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# Induction of labour in twin pregnancies. A prospective cohort study

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## ABSTRACT

**INTRODUCTION.** In dichorionic twin pregnancies, the Danish national guidelines recommend induction of labour (IOL) at 38 weeks of gestation. This recommendation is rooted in the heightened risks of caesarean section and perinatal death associated with later gestational ages. Additionally, this procedure demonstrates a rate of successful vaginal delivery well above 60%. However, documentation remains inadequate regarding potential variances in outcomes between induction methods such as amniotomy, prostaglandins and balloon catheter. Therefore, we aimed to address this knowledge gap.

**METHODS.** This was a single-centre cohort study encompassing 921 twin pregnancies between 2007 and 2019 at Lillebaelt University Hospital, Kolding, Denmark. The research database was updated prospectively.

**RESULTS.** Maternal mortality was zero. Perinatal mortality was 100% between weeks 22 and 24, gradually declining to 0% beyond 34 weeks. The overall frequency of caesarean section (planned and emergency) was 35%. Among those who underwent IOL, the rates of emergency caesarean section were 28% (32/114) for amniotomy, 41% (36/87) for prostaglandin and 53% (8/15) for balloon methods.

**CONCLUSIONS.** The notably high rates of caesarean section associated with IOL by prostaglandin or balloon catheter in twin pregnancies warrant consideration when planning IOL.

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In twin pregnancies without contraindications for vaginal delivery, determining the optimal gestational age of elective induction of labour (IOL) involves considering several factors [1, 2]. These include 1) the escalating risk of perinatal death beyond 38 weeks of gestation, 2) the decreasing risks of neonatal respiratory disorders as gestational age progresses, 3) the varying risks of emergency caesarean section (CS) at different gestational ages, 4) the likelihood of successful vaginal delivery following IOL and 5) the preferences and perspectives of pregnant women.

Thus, one of the presumptions for the Danish national recommendation of vaginal delivery before 38 + 0 weeks is an acceptable chance of successful vaginal delivery after IOL [1, 2]. This presumption is backed by two recent studies, which reveal proportions of vaginal delivery of 67% [3] and 72% [4]. However, only a limited number of studies have evaluated outcomes following different IOL methods, such as primary amniotomy, cervical priming using prostaglandin preparations and cervical dilatation by use of double-balloon catheters. Consequently, our objective was to address this knowledge gap.

## Methods

This cohort study included all multiple pregnancies from the catchment area of the Department of Obstetrics and Gynaecology, Lillebaelt University Hospital, Kolding, Denmark, from January 2007 to April 2019. Data from gestational week eight through 28 days post-delivery were consistently entered into the research database by the same chief physician (EEA) in a prospective manner. Information concerning mothers or infants who received care at external hospitals was gathered from hospital discharge records. We previously published data on this cohort [3].

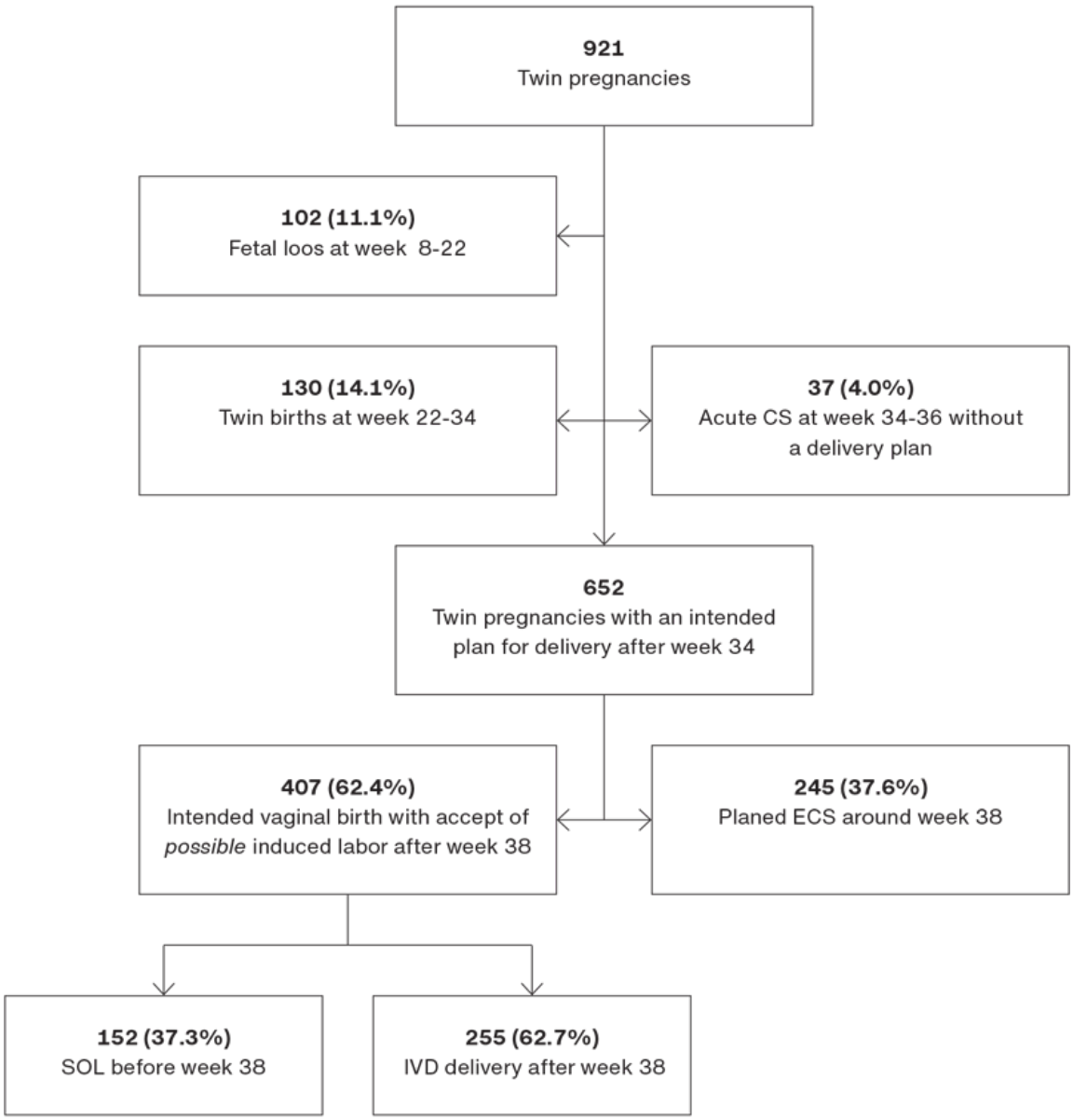
All women were provided a first-trimester scan at week 12 to confirm gestational age and chorionicity along with prenatal diagnostics. A second scan was then performed at week 20 to assess cervical length and screen for foetal malformations. From this stage, dichorionic (DC) twins underwent monthly monitoring, including assessment of foetal biometry and weight. In cases of growth discordance, umbilical artery Doppler assessment was conducted. Monochorionic (MC) twins underwent similar monitoring every two weeks, focusing on examinations of amniotic fluid volume and the peak systolic velocity of the middle cerebral artery. Pregnancies facing significant obstetric challenges between weeks 22 and 28 were promptly directed to Odense University Hospital. Following treatment, these cases were readmitted for continued care and ongoing monitoring in our department.

Every woman received guidance from an obstetric specialist before week 34. During these consultations, a personalised birth plan was formulated to align with individual preferences while adhering to obstetrical recommendations from the Danish Society of Obstetrics and Gynaecology (DSOG) and the International Federation of Gynaecology and Obstetrics (FIGO) [1, 2]. The women who opted for spontaneous delivery received information regarding IOL, particularly if they went beyond week 38. Additionally, the women provided informed consent for IOL.

IOL was typically conducted around week 38 for both DC and MC pregnancies. However, in cases involving preeclampsia, hypertension, cholestasis and other diseases, induction was performed earlier. Artificial rupture of the membranes (aROM) was conducted only if the cervix was deemed ripe (dilated 2-3 cm). The Bishop score was not used. Otherwise, women with no prior CS received prostaglandin treatment (vaginal dinoproston) until January 2016, and from then onwards oral misoprostol, stated as “medicine group”, followed by amniotomy. If amniotomy was impossible, CS was performed. In cases of no or weak labour contractions after 1-2 hours after amniotomy, intravenous oxytocin was administered as needed. Dinoproston vaginal suppository 3 mg was placed deep in the vagina (87 cases), possibly repeated after 6-8 hours. The maximum dose was 6 mg per day for up to two days. Oral misoprostol 25 µg tablets (15 cases) were given every two hours. The maximum dose was 200 µg per day for up to two days. Both prostaglandin regimes were deemed equivalent by the DSOG. Women with prior CS were offered mechanical dilation of the cervical canal using a double-balloon catheter for 12 hours. This procedure was succeeded by amniotomy and intravenous oxytocin if needed.

An emergency CS was conducted on women (n = 37) who had not finalised their birth plan decisions and were urgently admitted to the hospital due to a pathological obstetric condition. These cases were subsequently excluded from the study group (**Figure 1**).

**FIGURE 1** Flow chart of 921 twins pregnancies from week eight to week 34.0 in which the women had decided on the intended delivery mode.




CS = caesarean section; ECS = elective caesarean section; IVD = induced vaginal delivery; SOL = spontaneous onset of labour.

The primary outcome was emergency CS. Secondary maternal outcomes are outlined in **Table 1**, and secondary neonatal outcomes are outlined in **Table 2**.

**TABLE 1** Twin delivery outcomes focussing on the different modes of deliveries, particularly term deliveries.

| Outcome of 652 twin deliveries ≥ 34 wks | SOL ($N_s$ = 152) | ECS ($N_e$ = 245) | aROM ($N_a$ = 138) | Medicine[a] ($N_m$ = 102) | Balloon[a] ($N_b$ = 15) | p value |
|---|---|---|---|---|---|---|
| *Preterm deliveries ($N_p$ = 196), n* | | | | | | NR |
| Delivery < 37 + 0 wks | 88 | 69 | - | - | - | |
| Pathologic inductions < 37 + 0 wks | - | - | 24 | 15 | 0 | |
| *Term deliveries ($N_t$ = 456), n (%)* | NR | | | | | |
| Delivery with GA ≥ 37 + 0 | 64 (100) | 176 (100) | - | - | - | |
| Inductions with GA ≥ 37 + 0 | - | - | 114 (100) | 87 (100) | 15 (100) | |
| Nullipara among term deliveries, n (%) | 28 (44) | 100 (57) | 42 (37) | 49 (56) | 0 | NS |
| *Acute CS intrapartum, n (%)* | | | | | | |
| For nullipara | 9 (32) | 0 | 20 (48)$^{A}$ | 25 (51)$^{C}$ | 0 | < 0.05$^{A-B}$ |
| For parous | 8 (22) | 0 | 12 (17)$^{B}$ | 11 (29)$^{D}$ | 8 (53) | < 0.05$^{C-D}$ |
| Vacuum delivery of either twin A or twin B, n (%) | 6 (9) | NR | 16 (14) | 12 (14) | 1 (7) | NS |
| Twin B born by acute CS, n (%) | 5 (8) | NR | 14 (12) | 10 (11) | 1 (7) | NS |
| *Reoperation, n (%)* | NS | | | | | |
| IUP or vaginal | 2 (3) | - | 3 (3) | 5 (6) | 5 (33) | |
| Abdominal | 1 (2) | 3 (2) | 2 (2) | 0 | 0 | |
| Cicatrices infection, n (%) | 2 (3) | 10 (6) | 2 (2) | 4 (6) | 2 (13) | NS |
| Cystitis/endometritis, n (%) | 4 (6) | 9 (5) | 9 (8) | 8 (9) | 0 | NS |
| *Blood loss* | | | | | | |
| Incl. reoperation > 1,000 ml, n (%) | 7 (11) | 39 (16) | 23 (20) | 15 (17) | 5 (33) | NS |
| Volume, mean (± SE), ml | 586 (± 36)$^{A}$ | 693 (± 51) | 735 (± 82) | 875 (± 140)$^{B}$ | 1,067 (± 251) | < 0.05$^{A-B}$ |
| Time in maternity ward until birth of twin A, mean (± SE), hrs | 9.3 (± 1.3)$^{A}$ | NR | 8.1 (± 0.4)$^{A}$ | 27.7 (± 1.9)$^{B}$ | 23.1 (± 4.4)$^{C}$ | < 0.01$^{A-B}$<br>< 0.01$^{A-C}$ |
| Duration from the onset of active labour to birth of twin A, mean (± SE), hrs | 5.3 (± 0.4)$^{A}$ | NR | 5.0 (± 0.2)$^{A}$ | 7.8 (± 0.6)$^{B}$ | 6.9 ± 1.0 | < 0.01$^{A-B}$ |
| Time in the post-natal ward, mean (± SE), days | 7.5 (± 0.5) | 6.9 (± 0.3) | 6.9 (± 0.6) | 8.2 (± 0.5) | 7.5 (±1,3) | NS |
| Cabergoline to stop breastfeeding, in 1st wk, mean (± SE), % | 14.4 (± 2.8)$^{A}$ | 24.9 (± 2.8)$^{B}$ | 13.8 (± 2.9) | 18.6 (± 3.8) | 13.3 (± 6.1) | < 0.01$^{A-B}$ |

aROM = artificial rupture of the membranes; CS = caesarean section; ECS = elective CS; GA = gestational age; IUP = intrauterine palpation; NR = not relevant; NS = not significant; SE = standard error; SOL = spontaneous onset of labour.
a) Prostaglandin or balloon used for the unripe cervix.

**TABLE 2** Neonatal outcome of 1,304 newborn twins from the 652 pregnancies delivered by week 34 + 0 or later, by mode of delivery.

| | SOL | ECS | aROM | Medicine | Balloon | p value |
|---|---|---|---|---|---|---|
| *Outcome of 1,304 twins either A or B with GA ≥ 34 wks* | | | | | | |
| Total, $N_{\geq 34\ wks}$ | 304 | 490 | 276 | 204 | 30 | |
| Sub-/antepartum death, n | 0 | 0 | 0 | 0 | 0 | - |
| Neonatal death ≤ 28 days, n | 0 | 0 | 0 | 0 | 0 | - |
| Apgar score < 7 at 5 min. for 1,304 twins, n (%) | 6 (2.0) | 4 (0.8) | 1 (0.4) | 4 (2.0) | 0 | NS |
| Asphyxia at birth, i.e. with pH < 7.00 in umbilical artery, n (%) | 2 (0.7) | 0 | 2 (0.7) | 0 | 0 | NS |
| Malformations in according to ICD-10 codes, n (%) | 14 (4.6) | 18 (3.7) | 7 (2.5) | 4 (2.0) | 0 | NS |
| *Outome of 912 twins born at term[a], n* | | | | | | |
| Total, $N_{term}$ | 128 | 352 | 228 | 174 | 30 | |
| Need of C-PAP < 8 hrs in NCU, n (%) | 15 (12) | 44 (13) | 25 (9.8) | 17 (9.2) | 1 (3.6) | NS |
| Need for multiple treatments in NCU, n (%) | 10 (7.8) | 15 (4.2) | 9 (3.5) | 15 (8.2) | 1 (3.6) | NS |
| Re-admission in the 1st mo., n (%) | 2 (2.0) | 13 (3.4) | 9 (3.5) | 7 (3.4) | 1 (3.6) | NS |
| Weight of twin, mean (± SE), g: | | | | | | |
| Twin A | 2,812 (± 34) | 2,808 (± 26) | 2,809 (± 25) | 2,846 (± 36) | 2,936 (± 55) | NS |
| Twin B | 2,719 (± 41) | 2,759 (± 28) | 2,801 (± 38) | 2,748 (± 38) | 2,762 (± 130) | NS |

aROM = artificial rupture of the membranes, medicine or balloon used on the unripe cervix; C-PAP = continuous positive airway pressure; ECS = elective caesarean section; GA = gestational age; NCU = neonatal care unit; NS = not significant; SE = standard error; SOL = spontaneous onset of labour.
a) From 456 twin deliveries at term, see Table 1

## Statistics

Baseline characteristics and pregnancy outcomes were compared using Student's t-test for normally distributed continuous variables and the Mann-Whitney rank sum test for nn-normally distributed variables. The chi-squared test was employed for categorical variables, and Yates correction was applied for small counts. The analyses were performed using Stata (Software for Statistics and Data Science, version 16). A significance level of $p < 0.05$ was considered indicative of statistical significance. The results are presented with mean values ± standard error.

## Ethics

The Ethical Authority of the Region of Southern Denmark has approved the data collection and storage of this

project (file no. 18/53689 ) at Odense University Hospital in the database REDCap under project number OPEN-618.

*Trial registration:* not relevant.

## Results

The study cohort encompassed 921 twin pregnancies (Figure 1). Maternal mortality was zero. Before 22 weeks of gestation, 62 (6.7%) resulted in the loss of one foetus and 40 (4.4%) cases ended in spontaneous abortion. Between weeks 22 + 0 and 23 + 6, the combined perinatal and neonatal mortality rate was 100%, which declined to 1.9% between weeks 28 + 0 and 33 + 6. In the period from week 22 + 0 to 33 + 6, preterm deliveries occurred in 130 women, constituting 14.1% of the cohort. After 34 + 0 weeks of gestation (652 pregnancies, Figure 1), the perinatal mortality was zero, whereas 245 (38%) had a planned CS, 152 (26%) a spontaneous onset of labour (this figure includes women with premature prelabour rupture of foetal membranes) and 255 (39%) induced labour. The demographic characteristics of the groups are shown in **Table 3.**

**TABLE 3** The demographic characteristics of 652 women with twin births ≥ 34.0 weeks correlated to delivery mode.

| | SOL (N = 152) | ECS (N = 245) | IVD (N = 255) |
|---|---|---|---|
| Maternal age, mean (± SE), yrs | 31.4 (± 0.6) | 31.6 (± 0.4) | 31.4 (± 0.5) |
| *BMI before pregnancy, n (%)* | | | |
| 16.0-19.9 kg/m² | 18 (12) | 23 (9) | 32 (13) |
| 20.0-29.9 kg/m² | 117 (77) | 183 (75) | 197 (77) |
| 30.0-53.0 kg/m² | 17 (11) | 39 (16) | 26 (10) |
| Monochorionic twins n (%) | 31 (20) | 32 (13) | 28 (15) |
| Nulliparity, n (%) | 67 (44) | 100 (41) | 115 (45) |
| Non-smokers, n (%) | 138 (91) | 217 (88) | 232 (91) |
| ART, n (%) | 49 (32) | 84 (34) | 82 (33) |
| *Diseases in the pregnancy, n (%)* | | | |
| Breech presentation of twin A | 1 (< 1) | 178 (72) | 1 (< 1) |
| Gestational diabetes | 15 (10) | 20 (8) | 22 (9) |
| Gestational hypertension | 19 (12) | 42 (17) | 46 (18) |
| Intrahepatic cholestasis | 6 (4) | 13 (5) | 15 (6) |
| Antidepressant treatment | 2 (1) | 10 (4) | 8 (3) |
| CS in an earlier pregnancy, n (%) | 9 (6)* | 46 (19)* | 16 (6) |

ART = assisted reproductive technique; CS = caesarean section; ECS = elective CS; IVD = induced vaginal delivery, women with breech presentation were allocated to ECS; SE = standard error; SOL = spontaneous onset of labour.
*) $p < 0.05$.

The study group with inductions encompassed 216 pregnancies (91 nulliparous and 125 parous women) and 64 spontaneous deliveries exceeding 36 + 6 gestational weeks at birth. The primary outcome was emergency CS, which was 26% (17/64) after spontaneous onset of labour, 28% (32/114) after induction by amniotomy, 41% (36/87) after induction by prostaglandin and 53% (8/15) after induction by balloon catheter. Among those with

planned elective CS, 38% (93/245) had emergency CS before the scheduled date of elective CS. Among the types of labour induction, the overall rate of emergency was 35% (76/216) (Table 1).

For parity, the CS rates after IOL by amniotomy were 48% (20/42) for nulliparous women and 17% (12/72) for parous women ($p < 0.05$). After IOL by prostaglandin, the rates were 51% (25/49) for nulliparous and 29% (11/38) for parous women ($p < 0.05$).

In the entire cohort, approximately one-seventh of pregnancies were MC. A sensitivity analysis conducted using data exclusively from DC pregnancies revealed no significant differences between the planned delivery methods for DC and MC twin pregnancies (data not shown). Secondary maternal outcomes are outlined in Table 1. The neonatal outcomes are summarised in Table 2.

## Discussion

Among twin pregnancies in parous women exceeding 36 + 6 weeks of gestation, the risk of emergency CS was 17% after IOL by aROM, 29% after IOL by prostaglandin and 53% after labour induction by balloon catheter (those with prior CS). Among nulliparous women, the rates were 48% after amniotomy and 51% after prostaglandin.

A limitation of the study is that it was not powered to identify smaller, albeit potentially clinically significant, differences in secondary outcomes and differences between DC and MC twin pregnancies [5]. Furthermore, one must consider that external validity depends very much on local obstetric traditions, including the general CS rate, which differs considerably among clinics and countries.

The few studies on IOL in twin pregnancies have not investigated the importance of parity. These studies report overall rates of emergency CS ranging from 28% to 61% [4, 6, 7] compared to the 35% recorded in our study population. However, the literature on IOL in singleton pregnancies at or beyond 37 weeks of gestation has not reported important differences between nulliparous and parous women. For instance, in one study on IOL with misoprostol, the rates of emergency CS were 21% among nulliparous women and 4% among parous women [8], supporting our findings in twin pregnancies (51% versus 29%).

Our finding of a 50% emergency CS rate after IOL with a balloon catheter in women with prior CS does not differ dramatically from similar results from singleton pregnancies, indicating rates of 40-50% [9, 10]. Another aspect to include in the evaluation of these IOL results is those after planned vaginal delivery and spontaneous onset of labour. We observed an emergency CS rate of 32% among nulliparous women and 22% among parous women (see Table 1). This is slightly lower than the 36% overall rate recently reported in a Norwegian cohort [4].

To our knowledge, national guidelines do not incorporate women' parity into their rationale for IOL two weeks before term. Nor do guidelines provide specific thresholds at which planned CS should be considered. However, based on our experience, many colleagues and pregnant women consider a 50% rate to be an appropriate threshold, considering that acute CS in twin pregnancies are more challenging than singleton pregnancies. Therefore, in nulliparous women with twins who are planning a vaginal birth, it may be reasonable to consider elective CS when IOL is considered necessary, particularly for women with a very unfavourable or unripe cervix. For parous women with prior CS, similar considerations could be relevant before IOL with a balloon catheter.

This study was conducted before the revision of the Danish national guidelines in 2020. The updated guidelines recommend IOL for DC twins between 37 + 0 and 38 + 0 weeks of gestation to ensure delivery by 38 + 0 weeks. Conversely, MC twins should be delivered no later than 37 + 0 weeks. Our study concluded its inclusion period in 2019, preceding the revision of these guidelines.

## Conclusions

Based on our findings and the available literature, the influence of parity, the method of inducing labour, their combination and the associated risk of CS should be highlighted when counselling on delivery in twin pregnant mothers.

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