

## INDUCTION OF LABOUR IN TWIN PREGNANCIES

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### ABSTRACT

Medically-indicated deliveries are common in twin pregnancies given the increased risk of various obstetric complications in twin compared to singleton pregnancies, mainly hypertensive disorders of pregnancy and foetal growth restriction. Due to the unique characteristics of twin pregnancies, the success rates and safety of labour induction may be different than in singleton pregnancies. However, while there are abundant data regarding induction of labour in singleton pregnancies, the efficacy and safety of labour induction in twin pregnancies have been far less studied.

In the current manuscript we summarize available data on various aspects of labour induction in twin pregnancies including incidence, success rate, prognostic factors, safety and methods for labour induction in twins. This information may assist healthcare providers in counselling patients with twin pregnancies when labour induction is indicated.

**Keywords:** Large for gestational age, Fetal macrosomia, Labor induction, Cervical ripening, Diagnosis, Maternal and neonatal morbidity, Cost-effectiveness

### Introduction

Twin pregnancies account for 1-4% of all births [5,6]. [1,2]. The incidence of twin pregnancies has increased significantly in recent decades [3,4]: the rate of twin pregnancies in the United States appears to have increased from 1.8% in 1971 to 3.3% in 2018 [4]. As with single pregnancies, in twin pregnancies there is often a need to induce labour before its spontaneous onset due to maternal or fetal indications. Twin pregnancies are associated with an increased risk of preterm birth (PTB), compared to singleton pregnancies; this condition can occur in 40-60% of all twin pregnancies [7-9]. Although many cases of PTB in twin pregnancies are spontaneous, there has

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been an increase in the rate of medically indicated PTB in twins. In Australia, the incidence of medically indicated PTB in twin pregnancies increased from 28% in 2007 to 49% in 2017 [8]. This high rate of medically indicated preterm births can be attributed to the relatively high incidence of complications in twin pregnancies, principally hypertensive disorders of pregnancy and fetal growth restriction [10-14]. Furthermore, in twin pregnancies, perinatal mortality and morbidity rates have been shown to increase around 38 weeks' gestation [15-18]. For this reason, many guidelines [7,19-22] recommend elective delivery of twins between 36 and 38 weeks gestation depending on chorionicity and other perinatal parameters.

Due to the specific characteristics of twin pregnancies, induction of labour has different success and safety rates compared to single pregnancies. However, while there are abundant data regarding induction of labour in single pregnancies [23-26], induction of labour in twin pregnancies has been much less studied [5,6,27-42].

### **The safety of vaginal delivery in twin pregnancies**

The best mode of delivery in twin pregnancies has been the subject of heated discussion in recent decades [43]. Until 2013, most data were based on retrospective studies and small prospective cohort studies, with contradictory results [43-49]. While some studies reported that vaginal delivery is associated with an increased risk of neonatal morbidity [44-46], others found no significant differences in obstetric complication rates between vaginal delivery and elective caesarean section [47-50]. A large multicentre randomized controlled trial, the Twin Birth Study

(TBS), was published in 2013 [51]. The TBS compared the perinatal outcomes in women with dichorionic-diamniotic twin pregnancies (DCDA) or monochorionic-diamniotic twin pregnancies (MCDA), in which the first twin was in cephalic presentation at 32 weeks' gestation or later, according to the expected mode of delivery - vaginal vs caesarean section. The results indicated that a planned caesarean section did not significantly decrease or increase the risk of perinatal death or severe neonatal morbidity, compared to a planned vaginal delivery (2.2% vs. 1.9%,  $p = 0.49$ ). Similarly, the rate of maternal death or severe short-term maternal morbidity was not significantly different between the groups, confirming the safety of both modes of delivery in twin pregnancies with the study criteria.

It is important to note that women with twin pregnancies that delivered before 32 weeks gestation were not included in the TBS, which makes the evidence regarding the optimal mode of delivery in these gestations less clear. However, there are data from large retrospective studies of twins born <32 weeks' gestation showing that there is no difference in the risk of adverse neonatal outcomes between a vaginal delivery and a primary caesarean section [52,53]. So, planned vaginal delivery appears to be as safe as planned caesarean section in twin pregnancies and, in cases where delivery is indicated, the option of induction of labour should be considered.

### **Rate of induction of labour in twin pregnancies**

Of the nearly 130 million births that occur worldwide every year, approximately 10% are the result of induction of labour [54], and this proportion has increased in recent decades. Moreover, labour induc-

tion rates vary widely between countries [55], reaching 20-30% in the US, Canada, and the UK [25,56,57]. However, data regarding labour induction rates, particularly in twin pregnancies, are limited and few studies have been published that have examined this issue more than two decades ago. In Australia, the overall rate of induction of labour in twin pregnancies between 1990 and 1999 was 25%, and most of these cases (19-21%) occurred at term (37 weeks gestation) [58]. In the United States, the rate of induction of labour in twin pregnancies increased almost 2.5 times, from 5.8% in 1989 to 13.7% in 1999 [59]. In France, the labour induction rate reported in a single centre was 25% between 1993 and 1998 [60]. In contrast, lower rates of induction of labour have been reported in the preterm period (<37 weeks' gestation), ranging from 5% to 8.6% [58,61]. While labour induction rates in twin pregnancies appear to be like those reported for singles, there are no studies directly comparing labour induction rates between twins and single pregnancies within the same setting.

### **Possible differences in induction of labour between single and twin pregnancies**

Several observations raise the possibility that the success rate and safety of inducing labour in twin pregnancies may be different from single pregnancies.

Oxytocin, which is crucial for labour, is a non-peptide hormone secreted mainly by the posterior pituitary gland [62]. Its concentration in maternal plasma increases towards term but does not change significantly before and during labour [63]. Around the onset of labour, uterine sensitivity to oxytocin increases significantly due to increased myometrial expression of oxytocin receptors [64-66]. The elon-

gation of the human myometrium in vitro has been linked to the up-regulation of contraction-associated proteins such as cyclooxygenase 2 (COX-2) [67] and the oxytocin receptor [68], pro-inflammatory factors such as interleukin-8 [69], as well as the release of cytokines from the myometrium [70], which are key inflammatory mediators involved in the onset of labour.

Considering the potential differences between twin and single pregnancies, it has been shown that excessive uterine distention and early activation of contractile pathways may be greater in twins because of increased uterine volume. In studies of myometrial function, there are small but significant differences between samples from twin and single pregnancies, including an increased response to oxytocin [71] and an altered response to specific tocolytic agents and progesterone when uterine contractions were stimulated with oxytocin [72,73]. These results suggest that there may be differences in the expression pattern of a few proteins associated with uterine contractions and the modulation of these proteins in twins.

In agreement with these results, one study demonstrated differences in the frequency and duration of uterine contractions between twin and single pregnancies, in addition to a greater response to oxytocin in twins [74]. These differences may influence maternal receptivity to induction of labour in twin pregnancies, although fetal factors (such as fetal size and the risk of having a non-reassuring FHR in response to uterine contractions) may also contribute to the outcome of labour induction in twins [5,75-78].

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Another possible factor that may contribute to discrepancies in labour induction outcomes between twin and single pregnancies is the cervical factor.

There is some evidence that a shorter cervical length is associated with a higher probability of successful induction of labour [79-81]. Therefore, the evidence that twin pregnancies are associated with a shorter cervical length on average per gestational week than single pregnancies [82,83], may result in a higher rate of successful induction of labour in twin pregnancies [84]. Indeed, in studies comparing labour induction between twin and single pregnancies, Bishop's score was higher in twin pregnancies, reflecting a more mature cervix prior to labour induction [5,85].

At the same time, it is possible that the probability of successful induction of labour is influenced by other factors, such as gestational age at the time of induction. Several studies have reported that the likelihood of successful cervical ripening and induction of labour is inversely correlated with gestational age, and that the risk of failure to induce labour during the preterm period is greater than in cases of induction of labour at term [86-88]. Therefore, induction of labour in twin pregnancies is likely to occur at an earlier gestational age than in singleton pregnancies, resulting in a lower rate of successful induction of labour in twins.

These observations suggest that the data on induction of labour in single pregnancies cannot be used for twins and that specific studies on twins are needed to determine the success rate, safety, and prognostic factors for induction of labour in twin pregnancies.

## Success rate of induction of labour in twin pregnancies

The main objective of labour induction is to facilitate vaginal delivery. However, pregnant women undergoing induction of labour should be aware of the potential risk of induction failure and the need for an unplanned caesarean section, which may be associated with less favorable outcomes than a planned one [33,89].

The cesarean section rate after induction of labour in twins varies considerably between studies (7%-46%). This variability can be partially explained by differences between trials with respect to study population and induction protocols [6,28,29,31-42,84,90-92] (Table 1).

Only a few studies have compared the risk of caesarean section after induction of labour in twins compared to single pregnancies. Loscul et al. compared the risk of caesarean section between 1995 twin pregnancies and 2771 single pregnancies during induction of labour and found that the caesarean section rate was higher in the twin pregnancy group (23.0% vs. 19.4%,  $P = 0.002$ ; aOR = 1.8, 95% CI 1.4-2.2) [5]. Similarly, Okby et al. reported a higher rate of caesarean section in cases of labour induction in twin pregnancies compared to single pregnancies (31.2% vs. 17.1%,  $P < 0.001$ ; OR = 2.2, 95%-CI 1.76-2.73) [6]. In contrast, a cohort study by Taylor et al. found no significant differences between the two groups, although it was based on a relatively small cohort of approximately 100 pregnant in each group [30].

A retrospective cohort study by Krispin et al. evaluated the association of chorionicity with the mode of delivery after induction of labour in twins and found comparable high rates of vaginal deliveries among pregnant DCDA (92.1%) and MCDA (94.2%) twins [92].

**Table 1 - Summary of studies on labour induction in twin pregnancies**

References	Study design	Induction method	Group case (n=pregnancy)	Control group (n=pregnancy)	Rate C-section in group case (%)	Rate C-section in control group (%)	C-section risk factors	Comments and limits
<b>Induction of labour in twin vs. single pregnancies</b>								
[5] Loscul et al.	Multicentre retrospective	Oxytocin Prostaglandins Cook balloon	1995 induced twins	2771 single pregnancies	459 (23%)	537 (19.4%)	-Twins -Induction method -Age > 35 -BMI > 25 -Nulliparity -Bishop <6	-Large cohort -Unknown chorionicity -No details of other maternal complications
[6] Okby et al.	Monocentric retrospective	Unknown	191 induced twins	25722 single pregnancies	60 (31.2%)	4398 (17.1%)	-Twins -Gestational age -Maternal age -Nulliparity -Hypertension -Gestational diabetes	-Bishop unknown -Unknown chorionicity -More blood transfusions in twins -No details about induction methods
[27] Fausett et al.	Monocentric retrospective	Oxytocin	62 induced twins	62 single pregnancies	6 (10%)	6 (10%)		-No distinction between induction of labour and augmentation -High Bishop before induction -Unknown chorionicity
[28] Manor et al.	Monocentric perspective	Cook balloon	17 induced twins		2 (11.8%)			-Limited cohort -No control group
[30] Taylor et al.	Monocentric retrospective	Oxytocin Prostaglandins Cook balloon	100 induced twins	100 single pregnancies	19 (19%)	21 (21%)	-Maternal age -Nulliparity -Cervical dilation	-Limited cohort -No sub-analysis according to induction method

Induzione del travaglio vs taglio cesareo elettivo nelle gravidanze gemellari								
[31] Dougan et al.	Multicentre TBS secondary analysis	Unknown	409 induced twins	938 twins with elective C-section	169 (41.3 %)	N/A		-Secondary analysis -Bishop unknown -No sub-analysis according to induction method -Similar neonatal outcomes -More composite maternal outcomes in induction
[32] Zaffman et al.	Monocentric retrospective	Cook balloon Oxytocin	212 induced twins	241 twins with elective C-section	62 (29.2 %)	N/A		-Similar neonatal outcomes -Minor composite maternal outcomes in induction -Distinction between term and preterm induction
[33] Grossman et al.	Monocentric retrospective	Dinoprostone Cook balloon Oxytocin	105 induced twins	106 twins with elective C-section	41 (39%)	N/A		-More composite maternal outcomes in induction -Bishop unknown -No sub-analysis according to induction method
[40] Simoes et al.	Monocentric retrospective	Oxytocin Prostaglandins	69 induced twins	116 twins with elective C-section	16 (23.2 %)	N/A		-Bishop unknown
Induction of labour in twin pregnancies by specified induction methods								
[29] Huber et al.	Monocentric retrospective	Prostaglandins	154 induced twins with misoprostol	32 twins induced with dinoprostone	71 (46.1 %)	14 (43.7 %)		-Limited cohort -Bishop unknown
[35] Meidan et al.	Multicentre TBS secondary analysis	Prostaglandins No Prostaglandins	153 induced twins with prostaglandins	215 twins induced without prostaglandins	62 (40.5 %)	87 (40.5 %)	-Age > 30 -Nulliparity -Second twins no cephalic -National rate of PMR >10/1000	-Secondary analysis -Bishop unknown -No differences between maternal and fetal outcomes
[41] Bush et al.	Monocentric retrospective	Oxytocin Prostaglandins	57 induced twins with prostaglandins	77 twins induced with oxytocin	18 (31.6 %)	13 (16.9 %)		-Limited cohort -No differences between fetal outcomes

Induction of labour versus expectant management in twin pregnancies								
[34] Suzuki et al.	Monocentric RCT	Prostaglandins	17 induced twins	19 treated with wait-and-see management	3 (18%)	6 (32%)		-Limited cohort
[37] Hamou et al.	Monocentric retrospective		653 induced twins		124 (19%)	1452 (49.4%)	-Age	-Bishop unknown
[38] Travares et al.	Monocentric retrospective	Dinoprostone Oxytocin	33 induced twins	42 twins with spontaneous labour	20 (60.6%)	10 (23.9%)	-Induction of labour	-Limited cohort -No differences between fetal outcomes
[39] Jonsson	Monocentric retrospective	Oxytocin Prostaglandins Cook Balloon Amniotomy	220 induced twins	242 with spontaneous labour	47 (21.4%)	30 (12.4%)	-Maturation required -Induction of labour -Age>35 -Nulliparity	
[42] Harle et al.	Monocentric retrospective	Oxytocin Prostaglandins Cook Balloon	36 induced twins	45 treated with wait-and-see management	3 (8.3%)	6 (13.3%)		-Limited cohort -Bishop unknown -No differences between maternal and fetal outcomes
Induction of labour in dichorionic vs. monochorionic twin pregnancies								
[92] Krispin et al.	Monocentric retrospective	Oxytocin Cook Balloon Amniotomy	203 induced dichorionic twins	87 induced monochorionic twins	16 (7.89%)	5 (5.75%)		- Bishop unknown

### Prognostic factors for induction of labour in twin pregnancies

The identification of factors associated with the success or failure of labour induction is crucial for better counselling and risk stratification in choosing the best mode of delivery in cases where delivery is indicated. factors including increased maternal body mass index (BMI) [99,102,103], increased gestational weight [104], gestational age <37 weeks [105], late maternal age [106] and hypertensive disorders of pregnancy, as an indication for induction of labour, [107] were found to be associated with an increased risk of labour induction failure, although not consistently in all studies.

In single pregnancies, several studies have identified certain predictive factors for caesarean section after induction of labour [93-96]. While some factors such as multiparity [97-99], a favorable Bishop score [75,76,100], fetal weight, maternal height and the presence of diabetes [101] are well established as predictors of successful induction of labour, other an intrapartum caesarean section. In contrast, data on risk factors for labour induction failure in twin pregnancies are relatively limited (Table 2). Among the 2804 pregnant women included in the Twin Birth Study [31], 409 underwent induction of labour, and of these, 169 (41%) underwent an intrapartum caesarean section.



Nulliparity, advanced maternal age, high local perinatal mortality rate and non-cephalic presentation of the second twin were found to be independently associated with caesarean section [35]. Similarly, Razavi et al. retrospectively studied factors associated with successful induction of labour in twin pregnancies at >24 weeks' gestation and found that multiparity and maternal age <35 years were associated with successful vaginal delivery [90].

Finally, Han et al. [84], in an attempt to develop a model based on clinical and ultrasound parameters to predict the risk of caesarean section after induction of labour in twin pregnancies near term (> 35 weeks gestation), found that maternal height, parity and cervix length were independently associated with the risk of caesarean section with good confidence. Other factors reported to be associated with successful induction of labour in twin pregnancies include lower maternal BMI [91] and obstetric physician experience [108].

Predictive factor	References
Maternal age < 30 years	Mei-Dan et al [35]
Maternal age < 35 years	Razavi et al. [90]
Multiparity	Mei-Dan [35] and Razavi [90]
Higher maternal height	Han et al. [84]
Low maternal BMI	Park et al. (91]
Decreased cervix length	Han et al. [84]
Cephalic presentation of the second twin	Mei-Dan et al. [35]
Low local perinatal mortality rate	Mei-Dan et al. [35]
Excellent doctor's experience	Park et al. [91]

**Table 2- Predictive factors for favourable labour induction in twin pregnancies**

### Safety of induction of labour and perinatal outcome in twin pregnancies

Data on the association between induction of labour and adverse maternal and perinatal outcomes are conflicting: this is partly due to variation between studies about factors such as indication for induction of labour, method of induction of labour and choice of control group (spontaneous onset of labour, planned caesarean section or expectant management) [31,32,34,37-39,109,110].

When induction of labour is medically indicated (as opposed to elective labour induction performed for post-term pregnancies or by maternal request), the reasonable alternative would be a planned caesarean section. Indeed, several studies have compared the risk of maternal complications between women in twin pregnancies undergoing labour induction and those undergoing planned caesarean section [31-33]. While one study reported a lower risk of maternal morbidity in the group undergoing induction of labour [32], the other two studies found a planned caesarean section to be safer for the mother [31,33].

In a secondary analysis of TBS, 409 women undergoing induction of labour were compared with 938 women undergoing a planned caesarean section [31]. The risk of perinatal mortality or severe neonatal morbidity was similar between those having a planned caesarean section and those having undergone induction of labour (1.7% vs. 2.0%,  $p = 0.61$ ). However, the risk of maternal mortality and morbidity was lower in the planned caesarean section group than in the labour induction group (7.3% vs. 11.3%;  $p = 0.01$ ; aOR 0.6 (95%-CI 0.4-0.9)), mainly due to a lower rate of haemorrhage in the caesarean section group (6.2% vs. 9.6%,  $p = 0.02$ ), defined as: 1500 ml blood loss, need for blood transfusion or



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need for dilatation and curettage after delivery. Similarly, in a small retrospective study comparing

women with a twin pregnancy undergoing induction of labour (n = 105) or planned caesarean section (n = 106), the risk of adverse maternal outcome (defined as severe postpartum haemorrhage - blood loss >1500 cc, hysterectomy, transfusion, intensive care unit admission, use of multiple uterotonic drugs, or maternal death) was considerably lower in the planned caesarean section group (11.3% vs. 30.5%, p = 0.001) [33]. The increased risk of maternal complications in pregnant women undergoing induction of labour is mainly determined by the subgroup of women undergoing urgent intrapartum caesarean section, which is associated with less favorable maternal and neonatal outcomes compared to successful vaginal delivery or planned caesarean section [33,90].

Since the rate of labour induction failure in twin pregnancies appears to be higher than in single pregnancies, this possibility should be discussed with patients when labour induction counselling is performed. In addition, physicians should pay attention to early signs of failure of labour progression or deterioration of fetal well-being, to avoid performing caesarean sections when fetal compromise has already occurred.

### **Methods of induction of labour**

The methods currently available for induction of labour in twin and single pregnancies can be divided into two main categories depending on the state of the cervix prior to induction of labour: cervical ripening agents (prostaglandin analogues, balloon catheters) and favorable cervix induction methods (e.g.

amniotomy, oxytocin) [5,28,29,35,39,40,42,111-113].

### **Prostaglandin analogues (PG)**

In case of an unfavorable cervix (usually defined as a Bishop score <6 or <8 [114,115]), two types of prostaglandins can be used for maturation purposes [96,106,113,116-118]: PGE1 (i.e., misoprostol) and PGE2 [113,119]. However, few studies are available on the efficacy and safety of these agents in twin pregnancies. Simoes et al. evaluated the use of 100 mcg of oral misoprostol for induction of labour in nulliparous pregnant women with a twin pregnancy nearing term (>35 weeks) compared to those who had a caesarean section and found that induction of labour was successful (defined as vaginal delivery of at least one twin) in approximately 80% of cases [40], and was associated with a shorter duration of neonatal hospitalization.

Unlike PGE1 agents that can be administered by various ways (sublingually, intravaginally, orally), PGE2 analogues (dinoprostone) are only administered intravaginally. A small retrospective study compared the efficacy and safety of oral misoprostol versus vaginal dinoprostone for induction of labour in 186 pregnant women with twin pregnancies at > 34 weeks gestation (154 had been induced with misoprostol and 32 with dinoprostone). There were no differences between the groups about the success rate of vaginal delivery (54% vs. 56%), the average interval between induction of labour and delivery (30 h vs. 27 h) and neonatal outcomes [29]. It appears that, according to the limited data available, oral misoprostol and vaginal dinoprostone are equally effective and safe for cervical ripening in twin

pregnancies.

### **Cervical Balloon catheter**

The balloon catheter is considered one of the safest methods for cervical ripening compared to other procedures, without compromising its efficacy [113,120]. As in the case of prostaglandins, scientific evidence regarding the use of the balloon catheter for cervical ripening in twin pregnancies is limited. Maniero et al. reported a small case series of 17 twin pregnancies at 36-42 weeks gestation undergoing cervical maturation by balloon catheter with (n = 4) or without (n = 13) concomitant oxytocin infusion [28]. Vaginal delivery was obtained in 15 (88%) cases and in 80% delivery occurred within 24 h of catheter insertion. All newborns had a 5-minute Apgar score of 10. The authors concluded that the balloon catheter appears to be safe and effective for cervical maturation in twin pregnancies.

### **Oxytocin**

Leroy et al., in one of the first studies on the use of oxytocin for induction and acceleration of labour in twin pregnancies [112], described the use of oxytocin in 145 twin pregnancies in the years 1948 and 1977. Oxytocin was found to be safe, with lower rates of perinatal mortality for both first and second twins compared to non-use of oxytocin.

A more recent study involving 62 twins and 62 single pregnancies found that multiple pregnancies did not affect the efficacy of oxytocin for induction and acceleration of labour [27]. In addition, uterine tachysystole and non-reassuring fetal heart rate were less frequent in the twin pregnancy group [27]. In contrast to single pregnancies, studies comparing

different oxytocin administration regimens for induction of labour in twin pregnancies are lacking. Therefore, it seems reasonable to apply the standard protocols for induction of labour used in single pregnancies to twins as well [121-123].

### **Particular conditions**

Several studies have confirmed that trial labour after a previous caesarean section (TOLAC) is also a safe option in twin pregnancies [12-127]. However, while data on single pregnancies suggest that induction of labour may be associated with a small increase in the risk of uterine rupture [128], little is known about the safety of induction of labour in twin pregnancies in a uterus that has undergone a previous hysterotomy. There is some evidence that the risk of uterine rupture is higher in cases of TOLAC in twin pregnancies than in single pregnancies [129].

Another clinical situation for which there are limited data in twin pregnancies is induction of labour in the early preterm period. While in single pregnancies early gestational age is associated with a failure to induce labour [87,130,131], it is unclear whether the same applies to twin pregnancies.

Considering the limited data on induction of labour in DCDA twin pregnancies compared to MCDA [92], we recommend that uncomplicated MCDA twin pregnancies should be managed like DCDA twin pregnancies about induction of labour.

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