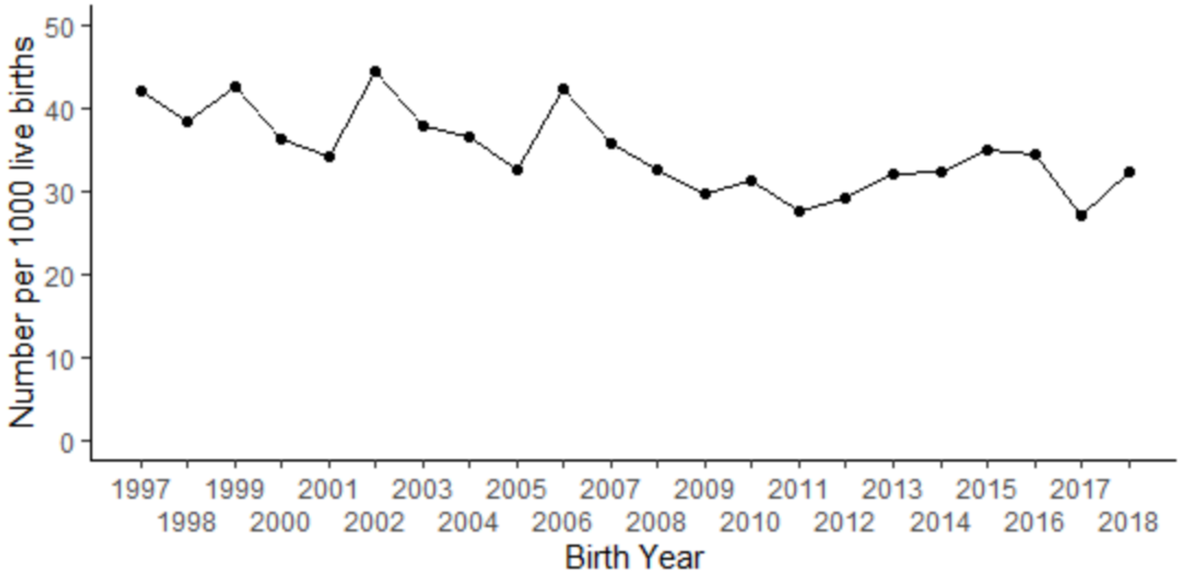

Figure 1 The rate of multiple birth in Iceland, 1997-2018

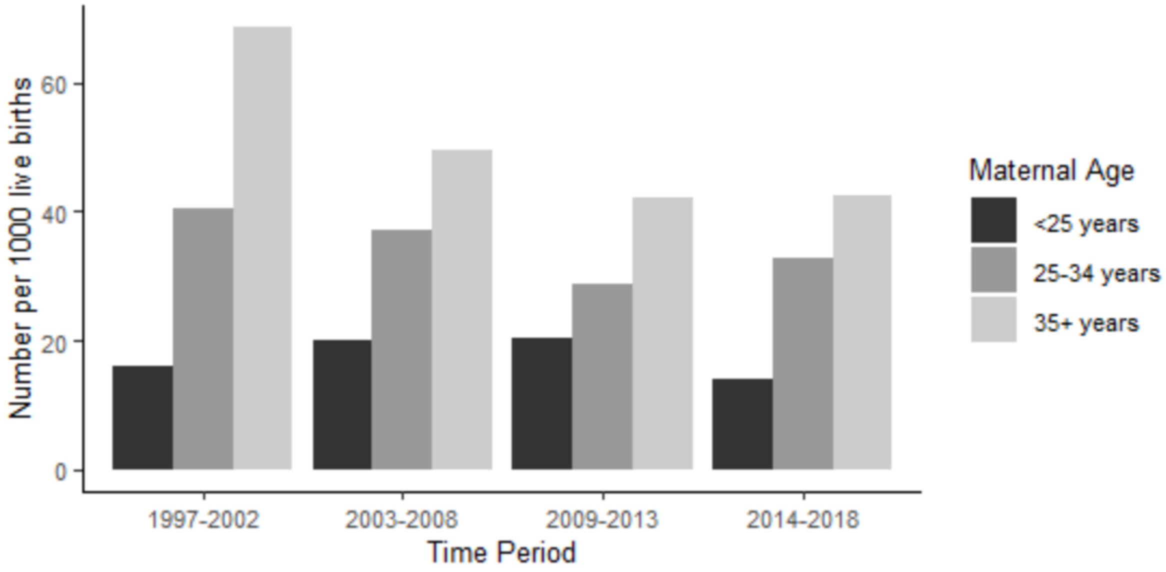

Figure 2 The incidence proportion of multiple births by birth year period, stratified by maternal age, Iceland, 1997-2018

Table 2 Odds ratios and 95% confidence intervals for the risk of multiple live birth, overall and by grouped maternal age, according to birth year period, n = 3314, Iceland, 1997-2018

Birth Year Period	**1997-2002**	**2003-2008**	**2009-2013**	**2014-2018**
Overall				
OR (95% CI)	Reference	0.91 (0.83 - 1.00)	0.75 (0.68 - 0.83)	0.81 (0.73 - 0.89)
**AOR (95% CI)*	Reference	0.91 (0.83 - 1.00)	0.76 (0.69 - 0.84)	0.82 (0.74 - 0.91)
Age <25				
OR (95% CI)	Reference	1.25 (0.93 - 1.68)	1.27 (0.93 - 1.75)	0.87 (0.59 - 1.27)
**AOR (95% CI)*	Reference	1.24 (0.92 - 1.67)	1.28 (0.92 - 1.78)	0.88 (0.59 - 1.30)
Age 25-34				
OR (95% CI)	Reference	0.91 (0.81 - 1.03)	0.72 (0.63 - 0.81)	0.83 (0.73 - 0.94)
**AOR (95% CI)*	Reference	0.93 (0.82 - 1.04)	0.75 (0.66 - 0.85)	0.87 (0.76 - 0.99)
Age 35+				
OR (95% CI)	Reference	0.75 (0.63 - 0.89)	0.59 (0.49 - 0.70)	0.59 (0.49 - 0.70)
**AOR (95% CI)*	Reference	0.73 (0.62 - 0.86)	0.58 (0.48 - 0.69)	0.58 (0.48 - 0.70)

*Adjusted for parity, marital status, employment status, country of origin, residential area

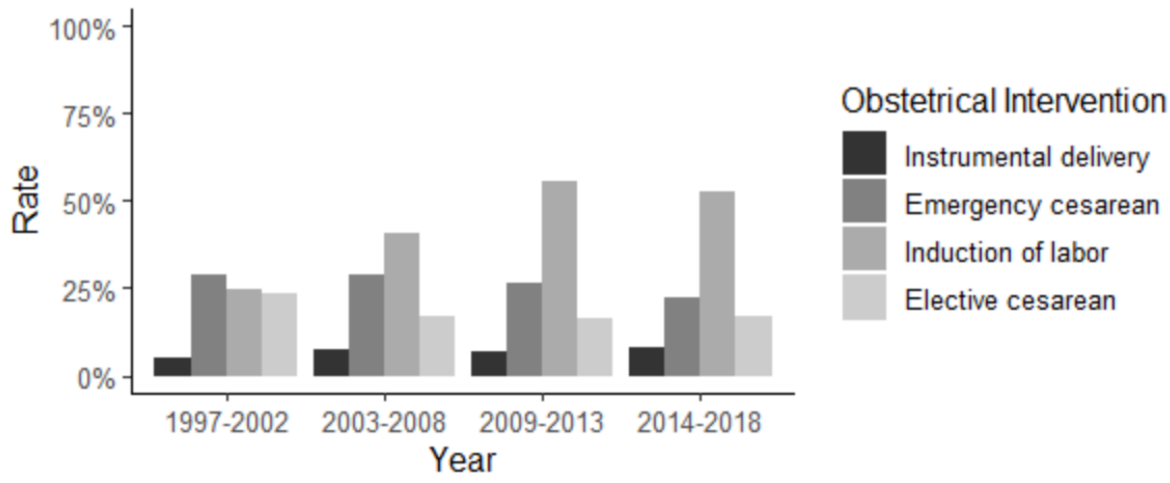

Figure 3 Obstetrical intervention rates for multiple live births by birth year period, Iceland, 1997-2018

Table 3 Odds ratios and 95% confidence intervals for the risk of obstetrical intervention for multiple live births according to birth year period, n = 3314, Iceland, 1997-2018

Birth Year Period	**1997-2002**	**2003-2008**	**2009-2013**	**2014-2018**
Induction of labor				
OR (95% CI)	Reference	2.14 (1.76 - 2.59)	3.81 (3.10 - 4.69)	3.43 (2.79 - 4.24)
AOR (95% CI)	Reference	2.27 (1.85- 2.79)	4.25 (3.40- 5.33)	4.06 (3.23- 5.12)
Instrumental delivery				
OR (95% CI)	Reference	1.61 (1.11 - 2.36)	1.39 (0.92 - 2.11)	1.76 (1.18 - 2.63)
AOR (95% CI)	Reference	1.41 (0.96 - 2.09)	1.11 (0.71 - 1.71)	1.40 (0.91 - 2.14)
Elective cesarean				
OR (95% CI)	Reference	0.65 (0.52 - 0.81)	0.62 (0.48 - 0.79)	0.67 (0.52 - 0.85)
AOR (95% CI)	Reference	0.66 (0.53- 0.84)	0.62 (0.48 - 0.80)	0.64 (0.49 - 0.83)
Emergency cesarean				
OR (95% CI)	Reference	1.00 (0.82 - 1.22)	0.88 (0.70 - 1.09)	0.71 (0.57 - 0.89)
AOR (95% CI)	Reference	0.95 (0.78 - 1.17)	0.81 (0.64 - 1.01)	0.63 (0.49 - 0.80)

**Odds ratios adjusted for maternal age, gestational age, parity, marital status, employment status, country of origin, residential area*