Induction of Labour in Growth Restricted and Small for Gestational Age Foetuses – A Historical Cohort Study

Ist die Geburtseinleitung bei intrauteriner Wachstumsrestriktion und Small-for-gestational-Age-Feten problematisch? Eine historische Kohortenstudie

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ABSTRACT

Purpose Induction of labour for small-for-gestational-age (SGA) foetus or intrauterine growth restriction (IUGR) is common, but data are limited. The aim of this study was therefore to compare labour induction for SGA/IUGR with cases of normal foetal growth above the 10th percentile.

Material and Methods This historical multicentre cohort study included singleton pregnancies at term. Labour induction for SGA/IUGR (IUGR group) was compared with cases of foetal growth above the 10th percentile (control group). Primary outcome measure was caesarean section rate.

Results The caesarean section rate was not different between the 2 groups (27.0 vs. 26.2%, p = 0.9154). In the IUGR group, abnormal CTG was more common (30.8 vs. 21.9%, p = 0.0214), and foetal blood analysis was done more often (2.5 vs. 0.5%, p = 0.0261). There were more postpartum transfers to the NICU in the IUGR group (40.0 vs. 12.8%, p < 0.0001), too.

Conclusion Induction of labour for foetal growth restriction was not associated with an increased rate of caesarean section.

ZUSAMMENFASSUNG

Ziel Die Datenlage zu Geburtseinleitungen bei einem Small-for-gestational-Age-Fetus (SGA-Fetus) oder einer intrauterinen Wachstumsrestriktion (IUGR) ist limitiert, sodass das Ziel dieser Untersuchung war, Geburtseinleitungen bei SGA-/IUGR-Feten mit Geburtseinleitungen bei Schwangerschaften mit einem fetalen Schätzgewicht oberhalb der 10. Perzentile zu vergleichen.

Material und Methodik In diese multizentrische Kohortenstudie wurden Einlingsschwangerschaften am Termin eingeschlossen. Geburtseinleitungen bei SGA-/IUGR-Feten (IUGR-Gruppe) wurden mit Geburtseinleitungen bei Feten mit einem fetalen Schätzgewicht oberhalb der 10. Perzentile (Kontrollgruppe) verglichen. Der primäre Zielparameter war die Kaiserschnittrate.

Ergebnisse Es gab keinen Unterschied bezüglich der Kaiserschnittrate zwischen den beiden Gruppen (27,0 vs. 26,2 %, p = 0,9154). In der IUGR-Gruppe lag jedoch häufiger ein pathologisches CTG (30,8 vs. 21,9 %, p = 0,0214) vor, und es wurden mehr Fetalblutanalysen (2,5 vs. 0,5 %, p = 0,0261) durchgeführt. Die Rate an kindlichen Verlegungen in die Kinderklinik war ebenfalls in der IUGR-Gruppe höher (40,0 vs. 12,8 %, p < 0,0001).

Schlussfolgerung Geburtseinleitungen bei wachstumsrestringierten Feten sind nicht mit einer höheren Rate an Kaiserschnitten assoziiert.

Introduction

Reduced foetal growth requires special monitoring during pregnancy. It is important to differentiate between foetuses which are constitutionally small (small for gestational age; SGA) and growth restricted foetuses (intrauterine growth restriction, IUGR), although there is no universal international definition. According to the Royal College of Obstetricians and Gynaecologists (RCOG), the term SGA is used to describe a foetus with a foetal abdominal circumference of less than the 10th percentile or a foetal estimated weight which is below the 10th percentile [1]. However, the American College of Obstetricians and Gynaecologists refers to an estimated weight lower than the 10th percentile as foetal growth restriction [2]. In a survey, a number of experts voted on the parameters which should be used to diagnose foetal growth restriction. Foetal abdominal circumference and foetal estimated weight which is less than the 3rd percentile were the dominant parameters for both early and late IUGR. Pathological Doppler sonography of the umbilical artery was additionally considered to be a relevant characteristic for early IUGR [3]. A higher rate of intrauterine foetal death has been reported for both SGA and IUGR foetuses [4, 5] along with increased perinatal morbidity and mortality [6], making it often necessary to end the pregnancy at an early stage [6]. If ending the pregnancy is indicated, it is important to weigh up the respective benefits and disadvantages of primary caesarean section versus attempting vaginal delivery though the induction of labour. Although inducing labour is not possible in the early weeks of pregnancy, it becomes an option when the pregnancy is close to or at term. The DIGITAT trial showed that inducing labour for IUGR is possible without increasing the rate of surgical deliveries and without short-term negative neonatal outcomes [7]. Prostaglandins are effective at inducing labour and are superior to oxytocin for inducing labour if the cervix is still immature, but uterine overstimulation is a well-known side effect [8]. Foetuses which are already suffering from chronic nutritional deficits are particularly at risk from this approach; however, data on the induction of labour for SGA/IUGR foetuses is limited. This study therefore aimed to compare the outcomes after inducing labour in growth-restricted and non-growth-restricted foetuses at term.

Material and Methods

Term singleton pregnancies born in the Department of Gynaecology and Obstetrics of Erlangen University Hospital 2011–2015) and Mannheim University Hospital (2010–2013) were included in this historical cohort study. Exclusion criteria were a prior history of caesarean section, breech presentation, premature rupture of membranes, intrauterine foetal death and structural or chromosomal anomalies. Gestational age was calculated based on the date of the last menstruation; the calculation was reviewed in the first trimester using the crown-rump length and corrected if necessary [9]. The induction of labour in pregnancies with an SGA/IUGR foetus (IUGR group) was compared with the induction of labour in pregnancies with eutrophic foetuses (control group). SGA/IUGR foetuses were defined according to the criteria of the DIGITAT trial [7] and consisted of foetuses with a foetal abdominal circumference and/or a foetal estimated weight of less than the 10th percentile and/or a levelling off of the percentile growth trajectory ("crossing of percentiles") with or without pathological Doppler sonography or oligohydramnios. A Bishop score was calculated prior to inducing labour. Labour was induced pharmacologically (dinoprostone, misoprostol), mechanically (double balloon catheter) or by the sequential use of mechanical and pharmacological methods (double balloon catheter und misoprostol/dinoprostone).

The primary outcome measure was the caesarean section rate. Secondary outcome measures included the induction-to-delivery interval in vaginal deliveries, the number of vaginal births within 24 or 48 hours, the number of unsuccessful inductions of labour (defined as no delivery within 72 hours), arterial umbilical blood pH, base excess (BE), Apgar score at 5 minutes, pathological CTG and the rate of transfers to a paediatric unit.

Statistical analysis

All statistical analyses were done with the SAS statistical software package (release 9.4, SAS Institute Inc., Cary, North Carolina, USA).

Qualitative variables are given as absolute and relative frequencies. The respective means and standard deviations were calculated for quantitative, approximately normally distributed characteristics. Quantitatively discrete data and ordinal data are given as medians and ranges.

T-test was used to compare two means (of approximately normally distributed data). Mann-Whitney U-test was used to compare other distributions. Relative frequencies were compared using Chi^2 test. Fisher's exact test was used if the conditions for Chi^2 test were not met.

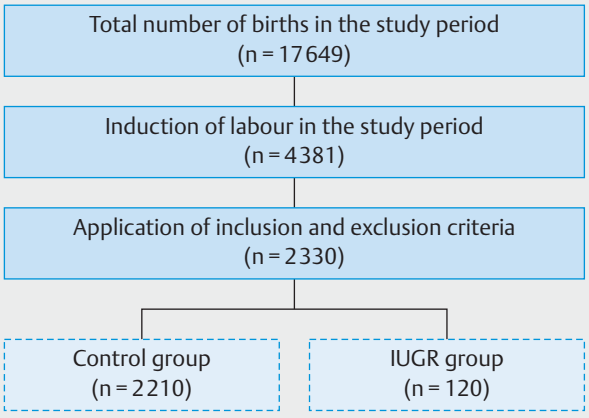
The results were considered significant if the p-value was less than 0.05.

Results

A total of 17 649 births occurred during the study period; 4381 of these births (24.8 %) were induced. After taking the inclusion and exclusion criteria into account, a total of 2330 cases were included

in this study: 120 women with an SGA/IUGR foetus and 2210 women with a eutrophic foetus with no indications of nutritional deficits (▶ **Fig. 1**).

Demographic characteristics are shown in ▶ **Table 1**. There was a significant difference between the two groups with regard to most parameters: patients with an SGA/IUGR foetus were younger (30.5 ± 5.4 vs. 28.7 ± 5.7, p = 0.0005), smaller (166 ± 6.6 vs. 163.9 ± 6.7, p < 0.0001), lighter (85.8 ± 17.0 vs. 75.3 ± 14.0, p < 0.0001) and had a lower body mass index (30.8 ± 5.6 vs. 28.0 ± 5.0, p < 0.0001). The gestational age at delivery was lower (283.5 ± 7.7 vs. 272.7 ± 8.6, p < 0.0001), the birth weight was lower (3534.6 ± 445.0 vs. 2519.8 ± 324.2, p < 0.0001) and the Bishop score was slightly lower (2 [0–6] vs. 1 [0–6], p = 0.0021). Although there were more pregnant women with gestational diabetes in the control group (17.3 vs. 7.5%, p = 0.0052), there were more cases with anhydramnios/oligohydramnios in the IUGR group (5.8 vs. 15.8%, p < 0.0001). Labour was induced more often with misoprostol in the control group (43.1 vs. 21.7%, p < 0.0001),



▶ **Fig. 1** Flow chart.

▶ **Table 1** Demographic data of the control and the IUGR groups.

Parameters	Control group (n = 2210)	IUGR group (n = 120)	p-value
Age (years)	30.5 ± 5.4	28.7 ± 5.7	0.0005
Height (cm)	166.8 ± 6.6	163.9 ± 6.7	< 0.0001
Weight (kg)	85.8 ± 17.0	75.3 ± 14.0	< 0.0001
Body mass index	30.8 ± 5.6	28.0 ± 5.0	< 0.0001
Gravidity	1 (1–14)	1 (1–9)	0.0834
Parity	0 (0–9)	0 (0–4)	0.0237
Gestational age (days)	283.5 ± 7.7	272.7 ± 8.6	< 0.0001
Birth weight (grams)	3534.6 ± 445.0 (n = 2196)	2519.8 ± 324.2	< 0.0001
Bishop score	2 (0–6)	1 (0–6)	0.0021
Hypertensive disorder of pregnancy (n, %)	209 (9.5%)	15 (12.5%)	0.2708
Gestational diabetes (n, %)	382 (17.3%)	9 (7.5%)	0.0052
Cholestasis of pregnancy (n, %)	37 (1.7%)	2 (1.7%)	1.0000
IUGR			
▪ estimated weight < 3rd percentile		45 (37.5%)	–
▪ umbilical artery (PI > 95th percentile) (n, %)		8 (6.7%)	–
▪ ARED flow (n, %)		1 (0.8%)	–
▪ MCA (PI < 5th percentile (n, %)		2 (1.7%)	–
▪ CPR < 1.0 (n, %)		12 (10.0%)	–
▪ anhydramnios, oligohydramnios (n, %)	129 (5.8%)	19 (15.8%)	< 0.0001
Method used to induce labour			
▪ balloon catheter	197 (8.9%)	14 (11.7%)	0.3062
▪ balloon catheter – dinoprostone	14 (0.6%)	4 (3.3%)	0.0117
▪ balloon catheter – misoprostol	796 (36.0%)	58 (48.3%)	0.0064
▪ balloon catheter – misoprostol – dinoprostone	14 (0.6%)	2 (1.7%)	0.1978
▪ dinoprostone	149 (6.7%)	14 (11.7%)	0.0394
▪ dinoprostone – misoprostol	87 (3.9%)	2 (1.7%)	0.3228
▪ misoprostol	953 (43.1%)	26 (21.7%)	< 0.0001

Data are presented as median (range) or mean with standard deviations; a p-value of < 0.05 is considered statistically significant. PI: pulsatility index; ARED: absent or reversed end-diastolic; CPR: cerebroplacental ratio; MCA: middle cerebral artery

▶ **Table 2** Indications for inducing labour.

Indications	Control group (n = 2210)	IUGR group (n = 120)	p-value
Post-term pregnancy ≥ 41 + 0 GW	1173 (53.6%)	5 (4.2%)	< 0.0001
Gestational diabetes	244 (11.1%)	0	0.0001
Maternal request	205 (9.4%)	3 (2.5%)	0.0106
Anhydramnios, oligohydramnios	129 (5.9%)	2 (1.7%)	0.0514
Suspicion of macrosomia	61 (2.8%)	0	0.0732
Decline in foetal movement	26 (1.2%)	2 (1.7%)	0.6543
IUGR, placental insufficiency, pathological Doppler sonography	36 (1.6%)	90 (75.0%)	< 0.0001
Pre-eclampsia, hypertensive disorder of pregnancy, HELLP syndrome	158 (7.2%)	12 (10.0%)	0.2552
Pathological CTG	56 (2.6%)	1 (0.8%)	0.3647
Cholestasis of pregnancy	36 (1.6%)	2 (1.7%)	1.0000
Other	66 (3.0%)	3 (2.5%)	1.0000

Data are presented as absolute or relative frequencies; p-values < 0.05 are considered statistically significant. CTG: cardiotocography

while dinoprostone was used more often in the IUGR group (6.7 vs. 11.7%).

▶ **Table 2** shows the indications for inducing labour. In the control group, labour was induced more often for post-term pregnancy ≥ 41 + 0 GW (53.6 vs. 4.2%, p < 0.0001) and gestational diabetes (11.1 vs. 0%, p = 0.0001) and on maternal request (9.4 vs. 2.5%, p = 0.0106). In the IUGR group, labour was more likely to be induced for IUGR, placental insufficiency or pathological Doppler sonography (1.6 vs. 75%, p < 0.0001).

The outcome parameters of the total population are given in ▶ **Table 3**. There was no difference between the two groups with regard to birth procedure (p = 0.9154). Caesarean section was required in around one quarter of cases (26.2 vs. 27%). Similarly, there were no real differences in the induction-to-labour interval (1580 vs. 1676 minutes, p = 0.4317), the rate of vaginal births within 24 hours (44 vs. 39%, p = 0.3242), the rate of vaginal births within 48 hours (83 vs. 85%, p = 0.6178) and the rate of unsuccessful inductions of labour (5 vs. 2%, p = 0.3177) between the two groups.

The rate of pathological CTGs was higher in the IUGR group (22 vs. 31%, p = 0.0214), and foetal blood analysis was also carried out more often in the IUGR group (0.5 vs. 2.5%, p = 0.0261). Umbilical blood pH values and Apgar scores were similar for both groups, only the rate of umbilical blood BE values of ≤ 12 was higher in the IUGR group (1.1 vs. 3.4%, p = 0.0462). The neonates in the IUGR group were more likely to require transfer to a paediatric unit post partum (13 vs. 40%, p < 0.0001). Epidural anaesthesia was less common in the IUGR group (41 vs. 32%, p = 0.0438).

▶ **Table 4** shows the outcome parameters after stratification for parity. The previously calculated significant differences between groups, such as the rate of pathological CTGs, foetal blood analysis, post partum transfers to a paediatric unit, umbilical blood BE values of ≤ 12, and epidural anaesthesia, were only found for primiparae and not for multiparae.

Discussion

This study compared outcomes after the induction of labour for growth-restricted foetuses at term with the induction of labour with non-growth-restricted foetuses, as it has often been suggested that inducing labour when foetuses are SGA/IUGR is associated with a higher rate of complications [10]. The results obtained in our study were unable to confirm that the rate of surgical deliveries would increase in this high-risk population. The rate of caesarean sections did not differ between the two groups (p = 0.9154). This is particularly remarkable because the Bishop score was lower in the IUGR group, and dinoprostone was used more often than misoprostol to induce labour. Inducing labour with misoprostol is associated with lower caesarean section rates than dinoprostone [11].

It should be noted, however, that pregnancies with severe foetal growth restriction had already been terminated in the early weeks of pregnancy. Nevertheless, inducing labour for IUGR foetuses at term requires special monitoring: the rate of pathological CTGs and rate of foetal blood analyses were higher in primiparae compared to non-growth-restricted foetuses. But this was not associated with poorer umbilical blood pH values or Apgar scores. No significant differences were found between the two multiparae groups, which indicates that prostaglandins can be used to manage IUGR foetuses and have a good safety profile [12].

Our results correspond to the findings of the DIGITAT trial. The DIGITAT trial compared 321 inductions of labour in term IUGR foetuses with 329 IUGR pregnancies managed expectantly. Neither the long-term nor the short-term outcomes were any worse in the induced labour cohort [7, 13]. Another small randomised controlled trial reported that only one out of 46 inductions of labour in IUGR foetuses presented with overstimulation and CTG abnormalities [14].

Nevertheless, the induction of labour in growth-restricted foetuses should be carried out in centres with an affiliated neonatology unit, as recommended in the guideline on "Intrauterine

▶ **Table 3** Outcome parameters.

Outcome parameters	Control group (n = 2210)	IUGR group (n = 120)	p-value
Birth procedure (n, %)			0.9154
▪ spontaneous delivery	1402 (63.4%)	77 (64%)	
▪ operative vaginal delivery	229 (10.4%)	11 (9%)	
▪ caesarean section	579 (26.2%)	32 (27%)	
Induction-to-labour interval (min)*	1580.0 (97–13.975)	1676.5 (371–6306)	0.4317
Vaginal birth within 24 hours (n, %)**	717 (44.0)	34 (38.6%)	0.3242
Vaginal birth within 48 hours (n, %)**	1356 (83.2%)	75 (85.2%)	0.6178
Unsuccessful induction of labour (no birth within 72 hours; n, %)**	86 (5.3%)	2 (2.3%)	0.3177
Arterial umbilical blood pH < 7.05 (n, %)	13 (0.6%)	1 (0.8%)	0.5247
Arterial umbilical blood pH < 7.10 (n, %)	43 (1.9%)	2 (1.7%)	1.0000
BE ≤ 12 (n, %)	23 (1.1%)	4 (3.4%)	0.0462
Apgar score at 5 min < 7 (n, %)	23 (1.0%)	2 (1.7%)	0.3692
BE ≤ 12 and Apgar score at 5 min < 7 (n, %)	5 (0.2%)	0	1.0000
Pathological CTG (n, %)	483 (21.9%)	37 (30.8%)	0.0214
Foetal blood analysis (n, %)	10 (0.5%)	3 (2.5%)	0.0261
Epidural anaesthesia (n, %)	906 (41.3%)	38 (31.9%)	0.0438
Oxytocin (n, %)	959 (43.9%)	47 (39.5%)	0.3509
Green amniotic fluid (n, %)	407 (18.4%)	17 (14.2%)	0.2400
Amniotic infection syndrome (n, %)	3 (0.1%)	0	1.0000
Postpartum transfer to a paediatric unit (n, %)	282 (12.8%)	48 (40.0%)	< 0.0001
Respiratory adaptation disorder (n, %)	84 (30.1%)	11 (23.4%)	0.3311
Hyperbilirubinaemia (n, %)	6 (2.2%)	0	0.5983
Hypoglycaemia (n, %)	61 (21.9%)	19 (49.4%)	0.0062
SGA (n, %)	0	9 (19.1%)	< 0.0001
Suspicion of infection (n, %)	89 (31.9%)	1 (2.1%)	< 0.0001
Other (n, %)	39 (14.0%)	7 (14.9%)	0.8676
Neonatal infection (n, %)	81 (3.7%)	2 (1.7%)	0.4413
Puerperal endometritis (n, %)	4 (0.2%)	0	1.0000

BE: base excess; p-values < 0.05 were considered statistically significant; * Caesarean sections and unsuccessful inductions of labour were excluded; ** Caesarean sections were excluded

Growth Restriction" [15]. Neonates from the IUGR group had to be transferred to a paediatric unit significantly more often post partum. These transfers often occurred due to hypoglycaemia, which is to be expected in this high-risk group. Postpartum transfers for this reason are well-known to occur with SGA/IUGR foetuses, irrespective of the method of delivery and, depending on the publication, are also reported to be higher in cases of caesarean section compared to vaginal delivery [16].

Although this study is limited due its retrospective design, it nevertheless has some advantages compared to other studies. The groups in our study had clearly identifiable profiles, and cases of premature rupture of membranes or with a history of caesarean section were excluded as these factors significantly affect the success of labour induction [17]. Moreover, it again became clear that parity has a significant impact on several factors [18]. Many of the significant differences between the two groups which were found for primiparae did not occur with multiparae. Evaluating the outcome parameters stratified according to parity is therefore essential.

CONCLUSION FOR CLINICAL PRACTICE

Induction of labour in growth-restricted foetuses is not associated with a higher rate of caesarean sections. Nevertheless, inducing labour in growth-restricted foetuses should be done in centres with an affiliated neonatology unit, as a higher rate of postpartum transfers to a paediatric unit can be expected.

▶ **Table 4** Outcome parameters stratified according to parity.

Outcome parameters	Primiparae			Multiparae		
	Control group (n = 1372)	IUGR (n = 89)	p-value	Control group (n = 838)	IUGR (n = 31)	p-Wert
Birth procedure (n, %)			0.3803			0.2211
▪ spontaneous delivery	672 (49.0%)	49 (55%)		730 (87.1%)	28 (90%)	
▪ operative vaginal delivery	203 (14.8%)	9 (10%)		26 (3.1%)	2 (6%)	
▪ caesarean section	497 (36.2%)	31 (35%)		82 (9.8%)	1 (3%)	
Induction-to-delivery interval (min)*	1818.0 (288–9723)	1735.0 (407–6306)	0.8816	1285.0 (97–13.975)	1541.5 (371–4209)	0.5158
Vaginal birth within 24 hours (n, %)**	304 (34.7%)	21 (36%)	0.8207	413 (54.7%)	13 (43%)	0.2203
Vaginal birth within 48 hours (n, %)**	693 (79.2%)	47 (81%)	0.7384	663 (87.8%)	28 (93%)	0.5654
Unsuccessful induction of labour (no birth within 72 hours; n, %)**	59 (6.7%)	2 (3.4%)	0.5784	27 (3.6%)	0	0.6190
Arterial umbilical blood pH < 7.05 (n, %)	10 (0.7%)	1 (1.1%)	0.5011	3 (0.4%)	0	1.0000
Arterial umbilical pH < 7.10 (n, %)	35 (2.6%)	2 (2%)	1.0000	8 (1.0%)	0	1.0000
BE ≤ 12 (n, %)	17 (1.3%)	4 (5%)	0.0334	6 (0.7%)	0	1.0000
Apgar score at 5 min < 7 (n, %)	22 (1.6%)	2 (2%)	0.6526	1 (0.1%)	0	1.0000
BE ≤ 12 and Apgar score at 5 min < 7 (n, %)	5 (0.4%)	0	1.0000	0	0	NE
Pathological CTG (n, %)	384 (28.0%)	34 (38%)	0.0388	99 (11.8%)	3 (10%)	1.0000
Foetal blood analysis (n, %)	10 (0.7%)	3 (3.4%)	0.0400	0	0	NE
Epidural anaesthesia (n, %)	737 (54.2%)	34 (38%)	0.0035	169 (20.2%)	4 (13%)	0.3528
Oxytocin (n, %)	772 (57.1%)	45 (51%)	0.2773	187 (22.4%)	2 (6%)	0.0346
Green amniotic fluid (n, %)	311 (22.7%)	14 (16%)	0.1273	96 (11.5%)	3 (10%)	1.0000
Amniotic infection syndrome (n, %)	3 (0.2%)	0	1.0000	0	0	NE
Postpartum transfer to a paediatric unit (n, %)	203 (14.8%)	42 (47%)	< 0.0001	79 (9.4%)	6 (19%)	0.1118
Respiratory adaptation disorder (n, %)	68 (33.7%)	10 (24%)	0.2462	16 (21%)	1 (17%)	1.0000
Hyperbilirubinaemia (n, %)	2 (1.0%)	0	1.0000	4 (5%)	0	1.0000
Hypoglycaemia (n, %)	36 (17.8%)	18 (44%)	0.0002	25 (32%)	1 (17%)	0.6599
IUGR (n, %)	0	6 (14%)	< 0.0001	0	3 (50%)	< 0.0001
Suspicion of infection (n, %)	72 (35.6%)	1 (2%)	< 0.0001	17 (22%)	0	0.3378
Other (n, %)	24 (11.9%)	6 (15%)	0.6252	15 (19%)	1 (17%)	1.0000
Neonatal infection (n, %)	64 (4.7%)	2 (2%)	0.4385	17 (2.0%)	0	1.0000
Puerperal endometritis (n, %)	2 (0.15%)	0	1.0000	2 (0.2%)	0	1.0000

A p-value < 0.05 was considered to be statistically significant; * Caesarean sections and unsuccessful inductions of labour were excluded; ** Caesarean sections were excluded; NE = not evaluable

Conflict of Interest

The authors declare that they have no conflict of interest.

Erstveröffentlichung

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