

CLINICAL ARTICLE

Obstetrics

Optimal timing for induction of labor in normotensive women: A retrospective cohort study

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Abstract

Objective: Labor induction is offered to reduce the risk of stillbirth at late term (41⁺⁰ to 41⁺⁶) but earlier induction in normotensive singleton pregnancies is supported by weak evidence. The aim of the present study was to investigate the optimal timing for induction in normotensive women.

Methods: This was a retrospective cohort study including 70293 singleton term births in Iceland during 1997–2018. Women with serious pre-gestational comorbidity, hypertension, stillbirth or previous cesarean birth were excluded. The risk of adverse maternal and neonatal outcomes for induction at each week from gestational age 37–41 weeks was compared with expectant management, defined as deliveries at a later gestational age. Risk ratios (RRs) and 95% confidence intervals (95% CI) were calculated using log-binomial regression adjusting for sociodemographics, parity, and pregnancy complications.

Results: The risk of cesarean was lower with induction at $\geq 40^{+0}$ than expectant management, especially at late term (RR 0.73, 95% CI: 0.63–0.83). Respiratory distress was diagnosed in 4.4% of infants after induction from 37⁺⁰ to 37⁺⁶ but 1.3% in the expectant management group (RR 3.08, 95% CI: 1.97–4.81). Induction between 37⁺⁰ and 38⁺⁶ compared with expectant management was associated with a reduced risk of shoulder dystocia, but this was non-significant in births of infants with normal birthweight.

Conclusion: Labor induction from 40⁺⁰ compared with expectant management was associated with reduced risk of cesarean birth in Icelandic women without an increase in risk of adverse maternal or neonatal outcomes. No additional benefit appeared to be from inducing at earlier gestations in low-risk pregnancies.

KEYWORDS

cesarean birth, early-term induction, expectant management, induction of labor, respiratory distress

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1 | INTRODUCTION

Labor induction rates have been on the rise for the last decade in many countries.¹⁻³ Traditionally, labor is induced where the risk of adverse outcomes associated with continuing the pregnancy is considered higher than with induced labor. Hypertensive disorders in pregnancy are strong indications for term induction as the risk for adverse outcome is high.⁴ However, most induced women in Iceland have low- to intermediate risk of adverse outcomes and the appropriate timing of induction is unclear for some intermediary-risk conditions such as gestational diabetes.^{5,6} Induction of labor is offered in healthy pregnancies that exceed the estimated due date by 1 week because late-term inductions reduce the risk of stillbirth.⁷ However, many healthy pregnant women request a labor induction before late term for convenience and ease of scheduling.⁸ Most randomized controlled trials on labor induction have focused on either a population with specific medical conditions^{9,10} or late-term inductions in a low-risk population.^{7,11,12} One of few exceptions was the American study ARRIVE that compared labor induction at 39 weeks with expectant management in a low-risk population.¹³ The trial showed that induction reduced the risk of cesarean birth, but it seems unclear if this applies in countries like Iceland with a low cesarean birth rate. In Iceland, an increase has been observed in the rate of early-term (37⁺⁰ to 38⁺⁶) inductions without a clearly recorded indication.¹⁴ There is a lack of trials estimating the potential harm of early-term inductions in a low to intermediary-risk population.

Based on previous evidence, the primary aim of the study was to assess if induction from 39 weeks in a normotensive low to intermediary-risk population was associated with reduced risk of cesarean birth without increasing instrumental deliveries. The secondary aim was to explore if induction was associated with adverse neonatal outcome, especially at early term. The risk of adverse maternal and neonatal outcomes for induced labor at each week from gestational age 37–41 weeks was compared with expectant management, defined as deliveries at a later gestational age.

2 | MATERIALS AND METHODS

This retrospective cohort study was based on data from the Icelandic Medical Birth Register (MBR), that includes data on all births in Iceland after 22 gestational weeks (live births and stillbirths) as notification is mandatory. The quality of Nordic MBR has been reported good although a validation study of the Icelandic MBR is lacking.¹⁵ International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) was used during the whole study period to record pregnancy and delivery complications, and interventions were coded by NOMESCO Classification of Surgical Procedures. Ultrasound estimated gestational age (at 20 weeks of gestation or earlier) was used for the analysis. Information about indications for inductions in the Icelandic population may be found in a previous publication.¹⁴

Iceland 1997 – 2018 Singleton term births, vertex

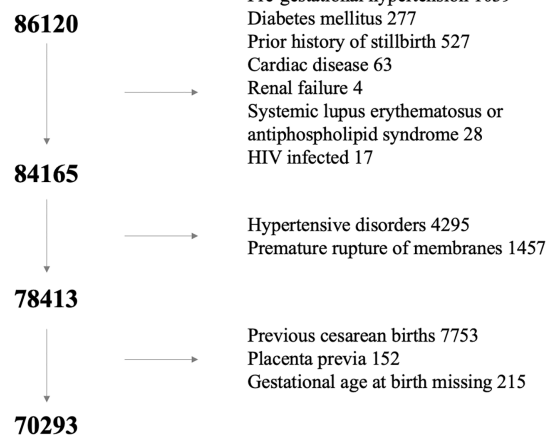


FIGURE 1 Flow chart of the study population.

The study population included 86 120 singleton term births (≥ 37 weeks) with vertex presentation in Iceland from 1997 to 2018 (Figure 1). Women with prior history of stillbirth or severe pre-gestational morbidity (see conditions and codes in Table S1) were excluded ($n = 1955$). Also, pregnancies complicated by hypertensive disorders in pregnancy or premature rupture of the membranes with onset of labor after 24 h or more were excluded ($n = 5752$) because expectant management was considered to have been an unlikely option at term. Further, women with a history of one or more previous cesarean births ($n = 7753$) were excluded as this highly modifies the association between induction and mode of birth. Placenta previa and morbidly adherent placenta ($n = 152$) were excluded as these are contraindications for vaginal delivery. Lastly, births with missing data on ultrasound estimated gestational age were excluded ($n = 215$). The final population was reduced to 70 293 singleton term births considered likely to have been at low- or intermediate risk for adverse outcome at the time of birth. Study size calculations were not performed but all available electronic data from the Icelandic MBR was used.

Induction of labor that was identified by: (1) ICD-10 O83.8 that is used in Iceland to register inductions, (2) the start of labor registered as induced and (3) the NCSP-codes for induction of labor with prostaglandin MAXC02 or balloon catheter MAXC09. Induction of labor at each week from term was compared with expectant management, defined as deliveries at a later gestational age (with any type of labor start). Expectant management is thought to be the appropriate comparison to induction of labor, rather than spontaneous labor at a particular gestational age that cannot be chosen.¹⁶ The five induction and expectant management groups were as follows: (1) induction at 37+0–37+6 and expectant management births from 38+0 or later, (2) induction at 38+0–38+6 and expectant management births from 39+0, (3) induction at 39+0–39+6 and expectant management births from 40+0, (4) induction at 40+0–40+6 and expectant management births from 41+0, (5) induction at 41+0–41+6 (late term) and expectant management births from 42+0.

Maternal and neonatal outcomes were defined by ICD-10 and NCSF codes (Table S1). The primary outcome was cesarean birth or instrumental vaginal birth (deliveries by vacuum and forceps) and the secondary outcomes were obstetric anal sphincter injury (OASIS), shoulder dystocia, birth trauma (including intracranial laceration and hemorrhage, subaponeurotic hemorrhage, injuries to the nervous system and bone fractures), respiratory distress, Apgar score under 7 at 5 min from birth and neonatal pneumonia or sepsis.

The following sociodemographic covariates were considered to confound the association between labor induction and the outcomes; maternal age, employment, and delivery ward (Table 1 and Figure S1). The pregnancy complications considered as possible confounders by indication of labor induction were gestational diabetes mellitus (GDM), suspected growth restriction (maternal care for poor fetal growth), cholestasis in pregnancy and poor obstetric history (Table S1 and Figure S1). Although these common

TABLE 1 Sociodemographic factors according to induction of labor (yes/no) for 70 293 singleton term births in Iceland during 1997–2018.

	Induction n (%)	Not induced n (%)	P value
Total number	10868	59425	
Parity			
Primiparous	4713 (43.4)	25357 (42.7)	0.180
Multiparous	6155 (56.6)	34068 (57.3)	
Missing	0	0	
Age at delivery			
≤25 years	2171 (20.0)	14678 (24.7)	<0.0001
26–30 years	3356 (30.9)	19971 (33.6)	
31–34 years	2496 (22.9)	13429 (22.6)	
≥35 years	2844 (26.2)	11336 (19.1)	
Missing	1	11	
Employment			
Employed	8043 (75.0)	43817 (74.6)	<0.0001
Student	1450 (13.5)	8586 (14.6)	
Unemployed	249 (2.3)	1044 (1.8)	
Disability pension	240 (2.2)	914 (1.6)	
Other	736 (6.9)	4350 (7.4)	
Missing	150	714	
Delivery ward			
University hospital	7785 (71.6)	33154 (55.8)	<0.0001
Midwifery unit ^a	186 (1.7)	8515 (14.3)	
Small hospital ^b	2049 (18.9)	9276 (15.6)	
Rural birthplaces	848 (7.8)	8480 (14.3)	
Missing	0	0	

^aMidwifery led unit in the capital area and home births.

^bSmall hospital defined as a delivery ward with more than 200 births per year and an obstetrician on call.

indications for induction are associated with an intermediate risk increase of negative outcomes, these births were not excluded as evidence from trials is unclear about the benefit of induction. Standardized birthweight for gestational age was calculated according to a Swedish growth curve¹⁷ and categorized into small for gestational age (SGA), appropriate for gestational age (AGA) and large for gestational age (LGA), defined by 10th and 90th percentiles.

2.1 | Statistical analysis

The risk related to each outcome was calculated in births induced at each gestational week from 37 to 41 weeks and compared with the risk in the corresponding expectant management group. Risk ratios (RRs) were calculated using log-binomial regression and reported with 95% confidence intervals (CI).¹⁸ Pregnancy complications were introduced separately into regression models that included parity, maternal age, employment, and delivery ward (births with missing data excluded). Adjustment was made for pregnancy complications that were significantly associated with each outcome in at least one of the five models. A residual confounding by obesity through macrosomia could exist even after adjustment for GDM as this was not diagnosed according to current standards before 2012 but underdiagnosed (Figure S1). Also, an effect modification by macrosomia on the association between induction and some of the outcomes could be suspected. Therefore, a sensitivity analysis was done in a subset of AGA births only. The risk of intrapartum cesarean birth was calculated for births each gestational week that started spontaneously or were induced, excluding pre-labor cesareans ($n = 861$). The risk of intrapartum cesarean by gestational week was shown stratified by the start of labor, birthweight categories and the presence of pregnancy complications. Significance level of 5% was used ($P < 0.05$ and 95% CI). SAS 9.4 was used for statistical analysis.

2.2 | Ethics statement

Informed consent was not required as previously existing, anonymized registry data was used and no interventions were applied. The study was approved by the National Bioethics Committee in Iceland (VSNb2019020007/03.01) and performed in accordance with the Declaration of Helsinki. Icelandic laws do not allow sharing of register data by scientist, but the same data may be applied for at the Icelandic Directory of Health.

3 | RESULTS

The study included 70 293 singleton term births in Iceland during 1997–2018. The total number of inductions was 10868 and about a third were late-term inductions. Compared with women that were not

TABLE 2 Proportion of complications in pregnancies where labor was induced at each gestational week compared with expectant management for 70 293 singleton term births from Iceland during 1997–2018.

	37 weeks		38 weeks		39 weeks		40 weeks		41 weeks	
	Induction n (%)	Expectant* n (%)	Induction n (%)	Expectant* n (%)	Induction n (%)	Expectant* n (%)	Induction n (%)	Expectant* n (%)	Induction n (%)	Expectant* n (%)
Pregnancy complications	n = 474	n = 68 008	n = 1064	n = 61 452	n = 1653	n = 45 162	n = 1847	n = 21 106	n = 3540	n = 3435
Nulliparous	204 (43.0)	29 012 (42.7)	363 (34.1)	26 356 (42.9)	518 (31.3)	19 831 (43.9)	78 (38.9)	9 920 (47.0)	1586 (44.8)	1908 (55.6)
GDM ^a	65 (13.7)	2511 (3.7)	211 (19.8)	2096 (3.4)	451 (27.3)	1135 (2.5)	348 (18.8)	369 (1.8)	269 (7.6)	9 (0.3)
Growth restriction ^b	86 (18.1)	460 (0.7)	114 (10.7)	313 (0.5)	113 (6.8)	163 (0.4)	87 (4.7)	39 (0.2)	30 (0.9)	0
Cholestasis ^c	73 (15.4)	353 (0.5)	88 (8.3)	230 (0.4)	71 (4.3)	126 (0.3)	45 (2.4)	43 (0.2)	20 (0.6)	4 (0.1)
Poor obstetric history ^d	15 (3.2)	666 (1.0)	41 (3.8)	537 (0.9)	76 (4.6)	201 (0.4)	66 (3.6)	69 (0.3)	31 (0.9)	2 (0.1)

*Expectant management defined as deliveries later: Births during the same week with pre-labor cesarean or labor that started spontaneously were excluded.

^aGestational diabetes mellitus defined by ICD-10: O24.4 or O24.9.

^bSuspected growth restriction defined by ICD-10: O36.5.

^cCholestasis in pregnancy defined by ICD-10: O26.6.

^dPoor obstetric history, defined by ICD-10: Z35.2

induced, women with induced labors were more likely to be younger than 25 years old or older than 35, less likely to be students but more likely to be unemployed or have disability pension (Table 1). The proportion of births with diagnosis of GDM, suspected growth restriction, cholestasis and poor obstetric history was higher in all the induction groups compared with expectant management (Table 2). About one in every five inductions between 37⁺⁰ and 37⁺⁶ were likely performed by the indication of growth restriction. One in every four women that were induced between 39⁺⁰ and 39⁺⁶ had a GDM diagnosis (Table 2).

The risk of intrapartum cesarean birth increased with gestational age from 38⁺⁰ and was especially high at post-term (≥42⁺⁰), both in deliveries that start spontaneously and induced births (Table S2). Compared with expectant management, the observed risk of cesarean birth was higher in induction groups from 37⁺⁰ to 37⁺⁶ but no difference in RR was found after adjustments. However, the RR of cesarean birth was decreased by 20% with induction after the estimated due date (40⁺⁰) compared with expectant management (Table 3). This association between induction and cesarean persisted when the population was restricted to AGA births. There was little association between induction and instrumental births, although reduced risk was seen with induction at 38⁺⁰ to 38⁺⁶ (Table 3). Induction from 39⁺⁰ was not associated with an increase in other negative outcomes studied (Table S3).

Induction between 37⁺⁰ to 37⁺⁶ was associated with increased risk of respiratory distress, which was diagnosed in 4.4% of infants after induction but 1.3% in the corresponding expectant management group (Table 4). This association persisted in AGA births (RR 3.47, 95% CI: 1.97–6.11). Further, early-term inductions were associated with increased risk of Apgar less than 7 at 5 min, but this association was non-significant after restriction to AGA births. We found a significant association between induction at 38⁺⁰ to 38⁺⁶ and shoulder dystocia that was non-significant after restriction to AGA births. Early-term induction was not associated with birth trauma, OASIS or neonatal pneumonia or sepsis.

4 | DISCUSSION

The results of the present study suggest that inductions from 40⁺⁰ compared to expectant management decreased the risk of cesarean births without increasing instrumental births or other negative outcomes. Further, inductions before 38⁺⁰ compared to expectant management were associated with increased risk of respiratory distress.

Decreased or unchanged risk of cesarean births following inductions compared with expectant management has been reported in previous observational studies,^{19–22} as well as meta-analysis of randomized controlled trials of late-term inductions.^{11,12} A decreased risk of cesarean was shown in the ARRIVE trial¹³ but it seemed uncertain if this would apply in populations with lower cesarean birth rates than the trial setting. In a previous paper we demonstrated that the rate of intrapartum cesarean birth was slightly reduced in Iceland during the time of doubling rate of inductions.²³ The results of this study support previous evidence that the prospect of normal vaginal

TABLE 3 Mode of delivery related to induction of labor compared with expectant management for 70 293 singleton term births in Iceland during 1997–2018.

Week of induction	Induction	Expectant ^a	RR 95% CI	
	n (%)	n (%)	Crude	Adjusted ^b
Cesarean birth				
37 ⁺⁰ –37 ⁺⁶	51 (10.8)	5058 (7.4)	1.50 (1.12–2.01)	1.01 (0.73–1.38)
38 ⁺⁰ –38 ⁺⁶	95 (8.9)	4606 (7.5)	1.21 (0.98–1.50)	0.84 (0.67–1.06)
39 ⁺⁰ –39 ⁺⁶	185 (11.2)	3403 (7.5)	1.55 (1.32–1.81)	1.07 (0.90–1.28)
40 ⁺⁰ –40 ⁺⁶	201 (10.9)	2124 (10.1)	1.09 (0.94–1.27)	0.73 (0.62–0.87)
41 ⁺⁰ –41 ⁺⁶	472 (13.3)	587 (17.1)	0.75 (0.65–0.85)	0.72 (0.63–0.83)
Instrumental delivery				
37 ⁺⁰ –37 ⁺⁶	32 (6.8)	5393 (7.9)	0.84 (0.59–1.20)	0.84 (0.57–1.24)
38 ⁺⁰ –38 ⁺⁶	56 (5.3)	5031 (8.2)	0.62 (0.47–0.82)	0.67 (0.50–0.90)
39 ⁺⁰ –39 ⁺⁶	112 (6.8)	4061 (9.0)	0.73 (0.61–0.89)	0.86 (0.70–1.06)
40 ⁺⁰ –40 ⁺⁶	170 (9.2)	2195 (10.4)	0.87 (0.74–1.03)	0.93 (0.78–1.10)
41 ⁺⁰ –41 ⁺⁶	377 (10.7)	449 (13.1)	0.79 (0.68–0.92)	0.90 (0.77–1.04)

Note: Bold font statistically significant association with an outcome according to adjusted risk ratio.

Abbreviation: CI, confidence interval.

^aExpectant management defined as births the following gestational week or later.

^bAdjustments were made for maternal parity, age, employment, delivery ward. In addition, the following indications for inductions were added; for cesarean birth, gestational diabetes, growth restriction and poor obstetric history was included and for instrumental delivery, gestational diabetes, growth restriction and cholestasis were included.

TABLE 4 Secondary outcomes related to early-term induction of labor compared with expectant management for 70 293 singleton term births in Iceland during 1997–2018.

Week of induction	Induction	Expectant ^a	RR 95% CI	
	n (%)	n (%)	Crude	Adjusted ^b
Obstetric anal sphincter injury (OASIS)				
37 ⁺⁰ –37 ⁺⁶	7 (1.5)	2126 (3.1)	0.46 (0.22–0.98)	0.56 (0.26–1.19)
38 ⁺⁰ –38 ⁺⁶	26 (2.4)	1982 (3.2)	0.75 (0.51–1.11)	0.92 (0.62–1.38)
Shoulder dystocia				
37 ⁺⁰ –37 ⁺⁶	3 (0.6)	749 (1.1)	0.57 (0.18–1.78)	0.59 (0.19–1.85)
38 ⁺⁰ –38 ⁺⁶	6 (0.6)	711 (1.2)	0.48 (0.22–1.08)	0.44 (0.20–0.99)
Birth trauma				
37 ⁺⁰ –37 ⁺⁶	3 (0.6)	825 (1.2)	0.52 (0.17–1.62)	0.46 (0.16–1.44)
38 ⁺⁰ –38 ⁺⁶	8 (0.7)	769 (1.3)	0.59 (0.30–1.21)	0.60 (0.28–1.13)
Respiratory distress				
37 ⁺⁰ –37 ⁺⁶	21 (4.4)	848 (1.3)	3.67 (2.36–5.72)	3.12 (2.00–4.88)
38 ⁺⁰ –38 ⁺⁶	19 (1.8)	759 (1.2)	1.45 (0.92–2.30)	1.29 (0.81–2.05)
Apgar <7 at 5 min				
37 ⁺⁰ –37 ⁺⁶	22 (4.6)	1344 (2.0)	2.41 (1.57–3.72)	2.17 (1.37–3.43)
38 ⁺⁰ –38 ⁺⁶	30 (2.8)	1215 (2.0)	1.43 (1.00–2.08)	1.48 (1.02–2.15)
Pneumonia or sepsis				
37 ⁺⁰ –37 ⁺⁶	9 (1.9)	689 (1.0)	1.89 (0.97–3.67)	1.65 (0.85–3.22)
38 ⁺⁰ –38 ⁺⁶	16 (1.5)	635 (1.0)	1.46 (0.89–2.41)	1.43 (0.86–2.36)

Note: Bold font statistically significant association with an outcome according to adjusted risk ratio.

Abbreviation: CI, confidence interval.

^aExpectant management defined as births the following gestational week or later.

^bAdjustments were made for maternal parity, age, employment, delivery ward. In addition, the following indications for inductions were added; for OASIS growth restriction was included, for shoulder dystocia and respiratory distress, gestational diabetes was included and for Apgar score, cholestasis was included. None of the tested induction indications was significantly associated with birth trauma or pneumonia/sepsis.

deliveries is not limited by labor induction. Importantly, the results of this study apply to Iceland and may not be generalizable to other populations, especially if different induction routines are used.²⁴ Results of an ongoing French-ARRIVE trial may further inform on potential benefit of labor induction on cesarean birth in a low-risk population.²⁵ Despite no apparent short-term harm of induction from 39⁺⁰, the lack of evidence regarding the potential effect on maternal mental health should be considered when assessing the benefit and harm of the intervention.

Our study showed increased risk of respiratory distress with induction between 37⁺⁰ to 37⁺⁶. Preterm birth is known to increase the risk of respiratory distress.^{26,27} Early-term induction versus expectant management has mostly been studied in high-risk populations reporting no increased risk of respiratory distress.^{9,10} However, large proportion of inductions in these trials were performed at a gestational age of 38⁺⁰ or later that may explain the discrepancy. Our results could be comparable to the DIGITAT trial that estimated the effect of induction beyond 36⁺⁰ in pregnancies complicated with suspected growth restriction and found that an increased proportion of neonates in the induction group were admitted to intermediate ward.²⁸

We found lowered risk of shoulder dystocia associated with early-term induction, an association that was non-significant in AGA births. The result is in line with previous evidence regarding the benefit of induction when LGA was suspected during pregnancy.⁹ A large proportion of the women in our study that gave birth at early-term had a diagnosis of GDM. To our knowledge, only one induction trial in women with GDM ($n=425$) has been published, and that trial failed to show a benefit of induction compared with expectant management.^{5,6} Larger studies are needed to determine the overall risk-benefit of early-term induction. Importantly, future trials on early-term labor induction should include measures of developmental outcomes in infancy and childhood.

Our study included all births in Iceland, a nation with access to free antenatal care and a low rate of cesarean births. Data regarding maternal parity and age was almost complete for all deliveries. The gestational age was calculated according to ultrasound estimation before 20 weeks for most deliveries and therefore thought to be accurate. Information on body mass index was only registered from 2013 in our data. Obese women are more likely to deliver macrosomic infants than normal weight women and despite the adjustment of GDM, residual confounding by obesity cannot be excluded. However, the result of the sensitivity analysis suggested that the association between induction and cesarean persisted after restriction to AGA births. Also, our data lacks information about the definite indication for labor inductions that may have resulted in insufficient adjustment for confounding by indication. We were unable to perform sibling analysis on our data or use negative controls to account for residual confounding. Information on admissions to neonatal unit is lacking in the birth register which is a limitation of the study as well as the lack of previous validation studies of the diagnostic codes in our register. Further, severe pregnancy complications like pre-eclampsia, can be expected to occur as women wait for a spontaneous onset of labor (expectant

management). Pregnancies complicated by pre-eclampsia were excluded in our study because information about the timing of the diagnosis was lacking, but this could make the expectant management group unrealistically healthy. However, comparing induction each gestational week with later deliveries could slightly overestimate differences between groups. Lastly, residual confounding from unmeasured factors cannot be excluded and should be kept in mind while interpreting results.

5 | CONCLUSIONS

Labor induction from 40⁺⁰ compared with expectant management slightly reduced the risk of cesarean birth without an increase in risk of adverse maternal or neonatal outcomes. No additional benefit appeared to be from inducing at earlier gestations in low-risk women. Inductions before 38⁺⁰ in women with intact membranes should continue to be limited to medical conditions like hypertensive disorders or severe growth restriction.

AUTHOR CONTRIBUTIONS

The study was designed by K. Einarsdóttir, A. Smáráson and J. Gunnarsdóttir. K. Einarsdóttir collected the data. J. Gunnarsdóttir analyzed the data and wrote the first draft of the paper. All authors interpreted the results and critically reviewed the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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