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Original Article

Comparison of maternal and fetal complications in pregnant women with breech presentation undergoing spontaneous or induced vaginal delivery, or cesarean delivery

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ABSTRACT

Objective: Breech presentation is the most common form of malpresentation, and associated with perinatal asphyxia and mortality, and maternal morbidity. Data associated with labor induction in breech presentation are limited. The aim of this study was to compare maternal and fetal complication rates in induced and spontaneous vaginal, and cesarean delivery with breech presentation.

Materials and Methods: Pregnant women with breech presentation were grouped: spontaneous vaginal delivery (Group 1, $n = 72$) induced or augmented vaginal delivery (Group 2, $n = 32$), and cesarean delivery (Group 3, $n = 253$). Fetal complications were as follows: clavicle fracture, femur fracture, humerus fracture, brachial plexus injury, cephalic hematoma, pneumothorax, need for intensive care unit (ICU), and 5th minute APGAR <7. Maternal complications were as follows: vaginal hematoma, deep vaginal laceration, perineal injury (≥3rd degree), decline in hemoglobin level (>2 g/dL), and postpartum endometritis. Data were collected and analyzed retrospectively.

Results: The highest fetal complication rate was in Group 2, and the lowest in Group 3 ($p = 0.001$). Clavicle fracture was significantly less in Group 3 compared with the other groups ($p = 0.024$). The rate of lower APGAR scores at the 5th minute was similar in all groups. Maternal complications were significantly higher in Group 2 compared with the other groups ($p = 0.001$). Fetal complications were 5.66-fold higher in Group 1 than in Group 3 ($p = 0.002$). Fetal and maternal complications were 9.48-fold and 7.48-fold higher, respectively, in Group 2 than in Group 3 ($p < 0.001$).

Conclusion: This study is the first in literature to have investigated and analyzed neonatal complications in breech delivery according to different delivery modes including induced vaginal delivery. Due to possible complications, the risks and benefits of a specific type of delivery should be considered in breech presentation.

Introduction

Breech presentation might be described as a presentation in which the buttocks of the fetus are adjacent to the birth canal. Towards the end of pregnancy, the fetal head, which is larger than the fetal hips, starts to gradually decrease in size compared to the other body parts. The fetal hips, which have remained larger are then directed towards the uterus fundus which is wider, and the fetal head is directed to the pelvis under the effect of gravity.

Therefore, the prevalence of breech presentation declines with the progression of pregnancy, and is higher in preterm labor. The prevalence has been reported as 20–25% before 28 weeks, 7–16% at 32 weeks, and approximately 4% at term [1–3]. It is the most common form of malpresentation.

Several risk factors such as multiparity, polyhydramnios, oligohydramnios, hydrocephaly, anencephaly, previous breech presentation, placenta previa, preterm gestation, uterine abnormality, older maternal age, maternal anticonvulsant therapy, multiple gestation, and fetal asphyxia might contribute to the occurrence of breech presentation [4–10]. A history of breech presentation in a

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previous pregnancy increases the risk of breech presentation to 9% in the subsequent pregnancy [11,12]. However, two consecutive pregnancies with breech presentation increases the risk to 25%, and 3 consecutive pregnancies with breech presentation may increase the risk up to 40% [11,12].

Breech presentation has been shown to be associated with trauma-related injury during birth, perinatal mortality, and maternal morbidity [13–15]. Perinatal asphyxia may result from breech presentation. Frontal bossing, prominent occiput, low-set ears, torticollis, and developmental dysplasia of the hip are seen more frequently in breech presentation [16,17]. In addition to birth trauma, adverse outcomes are also associated with factors that co-exist with breech presentation, such as preterm birth, intrauterine growth retardation or anomalies.

One choice is the trial of external cephalic rotation and then if labor is unsuccessful, cesarean delivery is applied. The other strategies are planned cesarean delivery without trial of external cephalic rotation, or planned vaginal delivery in patients at low risk. A higher risk of asphyxia, traumatic injury, neonatal morbidity or mortality has been shown in planned vaginal breech birth compared with planned cesarean breech birth in several studies [18–21]. Data associated with labor induction or augmentation in breech presentation are limited. Due to the possibility of fetopelvic disproportion, oxytocin is not preferred in the active phase [4,22–25]. In some studies, similar outcomes have been reported in breech presentation with induced or spontaneous labor [3,26].

The aim of this study was to compare maternal and fetal complication rates in induced vaginal breech delivery, spontaneous vaginal breech delivery, and cesarean breech delivery.

Materials and methods

The study included women admitted to our clinics with a clinical picture of breech presentation between January 2012 and September 2018. All patients with fetuses who had congenital anomalies (such as anencephaly or hydrocephaly, which might be associated with breech presentation) [8] were excluded. Women who had intrauterine death, multiple gestation, placenta previa, placental detachment, severe pre-eclampsia, and bleeding diathesis were also excluded, as were patients with incomplete data. The study was conducted with the formal approval of the institution and was registered as a clinical trial. All procedures were in accordance with the principles of the Declaration of Helsinki. The patient data were recorded and evaluated retrospectively. The study was approved by Istanbul Medeniyet University Göztepe Training and Research Hospital Ethics Committee. All patients provided written informed consent.

The patients were grouped according to the route of delivery. Group 1 consisted of women with breech presentation who delivered spontaneously by the vaginal route ($n = 72$). Group 2 comprised women with breech presentation who delivered through the induced or augmented vaginal route ($n = 32$). Group 3 included women with breech presentation who delivered via primary cesarean delivery ($n = 253$). The patients in this group did not have uterine scars. Indications for Cesarean section was breech presentation for all the patients in Group 3. Oxytocin infusion (1%) was applied for augmentation to 29 patients in Group 2; the indication for induction was inadequate uterine contractions, albeit with an adequate Bishop score. In 2 patients in Group 2, 1% oxytocin infusion was applied after a vaginal prostaglandin E2 ovule to induce delivery due to a low Bishop score of post-term pregnancy. The oxytocin infusion was administered after 25 μg vaginal prostaglandin E1 in 1 patient with mild pre-eclampsia. No induction or augmentation was applied to the patients in Groups 1 and 3.

Maternal and fetal complications were recorded and analyzed. Fetal complications were accepted as the following: clavicle fracture, femur fracture, humerus fracture, brachial plexus injury, cephalic hematoma, intracranial bleeding, pneumothorax, need for intensive care unit (ICU), and 5th minute APGAR <7. Maternal complications were as follows: vaginal hematoma, deep vaginal laceration, perineal injury (>2nd degree), decline in hemoglobin level (decline of >2 g/dL) and postpartum endometritis. Suspected fractures were evaluated using standard radiography. The need for ICU was defined as >24 h stay in the neonatal intensive care unit (NICU). Postpartum vaginal hematoma at least 3 cm in size was accepted as vaginal hematoma. Deep vaginal laceration was accepted as a laceration of near to total vaginal length that necessitates for surgical repair. Postpartum endometritis was diagnosed from the findings of fever (≥38.5 °C), groin pain, and uterine sensitivity in the postpartum first month after exclusion of other causes. Postpartum hemorrhage was defined as the difference of at least 2 g/dL between the last measurement of hemoglobin before delivery and the level of hemoglobin at the 24th hour postpartum.

Data obtained in the study were analyzed statistically using SPSS 25.0 software (IBM Corporation, Armonk, NY, USA). The conformity of the data to normal distribution was evaluated using the Shapiro–Wilk test. To compare the groups with each other according to age, the Kruskal–Wallis H test was used with Monte Carlo simulation results. When comparing the groups according to the categorical variables, the Fisher–Freeman–Holton test was used with Monte Carlo simulation results. A comparison of ratios in the columns is depicted by p values corrected using the Benjamini–Hochberg test. A multi-nominal logistic regression test was used to determine the cause–effect relationship between dependent groups and descriptive variables. Quantitative variables were stated as median (minimum–maximum) values in the tables. Variables were evaluated with a 95% confidence level, and $p < 0.05$ was accepted as statistically significant.

Results

Demographic and obstetric characteristics

The median age of the patients was 29 years (range, 18–40 years), with no difference found between the groups in respect of age. No statistically significant differences were determined between the groups in terms of uterine anomalies, diabetes mellitus (DM), hypertension (HT), and myoma uteri ($p > 0.05$). Nulliparity was significantly higher in Group 3 compared with Groups 1 and 2 ($p < 0.001$) (Table 1 and Fig. 1).

Gestational age and fetal birth weight

There were no significant differences between the groups according to preterm or term delivery, or birth weight (Table 2).

Fetal complications

The overall rate of fetal complications was significantly higher in Group 1 and 2 as compared with Group 3 ($p = 0.001$). The frequency of clavicle fracture was significantly lower in Group 3 compared with the other groups ($p = 0.024$). The rates of fetal complications and clavicle fractures were similar in Groups 1 and 2. The rate of other fetal complications and lower APGAR score at the 5th minute was similar in all groups ($p > 0.05$) (Table 3 and Fig. 1). The total complications may not be equal to the number shown as fetal complications because in some cases more than one complication developed in the same fetus.

Table 1
Demographic and obstetric characteristics in study groups.

	Spontaneous vaginal delivery (Group 1) ($n = 72$)	Induced vaginal delivery (Group 2) ($n = 32$)	Primary cesarean (Group 3) ($n = 253$)	Total ($n = 357$)	p
	Median (Min./Max.)	Median (Min./Max.)	Median (Min./Max.)	Median (Min./Max.)	
Age	29.5 (18/40)	28.5 (18/39)	28 (18/40)	29 (18/40)	0.484[a]
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Nulliparity	6 (8.3)	2 (6.3)	119 (47.0) [I, II]	127 (35.6)	**<0.001**[b]
Uterine anomaly	2 (2.8)	1 (3.1)	14 (5.5)	17 (4.8)	0.770[b]
DM	4 (5.6)	1 (3.1)	18 (7.1)	23 (6.4)	0.823[b]
HT	5 (6.9)	2 (6.3)	25 (9.9)	32 (9.0)	0.787[b]
Myoma uteri	2 (2.8)	1 (3.1)	15 (5.9)	18 (5.0)	0.665[b]

[a] Mann Whitney U test (Monte Carlo).
[b] Fisher Freeman Halton Test(Monte Carlo); Benjamini–Hochberg correction was used for multiple comparisons, Min., Minimum; Max., Maximum; I, significant compared to spontaneous labor; II, significant compared to induced delivery.

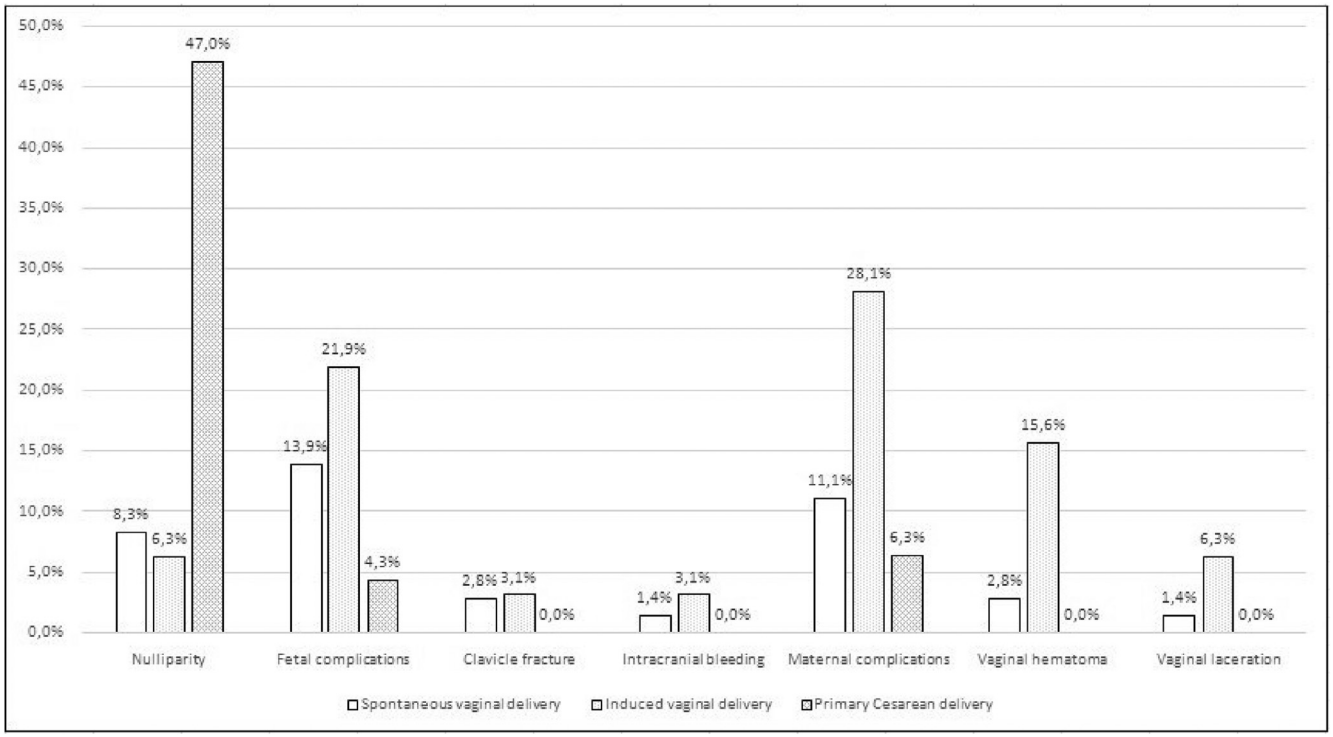

Fig. 1. Distribution of maternal and fetal complications in the groups.

Table 2
Gestational age and fetal birthweight in study groups.

	Group 1 ($n = 72$)	Group 2 ($n = 32$)	Group 3 ($n = 253$)	Total ($n = 357$)	p
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Preterm	19 (26.4)	7 (21.9)	89 (35.2)	115 (32.2)	0.177
Term	53 (73.6)	25 (78.1)	163 (64.4)	241 (67.5)	0.144
Birth weight <2500 gr	5 (6.9)	2 (6.3)	37 (14.6)	44 (12.3)	0.140
Birth weight >3800 gr	6 (8.3)	3 (9.4)	29 (11.5)	38 (10.6)	0.813

Fisher Freeman Halton Test (Monte Carlo).

Maternal complications

The overall rate of maternal complications was significantly higher in Group 2 in comparison with Groups 1 and 3 ($p = 0.001$); maternal complications were similar in Groups 1 and 3. Vaginal hematoma and vaginal laceration were most frequent in Group 2. The rates of perineal injury, decline in hemoglobin, and postpartum endometritis were similar in all groups ($p > 0.05$) (Table 4 and Fig. 1). The total complications may not be equal to the number shown as maternal complications because in some cases more than one complication developed in the same patient.

Table 3
Comparison of fetal complications in the groups.

	Group 1 ($n = 72$)	Group 2 ($n = 32$)	Group 3 ($n = 253$)	Total ($n = 357$)	*P*
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Fetal complications	10 (13.9)[III]	7 (21.9)[III]	11 (4.3)	28 (7.8)	**0.001**
Clavicle fracture	2 (2.8)[III]	1 (3.1)[III]	0 (0.0)	3 (0.8)	**0.024**
Femur fracture	1 (1.4)	0 (0.0)	1 (0.4)	2 (0.6)	–
Brachial plexus injury	0 (0.0)	1 (3.1)	0 (0.0)	1 (0.3)	–
Cephal hematoma	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.3)	–
Intracranial bleeding	1 (1.4)	1 (3.1)	0 (0.0)	2 (0.6)	–
Pneumothorax	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.3)	–
Need for ICU	2 (2.8)	2 (6.3)	3 (1.2)	7 (2.0)	0.085
5th min. APGAR <7	4 (5.6)	3 (9.4)	7 (2.8)	14 (3.9)	0.116

Fisher Freeman Halton Test (Monte Carlo); Benjamini–Hochberg correction was used for multiple comparisons; I, Significant compared to spontaneous labor; II, Significant compared to labor induction, III, Significant compared to primary Cesarean.

Table 4
Comparison of maternal complications in the groups.

	Group 1 ($n = 72$)	Group 2 ($n = 32$)	Group 3 ($n = 253$)	Total ($n = 357$)	*p*
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Maternal complications	8 (11.1)	9 (28.1)[I,III]	16 (6.3)	33 (9.2)	**0.001**
Vaginal hematoma	2 (2.8)	5 (15.6)[I,III]	0 (0.0)	7 (2.0)	**<0.001**
Vaginal laceration	1 (1.4)	2 (6.3)[III]	0 (0.0)	3 (0.8)	**0.005**
Perineal injury	0 (0.0)	1 (3.1)	0 (0.0)	1 (0.3)	–
Decline in hemoglobin	4 (5.6)	3 (9.4)	11 (4.3)	18 (5.0)	0.375
Postpartum endometritis	1 (1.4)	1 (3.1)	5 (2.0)	7 (2.0)	0.667

Fisher Freeman Halton Test (Monte Carlo); Benjamini–Hochberg correction was used for multiple comparisons; I, Significant compared to spontaneous labor; II, Significant compared to labor induction; III, Significant compared to primary Cesarean.

Logistic regression analysis for the complication risk according to delivery types

Spontaneous vaginal delivery vs. primary cesarean delivery was more likely in case of multiparity (OR, 12.80, 95% CI: 5.02–32.63, $p < 0.001$), while associated with increased likelihood of fetal complications (OR, 5.66, 95% CI: 1.92–16.64, $p = 0.002$) (Table 5).

Induced vaginal delivery vs. primary cesarean delivery was more likely in case of multiparity (OR, 27.00, 95% CI: 5.25–138.84, $p < 0.001$), while associated with increased likelihood of both fetal complications (OR, 9.48, 95% CI: 2.68–33.46, $p < 0.001$) and maternal complications (OR, 7.48, 95% CI: 2.52–22.20, $p < 0.001$) (Table 5).

Spontaneous vaginal delivery vs. induced vaginal delivery was associated with decreased likelihood of maternal complications (OR, 0.31, 95% CI: 0.10–0.92, $p = 0.036$) (Table 5).

Table 5
Multiple logistic regression analysis for the complication risk according to delivery types.

Groups	B	SE.	*P*	Odds ratio	95% CI	
					LB	UB
Spontaneous vaginal delivery vs. primary cesarean section						
Multiparity	2.549	0.477	**<0.001**	12.80	5.02	32.63
Fetal complications	−1.733	0.551	**0.002**	5.66	1.92	16.64
Maternal complications	−0.848	0.517	0.101	2.33	0.85	6.44
Induced vaginal delivery vs. primary cesarean section						
Multiparity	3.296	0.835	**<0.001**	27.00	5.25	138.84
Fetal complications	−2.249	0.644	**<0.001**	9.48	2.68	33.46
Maternal complications	−2.013	0.555	**<0.001**	7.48	2.52	22.20
Spontaneous vaginal delivery vs. induced vaginal delivery						
Multiparity	−0.746	0.897	0.405	0.47	0.08	2.75
Fetal complications	0.516	0.573	0.368	0.59	0.19	1.85
Maternal complications	1.165	0.556	**0.036**	0.31	0.10	0.92

Multiple Nominal Logistic Regression, B, regression coefficients; SE, Standard error, CI: Confidence Interval, LB: Lower bound, UB: Upper bound Bold font: shows the significant p-value.

Discussion

Our findings revealed that in pregnancies with breech presentation, primary cesarean section was associated with lesser likelihood of fetal complications than spontaneous vaginal delivery, and lesser likelihood of both fetal and maternal complications than induced vaginal delivery along with lesser likelihood of maternal complications in spontaneous vs. induced vaginal delivery Parissenti et al. [27] analyzed and defined risk factors of emergency cesarean delivery in 464 pregnant women attempting vaginal breech delivery at term. Nulliparity, higher birth weight, and induction were found to be risk factors for failed vaginal delivery. Similarly, in the current study, nulliparity was seen to be highest in the cesarean group. However, no differences were determined between the groups in respect of birth weight. The previous study reported that neonatal acidosis was significantly higher in high-risk patients (nulliparous, induction of labor) in the vaginal delivery group ($p = 0.013$) compared with the cesarean group. Other neonatal (e.g., low 5th minute APGAR score) and maternal (e.g., hematoma) complications were similar in the vaginal, unplanned, and planned cesarean delivery groups. The current study results also showed similar APGAR scores in all groups, although vaginal hematoma and laceration were most frequent with induced vaginal delivery. Babovic et al. [28] investigated the risk factors and complications of breech cesarean section and found that birth asphyxia was higher with successful vaginal delivery ($p = 0.035$). However, lower APGAR scores were shown to be at a similar rate in the cesarean and vaginal delivery groups ($p = 0.416$) (Babovic et al., 2016). Interestingly, the duration of stay in the ICU was shorter in the vaginal delivery group than in the emergency cesarean group ($p = 0.002$). A short stay in the ICU after vaginal delivery has also been confirmed in other studies [29,30]. Babovic et al. [28] used oxytocin augmentation in more than half of the patients in the vaginal delivery group in their study. However, the vaginal delivery group was not divided

according to the use of induction, and the group formed was heterogeneous.

An Australian study analyzed 5197 term breech pregnancies that were eligible for vaginal delivery [30]. Unlike the current study results and those of the above-mentioned studies, APGAR scores at the 5th minute were reported to be lower in the planned vaginal delivery group than in the planned cesarean group. The authors also found that neonatal ICU admission, birth trauma, and neonatal morbidity were higher in the planned vaginal delivery group. That study included patients who were induced for labor or progressed to cesarean section due to failure of labor in the planned vaginal delivery group, which made the group heterogenous.

Jarniat et al. [31] investigated the differences between spontaneous labor ($n = 178$) and induced labor ($n = 57$) of singleton breech pregnancies. Of the included pregnancies, 88.2% of spontaneous and 91.2% of the induced labor group had vaginal delivery, while the others had cesarean delivery ($p > 0.05$), and planned cesarean deliveries were excluded. Bleu et al. [32] also found a similar rate of cesarean delivery in the induced labor and spontaneous vaginal delivery groups. In these studies, the cesarean delivery rate was not increased in induced labor, in contrast with the findings of a meta-analysis including 7 studies [33]. In the meta-analysis, the cesarean rate was increased 1.48-fold in the induced labor group. Moreover, Jarniat et al. [31] found that neonatal acidosis, transfer to the neonatal unit, and low APGAR scores were similar in both spontaneous and induced delivery groups. There was no neonatal mortality or need for ICU in either group. Another study comparing spontaneous and induced labor by Macharey et al. [34] investigated spontaneous ($n = 195$) and induced ($n = 73$) labor in terms of cesarean rates and complications. No differences were determined between the 2 groups according to neonatal acidosis, low APGAR scores at the 5th minute, stillbirth, neonatal mortality, neonatology unit admission, and neonatal encephalopathy. However, in contrast to the previously mentioned study [31], the cesarean rate was significantly higher in the induced labor group. In the current study, fetal complications (clavicle fracture, need for ICU and low APGAR scores) were similar in the spontaneous and induced vaginal delivery groups. Emergency cesareans were excluded. However, in the study by Jarniat et al. [31], the complications in spontaneous and induced labor were analyzed, with emergency cesarean deliveries due to failure of labor included in both of those groups. In contrast to the Jarniat et al. [31] study, both preterm and term deliveries were included in the current study. The findings revealed that 26.4% and 21.9% of the patients in Groups 1 and 2 respectively had preterm deliveries. Hence, it may be concluded that preterm breech deliveries did not lead to any differences in fetal and neonatal complications between the spontaneous and induced vaginal delivery groups. Bleu et al. [32] also showed no differences between spontaneous and induced labor groups according to neonatal acidosis, neonatal mortality, low APGAR score at the 5th minute, and perineal laceration [32]. They also showed no differences in nulliparity between the groups.

In some studies, umbilical artery pH has been found to be lower in breech delivery than with cephalic presentation [35,36]. In one study, the decrease in pH was found not to be associated with neonatal indicators such as acidosis or ICU admission [32]. Some studies have indicated that worse neonatal indicators were not associated with long-term disability in children born with vaginal breech delivery [37,38]. In addition to the need for ICU, neonatal acidosis, vaginal hematoma and laceration, and APGAR scores, the current study investigated and analyzed clavicle and femur fractures, cephalic hematoma, intracranial bleeding, and brachial plexus injury. In respect of the analysis of these parameters, the current study may be one of the leading studies in the literature.

A meta-analysis included 7 studies and 2993 term singleton breech deliveries and compared induced labor ($n = 646$) and spontaneous labor ($n = 2347$) [33]. The cesarean rate was 33.59% and 24.93% in the induced and spontaneous labor groups, respectively. A 1.48-fold increased risk of cesarean delivery was found in the induced labor group. The need for neonatal ICU was 1.86-fold higher in the induced labor group. Low APGAR scores at the 5th minute, neonatal acidosis, neonatology unit admission, maternal fever, and intrapartum stillbirth were found to be similar in both groups. Neonatal death was not observed in any of these studies. The rate of cesarean delivery was found to be high in planned vaginal breech delivery in this meta-analysis, and in the current study, it was also found that fetal complications were higher in vaginal breech delivery, especially in induced labor. In the light of these findings, vaginal delivery for breech presentation may still be considered controversial. One meta-analysis revealed that planned vaginal delivery had increased perinatal morbidity and mortality with breech presentation [39]. Breech presentation has been accepted as a general contraindication for labor induction by some authors [40]. All of these views and evidence raised the thought that the safety of vaginal breech delivery or induction of breech labor was uncertain.

Study limitations and strengths

The pregnancies with breech presentation in this study were not classified as frank, complete or incomplete breech. However, the benefit of such a classification is uncertain. Patients undergoing emergency cesarean deliveries were excluded, and the proportion of these patients in the total sample of the cesarean group was low at approximately 4%. Study groups were homogenous in terms of gestational age at delivery, with similar rates for preterm or term cesarean and vaginal deliveries. However, superior to most of the reports in the literature, breech deliveries were analyzed by dividing them into 3 groups as vaginal delivery groups according to the use of induction and the cesarean group. There was also investigation and analysis of clavicle and femur fractures, cephalic hematoma, intracranial bleeding, pneumothorax, and brachial plexus injury. To the best of our knowledge, of the studies in literature analyzing breech delivery, this is the first study to have examined these parameters.

Conclusion

In conclusion, our findings revealed association of primary cesarean section with lesser likelihood of fetal and maternal complications in breech presentations, when compared to spontaneous/induced vaginal delivery and induced vaginal delivery, respectively. The fetal complication rate was highest with induced vaginal delivery, and the lowest in the cesarean group. The need for the ICU and lower APGAR scores at the 5th minute were similar in all groups. Investigation and analysis was made of clavicle and femur fractures, cephalic hematoma, intracranial bleeding, pneumothorax and brachial plexus injury in breech delivery for the first time in the literature. Future studies will be able to clearly define the rate of these complications in breech delivery. In general, maternal complications were highest with induced vaginal delivery. Vaginal hematoma and laceration were highest with induced vaginal delivery. Well-organized obstetric teams should decide the mode of delivery in breech presentation with the agreement of the patient. According to the highest maternal and fetal complication rates, the risks and benefits of a specific type of delivery should be considered when labor is to be induced. Beyond the general literature, breech deliveries in this study were analyzed by dividing them as induced or spontaneous vaginal delivery groups, and a

cesarean group. Nevertheless, there is a need for further studies to precisely reveal the issues associated with complications of breech delivery.

Declaration of competing interest

No funding was received for this study. There were no financial interests to disclose. The data that support the findings of this study are available from the corresponding author, [author initials], upon reasonable request. No potential conflict of interests was reported by the authors.

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All authors contributed to data collection, data analysis, writing, editing and preparing of manuscript.

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