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ORIGINAL ARTICLE

Ultrasonographic Measurement of Fetal Adrenal Gland Size for the Prediction of Success of Induction of Labor Among Primigravida Beyond 40 Weeks Gestation

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Abstract

Introduction As the pregnancy advances beyond term, the risk of perinatal morbidity and mortality increases. Hence to prevent these complications associated with postterm pregnancy, induction of labor is done, as per our institution protocol between 40 and 41 weeks of gestation. Induction has its own drawback, so it is essential to identify the women with high chances of failure of induction of labor, to prevent the morbidities associated with induction failure.

Aim To study the role of ultrasonographic fetal adrenal gland enlargement for the prediction of success of labor induction among primigravida beyond 40 weeks gestation.

Material and Methods Low-risk primigravidas beyond 40 weeks gestation, scheduled for induction of labor, were enrolled for the study. Fetal adrenal gland dimensions were measured by using abdominal probe Philips HD 7XE and general electronics logiq P6 pro or any ultrasound machine equipped with 7.5–10 MHz linear array probe and 3.5–5 MHz curved array probe.

Results The fetal adrenal gland length, width and ratio were statistically significant between the successful versus failed induction groups. The cutoff fetal zone ratio > 0.36 for the prediction of successful induction of labor had 90% sensitivity, 89% specificity, 93% PPV and 75% NPV.

Conclusion Fetal zone enlargement (fetal zone ratio > 0.36) is a strong predictor of successful induction of labor as compared to TVL and Bishop's score. It can be used for screening the women, who are destined for induction failure, so that adverse effects of induction of labor can be avoided.

Keywords Postterm pregnancy · Fetal adrenal gland · Fetal gland ratio · Fetal zone ratio · Fetal adrenal gland enlargement

Introduction

Prolonged pregnancy defined as pregnancy at and beyond 41 weeks of gestation is most common challenging condition, currently faced by obstetricians, because of increased morbidity and mortality [1, 2].

The risk of perinatal mortality increases twofold at 42 weeks, fourfold by 43 weeks and fivefold to sevenfold at 44 weeks [3]. The risk of meconium aspiration syndrome increases by 0.24–1.42%, risk of neonatal acidosis, 5-min APGAR score less than 7 and admission to NICU increases progressively [4]. Hence to prevent perinatal morbidities associated with postterm pregnancy, we often induce the patient as per our institution protocol between 40 and 41 weeks of gestation.

Postterm pregnancies per se do not put the mother at risk but the increased morbidity incidental to the hazards of induction like failed induction, increase in labor

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dystocia (9–12% vs 2–7% at term) and severe perineal injuries (3rd–4th degree) related to macrosomia (3.33% vs 2.6% at term), operative vaginal delivery and a doubling in the rate of cesarean delivery (14% vs 7% at term) [1].

So, it is essential to identify the women with high chances of failure of induction of labor, to prevent the morbidities associated with induction failure. Hence, there is a need for a marker for the prediction of successful induction. Various screening methods have been studied so far to predict the outcome of induction that includes digital assessment of cervix using Bishop's score, radiological assessment of cervical length using transvaginal ultrasound and biochemical factors such as fetal fibronectin, interleukin 8 and phIGFBP-1 [5–7].

Measurement of fetal adrenal zone enlargement has emerged as a new modality for the better prediction of success of induction of labor.

The adrenal glands are composed of two heterogenous type of tissue, the outer one is cortex derived from intermediate mesoderm and inner one is medulla which is derived from neural crest ectodermal in origin [8–11]. Adrenal cortex tissue first appears at 33 days of fertilization. It differs from its adult counterpart as it is composed of two distinct zones, the inner part is fetal zone and outer part is definite zone (Fig. 1). Inner fetal zone is enzymatically active region and produces large amount of adrenal androgens that are used by placenta for estrogen biosynthesis [11, 12]. On ultrasound, the fetal adrenal gland appears as oval or pyramidal in shape in longitudinal dimension and lentiform or discoid shape in transverse.

It visualized at the end of first trimester but is only reliably visualized by the end of 20 weeks of gestational age. Its size increases linearly from 12 to 17 weeks of gestation. It appears as echogenic central stripe with surrounding hypoechoic rim [13].

During midgestation, the fetal zone occupies most of the cortical volume and produces 100–200 mg/dl of DHEAS, an androgen and precursor of both androgen and estrogen. Fetal zone also produces cortisol that has a role in prenatal development of organs especially maturation of lungs. Cortisol has a role in expression of number of placental genes that result in raised level of corticotrophin-releasing hormone (CRH) and prostaglandins. Prostaglandins have a direct role in parturition, whereas CRH by various mechanisms such as inducing myometrial contractions, dilatation of uterine vessels, stimulation of smooth muscle contraction and increase production of PGF2a and PGE2 leads to successful labor. So, activation of fetal hypothalamus pituitary adrenal axis causes significant enlargement of fetal zone, which indicates fetal readiness for labor and by measuring it we can predict the success of IOL [11, 12].

In this study, we attempted to correlate the role of fetal zone enlargement as a marker for the prediction of successful induction of labor in prolonged pregnancy and compare it with transvaginal cervical length and Bishop's score.

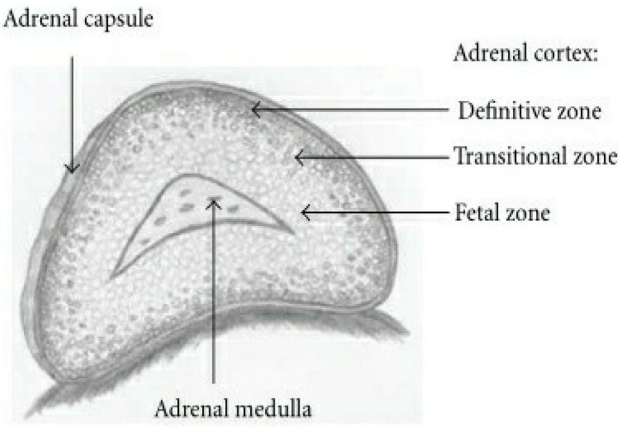

Fig. 1 Fetal adrenal gland

Aim

To study the role of ultrasonographic fetal adrenal gland enlargement for the prediction of success of labor induction among primigravida beyond 40 weeks gestation.

Primary Objectives

To measure the ultrasonographic fetal adrenal gland dimension and to determine the sensitivity, specificity, positive and negative likelihood ratio of fetal zone ratio (FZR) among primigravida beyond 40 weeks gestation with and without success of IOL.

Secondary Objectives

1. To measure the minimum cutoff value of fetal zone enlargement or fetal zone ratio (FZR) required for the prediction of success of IOL.
2. To correlate the time of induction to the onset of active labor and delivery with fetal adrenal gland size.
3. To compare fetal zone ratio (FZR), transvaginal cervical length and Bishop's score for successful IOL.

Materials and Methods

A cross-sectional analytical study was conducted on primigravida beyond 40 weeks gestation satisfying the inclusion and exclusion criteria. Suitable cases were enrolled for the study, and prior to induction, fetal adrenal gland dimensions were measured, and biophysical score (BPS) and Bishop's

score were done, followed by induction with dinoprostone gel.

Sample Size

Considering 86% of sensitivity of fetal zone ratio (FZR) at cutoff of 0.35 for the prediction of labor as established by the previous study and also considering the 33% prevalence of pregnancy beyond 40 weeks gestation in our institution, to estimate an absolute difference of 10% on either side $a = 5\%$, a sample of 140 cases was required.

Inclusion Criteria

1. Primigravida with singleton pregnancy, vertex presentation and intact membranes at or beyond 40 weeks, not in labor.
2. Regular menstrual cycles.
3. Women sure of dates and/or with first trimester ultrasound.

Exclusion Criteria

1. Fetal distress, meconium-stained liquor, cord prolapse or abruption after induction of labor in latent phase.
2. Placenta previa, abruption of placenta, cephalopelvic disproportion and scarred uterus (previous history of cesarean section or myomectomy).
3. Hypertensive disorders of pregnancy, diabetes mellitus, asthma, tuberculosis, anemia and epilepsy
4. Macrosomia, fetal growth restriction and congenital fetal anomalies
5. Women with decreased fetal movements and BPS < 6.

Prior institutional ethical clearance was obtained from the ethics committee, and written informed consent was taken from all the women. Fetal biometry, biophysical score and transvaginal cervical length were assessed. Fetal adrenal gland dimensions were measured by two consultants using abdominal probe Philips HD 7XE and general electronics logiq P6 pro or any ultrasound machine equipped with 7.5–10 MHz linear array probe and 3.5–5 MHz curved array probe. The closest adenal gland in the transverse plane was identified, length and width of the total gland as well as length and width of the fetal zone was measured after placing calipers directly over the intersection of the gland with the surrounding of soft tissue and the intersection of fetal zone and the surrounding gland (Fig. 2). Average of three measurements for each parameter was recorded. Bishop's score was recorded, and induction of labor was done by using dinoprostone gel. Labor was monitored as per the WHO protocols.

Successful induction was defined as women entering into active phase of labor (5-cm cervical dilatation) or delivered vaginally.

Failed induction was defined as failure of onset of active stage of labor after three doses of dinoprostone gel followed by amniotomy and titrated oxytocin infusion for 12 h.

Results

A total of 140 women were enrolled and were categorized into two groups: Group I (successful induction group) comprised of 103 women, and group II (failed induction group) comprised of 37 women.

Mean age was 23.24 ± 3.14 years, and majority 66 (47%) women were educated till secondary in the study population. The mean BMI of the study population was 23.22 ± 3.24 kg/m^2.

Among group I, mean of fetal zone length (l), mean of total gland length (L) and the mean ratio of l/L were 1.45 ± 0.24, 2.9 ± 1.2 and 0.50 ± 0.09, respectively, while in group II, mean of fetal zone length (l), mean of total gland length (L) and the mean ratio of l/L were 1.1 ± 0.12, 2.8 ± 0.34 and 0.39 ± 0.08, respectively (p value = 0.01). The comparison was statistically significant between the two groups. This showed that the successful induction had large fetal zone length ratio (Table 1).

The mean of fetal zone width (w), the mean of total gland width and the mean of ratio (w/W) were 0.40 ± 0.03, 0.99 ± 0.45 and 0.415 ± 0.05, respectively, in group I while the mean of fetal zone width (w), the mean of total gland width and the mean of ratio were 0.22 ± 0.02, 0.74 ± 0.24 and 0.29 ± 0.06, respectively, in group II. The fetal adrenal width and ratio were statistically significant between the two groups (Table 1).

The sensitivity and specificity of fetal zone width ratio (w/W) was 84.5% and 89.2%, respectively, which was better than the sensitivity and specificity of fetal zone length ratio (l/L). By using ROC curve comparative analysis, we determined that the fetal zone width ratio (w/W) showed superior predictive value compared with l/L. Accordingly, the fetal zone width ratio (w/W) was used as a measure of fetal zone enlargement (FZE) or FZR (Table 2, Figs. 3 and 4).

For the prediction of successful induction of labor, the cutoff value of Bishop's score was 4 based on ROC curve having maximum area under curve at Bishop's score 4, i.e., 0.78. Bishop's score of group I had mean of 4.49 ± 0.92 while the Bishop's score of group II had mean of 3.35 ± 1.03. The comparison was statistically significant between the two groups. This showed that the higher Bishop's score was more favorable for successful induction and suggests

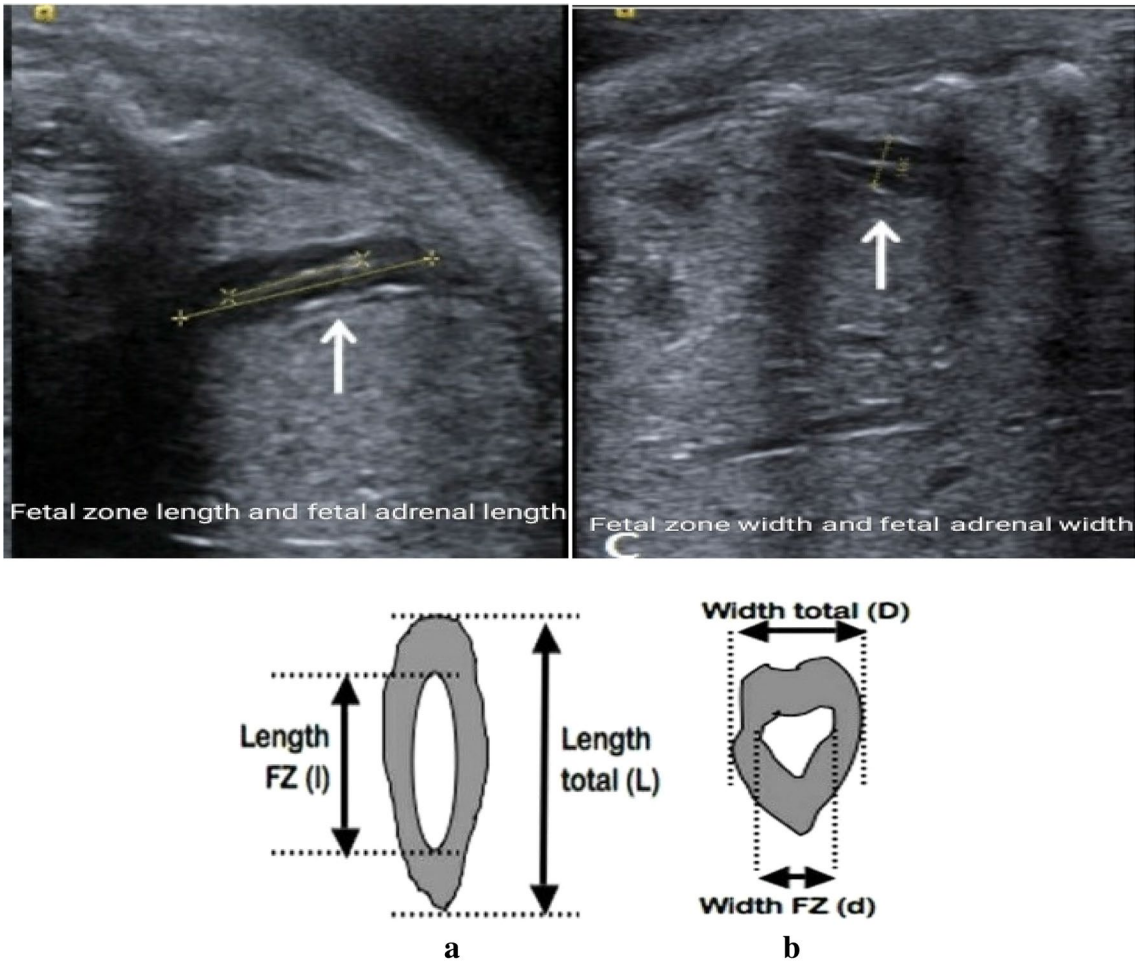

Fig. 2 Ultrasound image of fetal adrenal gland showing different measurement. **a** Fetal zone & adrenal gland lengths measurement, **b** Fetal zone and adrenal gland widths measurement

Table 1 Estimation and comparison of fetal adrenal length and width in successful and failed induction groups

	Successful IOL (group I) ($n=103$) (mean ± SD)	Failed IOL (group II) ($n=37$) (mean ± SD)	*p* value
Adrenal gland length			
Fetal zone length (l)	1.45 ± 0.24	1.1 ± 0.12	0.01
Total gland length (L)	2.9 ± 1.2	2.8 ± 0.34	0.54
Ratio (l/L)	0.50 ± 0.097	0.39 ± 0.08	0.01
Adrenal gland width			
Fetal zone width(w)	0.40 ± 0.03	0.22 ± 0.02	0.01
Total gland width(W)	0.99 ± 0.45	0.74 ± 0.24	0.01
Ratio(w/W)	0.415 ± 0.05	0.29 ± 0.06	0.01

cervical ripeness. For the prediction of successful induction of labor, the transvaginal length cutoff value was 2.5 cm based on ROC curve having maximum area under curve (AUC) at 2.5 cm, i.e., 0.88. The comparison of TVL was statistically significant between the groups. This shows that the shorter TVL is favorable for successful IOL (Table 3).

The cutoff value of FZR, TVL and Bishop's score was determined according to the ROC curves. For the prediction of successful induction, the cutoff value of FZR, Bishop score and TVL was 0.365, 4 and 2.5, respectively. The area under curve for the curve of FZR, Bishop score and TVL was 0.93, 0.78 and 0.88, respectively. On comparison, it was found that the AUC was the highest for FZR, and hence, the predictive ability of FZR for successful induction of labor was better than Bishop score and TVL. Sensitivity and specificity of FZR for the prediction of success of induction of labor was 0.90 and 0.89, respectively. The PPV and NPV of FZR was 0.93 and 0.75, respectively. Hence, it was the

Table 2 Cutoff value predictive value of fetal zone dimension (ratio) for prediction successful of IOL

	Cutoff value	Area under curve	Sensitivity	Specificity	NPV	PPV
l/L	0.405	0.82	85.4%	70.3%	93.9%	75.6%
w/W	0.365	0.92	84.5%	89.2%	81.3%	71

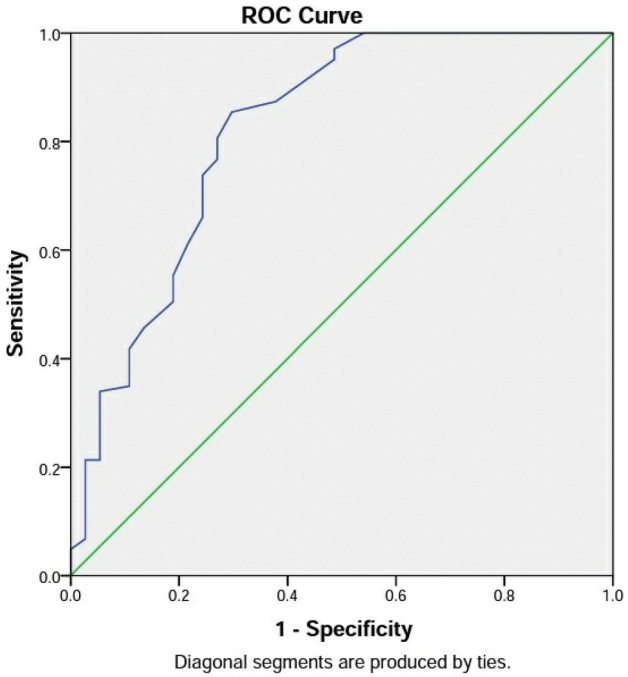

Fig. 3 ROC for fetal zone length ratio

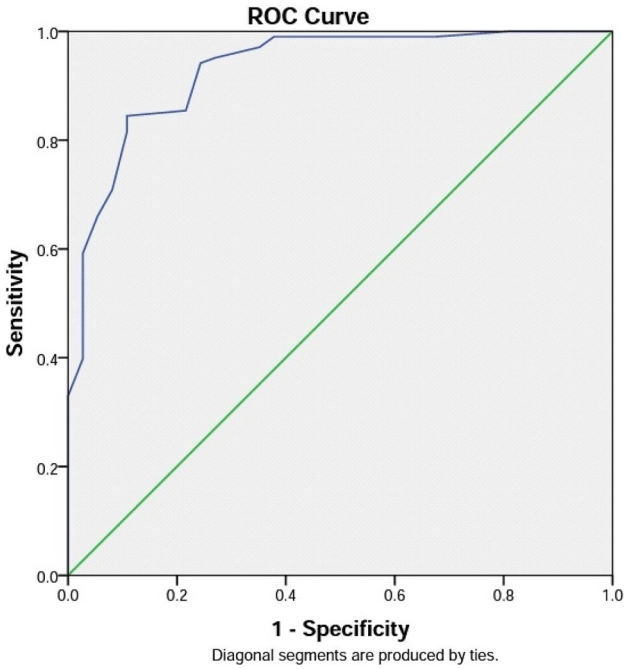

Fig. 4 ROC for fetal zone width ratio

Table 3 Estimation and comparison of Bishop's score and total vaginal length in successful and failed induction group

Bishop's score	Successful induction (group I) $n=103$	Failed induction (group II) $n=37$	p value
<4	6(5.8%)	33(89%)	0.01
>4	97(74%)	4(10.8%)	0.01
Mean ± SD	4.49 ± 0.92	3.35 ± 1.03	<0.001
TVL			
<2.5 cm	92(89.3%)	3(8.1%)	0.01
>2.5 cm	11(10.6%)	34(91.8%)	0.01
Mean ± SD	2.81 ± 0.17	3.18 ± 0.25	<0.001

most suitable marker in our study for the prediction of successful induction of labor in comparison with Bishop score and TVL. The combined sensitivity and specificity of all the parameters was found to be 0.93 and 0.81 while PPV and NPV was 0.92 and 0.78, respectively. The combined value was nearly similar to FZR alone; hence, FZR ratio is the good marker (Table 4).

Comparison of intrapartum complication such as fetal distress, abruption, meconium-stained liquor and non-progress of labor was statistically not significant between the groups.

In group I, 99 (70.7%) women delivered vaginally, 39 (27.8%) women had cesarean section and 2 (1.4%) women had instrumental delivery. The most common indication for cesarean delivery in the study population was failed induction, which comprised of 32 (86.4%) women (Table 5).

Majority 77 (74.7%) women had no postpartum complications in group I while it was 28 (75.6%) in group II (Table 6).

Mean birth weight of neonate in the study population was 2.95 ± 0.30 kg. About 55% of neonates had birth weight between 2.5 and 3 kg. About 60.7% of the neonates were male while 39.3% were female. Thirty out of 140 (21.4%) were admitted in NICU (Table 7).

Discussion

Prolonged pregnancy is associated with an increased risk of maternal and neonatal morbidity and mortality. Hence, induction of labor is a common practice in modern obstetrics

Table 4 Cutoff value for FZE, Bishop score and TVL using ROC curves performance characteristic for the prediction of successful IOL

Prediction criteria	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV
FZR (> 0.36)	0.365	0.93	0.90	0.89	0.93	0.75
Bishop's score (≥ 4)	4	0.78	0.84	0.64	0.87	0.60
TVL (≤ 2.5 cm)	2.5	0.88	0.89	0.70	0.52	0.94

Table 5 Comparison of delivery outcome in successful and failed induction groups

Mode of delivery	Successful IOL (group I) ($n = 103$) n (%)	Failed IOL (group II) ($n = 37$) n (%)	p value
Vaginal delivery	99 (96.1%)	0	0.01
Cesarean delivery	2 (1.9%)	37 (100%)	
Failed induction	0	32(86.4%)	
Arrest of descent and dilatation	1(0.7%)	3(8.2%)	
MSL with fetal distress	1(0.7%)	2(5.4%)	
Instrumental delivery	2 (1.9%)	0	

Table 6 Postpartum complication in the study population

Postpartum complications	Successful IOL (group I) ($n = 103$) n (%)	Failed IOL (group II) ($n = 37$) n (%)
No complication	77(74.7%)	28(75.6%)
Complication	26(25.2%)	9(29.7%)
PPH	8(7.7%)	6(16.2%)
Vaginal laceration	8(7.7%)	0
Paraurethral tear	6(5.8%)	0
Wound dehiscence	4 (3.8%)	3(8.1%)

to reduce these risks. However, induction of labor has its own complications.

In our study, prior to induction of labor, fetal adrenal gland dimensions were measured in transverse plane, length and width of both fetal zone as well as fetal adrenal gland were measured. Fetal zone length ratio (l/L) and fetal zone width ratio (w/W) were obtained.

The literature reviewed showed only one study till date that suggested the role of fetal zone enlargement for the prediction of successful IOL.

In our study, the rate of vaginal delivery, cesarean delivery and instrumental delivery was 70.7%, 27.8% and 1.5%, respectively. Out of that, 26.4% of the cesarean deliveries were due to failed induction, which is much higher in comparison with study done by Fitzgerald et al. The rate of vaginal delivery was little lower in comparison with study done by Fitzgerald et al. (70.7% vs 78.2%). This could be due to the difference in the ethnicity of population which was exclusively Indian in our study while the study population of Fitzgerald et al. was multiracial [14].

According to Fitzgerald et al., there was a positive correlation between fetal zone enlargement (FZR) and successful induction of labor which was consistent with the results of our study. They found that the FZR was significantly higher in successful IOL as compared to failed IOL. They labeled a cutoff of 0.35 which had sensitivity and specificity of 86% and 100%, respectively, with area under curve (AUC) = 0.92, whereas, in our study, cutoff ratio of 0.36 had sensitivity and specificity of 90% and 89%, respectively, with area under curve (AUC) = 0.93

In our study, the combined predictive value of FZR, Bishop's score and TVL had sensitivity and specificity of 0.93 and 0.81 while PPV and NPV was 0.92 and 0.78, respectively. The combined value of all three was comparable to FZR alone (Table 8).

The cutoff value transvaginal cervical length in our study was ≤ 2.5 cm with maximum sensitivity as compared

Table 7 Comparison of neonatal outcome in successful and failed induction groups

Outcome	Study population	Successful IOL (group I) ($n = 103$) n (%)	Failed IOL (group II) ($n = 37$) n (%)	p value
B.Wt (Mean ± SD)	2.95 ± 0.30	2.92 ± 0.31	3.02 ± 0.32	0.88
APGAR score—1 min (mean ± SD)	9.36 ± 0.92	9.14 ± 1.08	9.12 ± 1.06	0.43
APGAR score—5 min (mean ± SD)	9.24 ± 0.64	9.11 ± 0.82	9.28 ± 0.92	0.24
NICU admission				
Yes	30(21.4%)	12(11.6%)	18(48.6%)	0.06
No	110(78.6%)	91(88.3%)	19(51.3%)	0.08
NICU stay(days) Mean ± SD	1.84 ± 1.2	1.62 ± 1.1	1.82 ± 1.4	

Table 8 Comparison of FZR in predicting successful vaginal delivery in nulliparous women after induction of labor among other study

Studies	Sensitivity	Specificity	PPV	NPV	AUC
Present study (> 0.36)	0.90	0.89	0.93	0.75	0.93
Fitzgerald et al. (> 0.35)	0.86	1	1	0.50	0.92

to other studies. Cutoff value of TVL is similar to that of Katarzyna et al. study. Specificity of our study is comparable to that of Katarzyna et al. and Vallikkannu et al. study but less as compared to study done by Kanwar et al. PPV of our study (0.52) is minimum as compared to other study but NPV (0.94) is maximum (5,9,56).

For a predictive tool to be of value, it should have a high sensitivity, specificity, positive and negative predictive value. FZR > 0.36 is found to be a strong independent predictor of successful induction of labor in this study.

Strengths of the Study

1. The first Indian study to determine the minimum cutoff value of FZR (> 0.36) for the prediction of successful induction of labor
2. Our study population was a homogenous group of women of Indian ethnicity.
3. Our study population included only primigravida with singleton pregnancy beyond 40 weeks gestation and thus controlling many confounding factors.
4. All women were induced with dinoprostone gel, so procedure of induction was similar in all women.

Limitations of the Study

1. The results were limited to one hospital that may not be generlized for all settings.
2. Sample size was small, a larger sample size is recommended for more reliable interpretation of results.
3. The results of this study cannot be extrapolated in larger population.
4. There is a chance of inter- and intra-observer variability.

Conclusion and Recommendations

Fetal zone enlargement (fetal zone ratio > 0.36) is a strong predictor of successful induction of labor as compared to TVL and Bishop's score. It can be used for screening the women, who are destined for induction failure, so that adverse effects of induction of labor can be avoided.

If the prediction of success of induction of labor is low, then strict monitoring of labor, plotting partogram is important for early decision for LSCS. As the sample size is small, further studies with large sample size are suggested.

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Declarations

Disclosure of Potential Conflict of Interest None.

Ethical Statements Prior ethical clearance was obtained from Institutional Ethical Committee—Human Research of our institution.

Research Involving Human Participants and/or Animals Ethical clearance was obtained from Institutional ethical committee.

Informed Consent Written informed consent was obtained from all the participants.

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