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ORIGINAL ARTICLE

Role of Cervical Phosphorylated Insulin-Like Growth Factor-Binding Protein 1 (phIGFBP1) for Prediction of Successful Induction Among Primigravida with Prolonged Pregnancy

Aayushi Rathore[1] · Richa Sharma[1] · Rajarshi Kar[2] · Anupama Tandon[3] · Amita Suneja[1] · Kiran Guleria[1]

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Abstract

Purpose of the Study To estimate and to compare the levels of cervical phIGFBP-1 among primigravida with prolonged pregnancy, with and without successful induction of labor (IOL).

Methods A diagnostic study (cross-sectional study design) was conducted in our institution from November 2016 to April 2018 on 84 primigravida at ≥ 41 weeks with uncomplicated singleton pregnancy. The results were analyzed using SPSS software and receiver operating characteristics curves to determine the best cutoff using Youden Index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive (+ LR) and negative likelihood ratio (− LR) were calculated. *P* value < 0.05 was considered significant. Logistic regression analysis was used to determine the predictive ability of the three markers for successful IOL.

Results The cutoff level of phIGFBP-1, Bishop score (BS) and transvaginal cervical length (TVL) were 7.8 µg/l, 3 and 3.5 cm, respectively. The sensitivity, specificity, PPV, NPV, + LR and − LR of phIGFBP-1 (> 7.8 µg/l) were 0.87, 0.87, 0.89, 0.85, 6.76 and 0.15, respectively. Using logistic regression analysis, phIGFBP-1 was found to be the best predictor of successful IOL (OR 44.200; 95% CI 12.378–157.831, $p < 0.001$).

Conclusion phIGFBP-1 is a strong independent predictor successful IOL as compared to TVL and BS in primigravida with prolonged pregnancy.

Keywords phIGFBP1 · Bishop score · Transvaginal cervical length · IOL

Introduction

Induction of labor (IOL) is defined as artificial initiation of labor before its spontaneous onset for the purpose of delivery of fetoplacental unit [1]. IOL in prolonged pregnancies decreases the risk of perinatal deaths [2]. ACOG 2014 guidelines state that routine IOL should be considered at 41 weeks and is recommended at 42 weeks [3]. Predicting the outcome of IOL remains a clinical challenge.

Prolonged pregnancy is associated with increased risk of meconium stained liquor, meconium aspiration syndrome, poor neonatal APGAR, fetal macrosomia, birth injuries and still birth [4, 5].

At the same time, risk of maternal complications is also increased with increasing geatation like labor dystocia, 3rd and 4th degree perineal lacerations (related to macrosomia) and cesarean delivery [6].

As in Asian population the fetus and placenta matures faster than the western counterparts, hence IOL in prolonged

Aayushi Rathore is a Resident at Department of Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi, India; Richa Sharma is a Assistant Professor at Department of Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi, India; Rajarshi Kar is a Assistant Professor at Department of Biochemistry, UCMS & GTB Hospital, Delhi, India; Anupama Tandon is a Associate Professor at Department of Radio-Diagnosis, UCMS & GTB Hospital, Delhi, India; Amita Suneja is a Director Professor and Head at Department of Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi, India; Kiran Guleria is a Director Professor at Department of Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi, India.

✉ Aayushi Rathore
aayu9873@gmail.com

Extended author information available on the last page of the article

pregnancy is specially significant to prevent the associated complications. Nevertheless, IOL is itself associated with complications like uterine tachysystole (> 5 uterine contractions in 10 min), meconium-stained liquor and aspiration, failed IOL and fetal distress (fetal heart rate < 110 bpm). Hence, strict maternal and fetal monitoring is recommended following IOL [7].

Traditionally, Bishop score (BS) and transvaginal cervical length (TVL) were used to assess pre-induction cervical favourability. However, inter- and intra-observer variations reduce their positive predictive value [8–16].

Insulin-like growth factor binding protein 1 (IGFBP1) is an emerging pre-induction biomarker which has phosphorylated (decidua, secretory endometrium, liver and hepatoma cell line (HepG2) and unphosphorylated isoforms (amniotic fluid). It acts by binding with IGF I and IGF II but the exact mechanism of action is unknown [17].

Increased mechanical stress due to uterine contractions causes disruption of chorio-decidual interface and enhanced secretion of phIGFBP-1. Numerous studies have established the role of phIGFBP-1 in preterm deliveries, but very few have established its role in the success of IOL in prolonged pregnancy and to the best of our knowledge, none have estimated the cutoff level required to predict the outcome of IOL in prolonged pregnancy [18–22].

Commercially available strip test for detection of phIGFBP-1 in cervicovaginal samples (ActimPartus; Medix Biochemica) has detection limit ≥ 10 µg/l which indicates tissue disruption [23]. It is based on immunochromatography principle, and the test is considered positive if two blue lines appear. It is available at a cost of around INR 1300–1500 in India.

In this study, we attempted to explore the role of phIGFBP-1 as a biomarker for prediction of successful IOL in prolonged pregnancy and compared it TVL and BS. Findings of this study will be beneficial in identifying women at risk of failed induction and reduce unnecessary inductions.

Materials and Methods

This diagnostic study (cross-sectional study design) was conducted in Department of Obstetrics and Gynecology in our institution from November 2016 to April 2018.

Our aim was to study the role of cervical phIGFBP-1 for prediction of successful IOL among primigravida with prolonged pregnancy. The primary objective was to estimate and to compare the levels of cervical phIGFBP-1 women with and without successful IOL. The secondary objectives were to estimate the minimum cutoff value of cervical phIGFBP-1 required for successful induction, to correlate the time of induction to onset of active labor and delivery with levels of cervical phIGFBP-1, to determine the sensitivity, specificity, positive and negative likelihood ratio of cervical phIGFBP-1 and to compare cervical phIGFBP-1 levels with BS and TVL for successful IOL.

Ethical clearance was obtained from the institutional ethics committee. Primigravida with singleton pregnancy, vertex presentation, intact membranes at or beyond 41 weeks, not in labor, with regular menstrual cycles, sure of dates and/or with first trimester ultrasound and biophysical score ≥ 6 were included. Women with any pregnancy-related complications, macrosomia, fetal growth restriction, congenital fetal anomalies, decreased fetal movements and BPS < 6 were excluded.

Before IOL, the complications of prolonged pregnancy, risks and benefits along with procedure of IOL and the procedure of taking sample collection were explained. The patient was allowed to discuss her options with partner and family. Adequate time was given to her for decision and queries, if any, were resolved. Solid meals were permitted with IOL, and hydration was ensured. Pre-induction fetal heart assessment was done with non-stress test (NST). After taking informed consent, detailed history was taken, general physical examination and per-abdomen examination were done. Prior to IOL, fetal biometry, biophysical score were recorded and 0.2 ml of cervical secretions using tuberculin syringe from intracervical canal was taken. The sample was transferred into an Eppendorf tube, stored at − 10° C in refrigerator for maximum of 12 h and then sent to Biochemistry Department to be stored at − 70° C till further analysis. It was diluted appropriately and levels of phIGFBP-1 were estimated using sandwich ELISA kit from Biovendor, Germany following manufacturer's protocol. TVL and BS were recorded, and pelvic assessment was done to rule out cephalopelvic disproportion. As per institutional protocol, IOL was done followed by amniotomy and oxytocin infusion. Successful induction was defined as women entering into active stage of labor (4 cm cervical dilatation) or delivering vaginally. Failure of induction was defined as failure of onset of active stage of labor after 3 doses of dinoprostone gel or 5 doses of 25 µg misoprostol per vaginally, followed by amniotomy and titrated oxytocin infusion for 12 h. Fetal heart was monitored every 30 min in first stage and every 15 min in second stage of labor. The participants were followed until delivery and were divided into two groups depending upon the outcome of induction. Levels of phIGFBP-1 were estimated and correlated with the different outcome measures.

SPSS software was used for data analysis. ROC curves were made and best cutoff value of phIGFBP-1, BS and TVL were determined using Youden Index. Sensitivity, specificity, PPV, NPV, positive and negative LR were calculated. *P* value < 0.05 was considered significant. Unpaired student *t* test was used to compare the levels of phIGFBP-1, BS and TVL values between successful and failed inductions. Coefficient of correlation was used to determine the correlation

between phIGFBP-1, TVL and BS with time to active labor and time to delivery. Logistic regression analysis was used to determine the predictive ability of the three markers for successful IOL separately and in combination.

Results

There were 250 women fulfilling our inclusion criteria and were enrolled in this study. Out of these, 6 women delivered spontaneously, 3 women were lost to follow up, 1 woman developed obstetric complication (pre-ecclampsia) and therefore were excluded. Hence, 240 women completed the study and were followed until delivery. Out of 240, 84 women (including 45 successful induction and 39 failed induction cases) were randomly selected for further analysis. The study population was categorized into two groups: Group I (successful induction group) and Group II (failed induction group). The two groups were compared with respect to socio-demographic characteristics, maternal physical characteristics, delivery and neonatal outcomes, and the performance of phIGFBP-1, BS and TVL was compared between the two groups.

The mean age of the study population was 23.22 ± 3.21 years. 72.6% of the females were Hindus. 40.5% of the females were educated up to matriculate and only 11.9 females were illiterate. The mean BMI of the study population was 25.97 ± 3.45 kg/m^2. The study population largely comprised of females between 41 and 42 weeks (97.6%). 47.6% females delivered vaginally, 50% delivered by cesarean and 2.4% had instrumental delivery. 94% were induced using dinoprostone gel, while 6% were induced using misoprostol. The most common indication of cesarean delivery was failed induction (92.9%) followed by MSL with fetal distress among the successful induction group (4.8%). Antepartum complication occurred in 19% women after IOL; most common complication was MSL with fetal distress (15.5%). Postpartum complication occurred in 11.9% women after IOL; most common complication was PPH (8.3%). The mean birth weight of neonate in the study population was 3.03 ± 0.31 kg. The mean 1 min and 5 min APGAR score in the study population was 9.36 and 8.82. The mean number of days of NICU stay was approximately 1.9 days. There was one neonatal mortality in the study population (1.2%) that occurred due to neonatal sepsis (Table 1).

Based on the ROC curves, for the prediction of successful induction, the cutoff level of phIGFBP-1, BS and TVL were 7.8 µg/l, 3 and 3.5 cm respectively (using Youden Index). The area under curve (AUC) for the curve for phIGFBP-1, BS and TVL was 0.915, 0.700 and 0.782, respectively. On comparison, it was found that the AUC was the highest for phIGFBP-1, and hence, the prediction ability of phIGFBP-1 for successful IOL was better than BS and TVL (Figs. 1, 2, 3).

According to our study, the mean level of phIGFBP-1 in successful induction was 115.7 ± 269.71 µg/l, which was much higher than the levels in failed induction which was 3.99 ± 3.34 µg/l ($p = 0.008$). The mean BS was significantly higher in the successful induction group (2.38 ± 0.96) than the score in the failed induction group (1.69 ± 0.73, $p < 0.001$). It was found that successful induction was associated with a shorter TVL. The mean TVL in successful

Table 1 Comparison of socio-demographic, maternal, delivery and neonatal characteristics of the study population

	Study population ($N = 84$)	Group I ($n = 45$)	Group II ($n = 39$)	p value
	N (%)	*n* (%)	*n* (%)	
Mode of delivery				
Vaginal delivery	40 (47.6%)	40 (88.9%)	0 (0%)	
Cesarean	42 (50.0%)	3 (6.7%)	39 (100%)	
Instrumental delivery	2 (2.4%)	2 (4.4%)	0 (0%)	
Inducing agents				0.14
Dinoprostone gel	79 (94.0%)	44 (97.8%)	35 (89.7%)	
Misoprostol	5 (6.0%)	1 (2.2%)	4 (10.3%)	
Birth weight (kg) (Mean ± SD)	3.03 ± 0.31	3.05 ± 0.30	3.02 ± 0.32	0.68
Sex of baby				0.29
Male	40 (47.6%)	19 (42.2%)	21 (53.9%)	
Female	44 (52.4%)	26 (57.8%)	18 (46.1%)	
APGAR score-1 min (Mean ± SD)	9.36 ± 0.94	9.07 ± 1.09	9.69 ± 0.57	**0.002**
APGAR score-5 min	8.82 ± 0.62	9.71 ± 0.79	9.95 ± 0.32	0.068
NICU admission	14 (16.7%)	10 (22.2%)	4 (10.3%)	0.137
NICU stay (days) (Mean ± SD)	1.86 ± 1.66			
Neonatal mortality	1 (1.2%)	1 (2.2%)	0 (0%)	

p value <0.05 is considered significant in this study and has been highlighted in bold

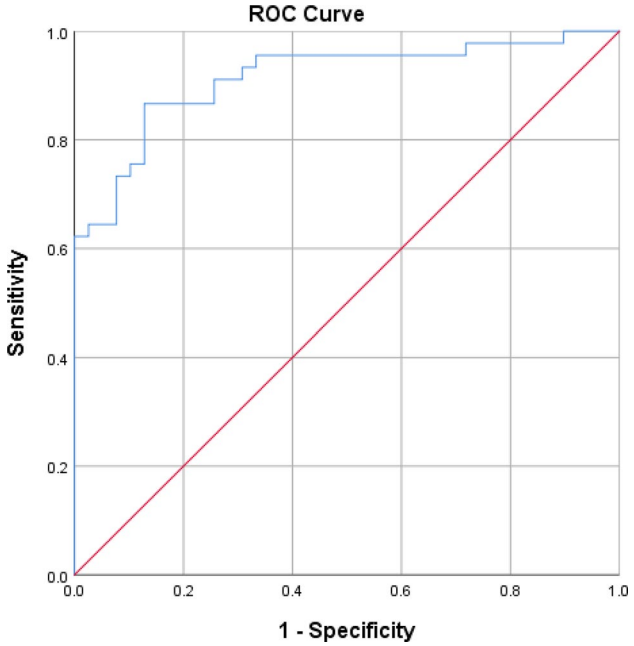

Fig. 1 ROC curve for phIGFBP-1

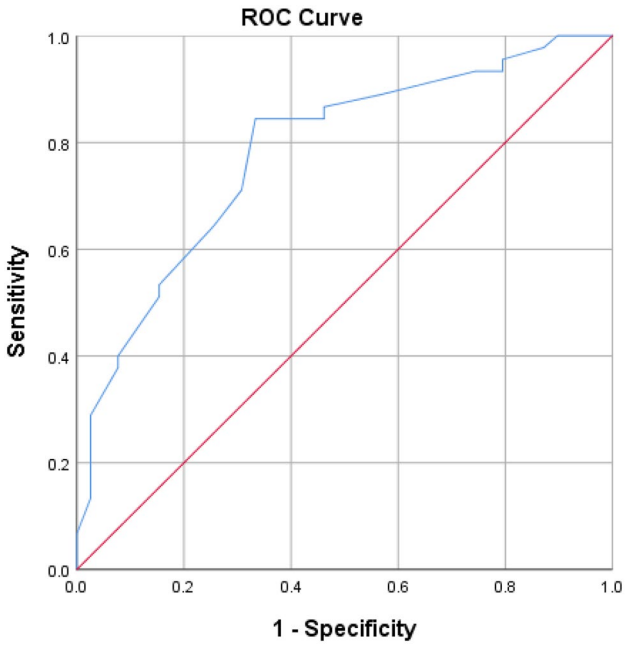

Fig. 3 ROC curve for transvaginal cervical length

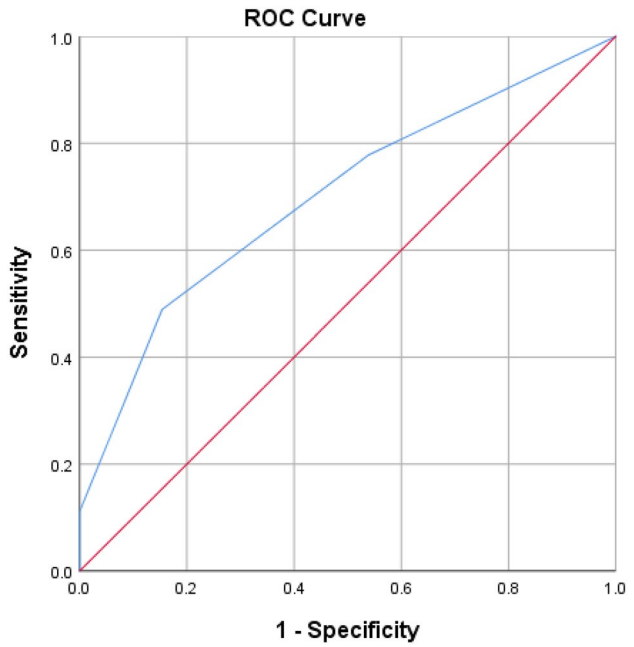

Fig. 2 ROC curve for Bishop Score

induction group was 3.11 ± 0.56 cm and in failed induction group the length was 3.71 ± 0.54 cm ($p < 0.001$).

The sensitivity, specificity, PPV, NPV, + LR and − LR of phIGFBP-1 (> 7.8 µg/l) were 0.87, 0.87, 0.89, 0.85, 6.76 and 0.15, respectively. The sensitivity, specificity, PPV, NPV, + LR and − LR of TVL (≤ 3.5 cm) were 0.84, 0.67, 0.75, 0.79, 2.53, 0.23 and 0.51, respectively. The sensitivity, specificity, PPV, NPV, + LR and − LR of BS (≥ 3) were 0.49, 0.85, 0.79, 0.59, 3.18, 0.60 and 0.34, respectively (Table 2).

Using univariate and multivariate logistic regression analysis, it was found that women having successful IOL were more likely to have a phIGFBP-1 levels > 7.8 µg/l ($p < 0.001$), BS ≥ 3 ($p = 0.002$) and TVL ≤ 3.5 cm ($p < 0.001$). All three variables were found to independently predict the success of IOL. However, phIGFBP-1 level > 7.8 µg/l was the best predictor of successful IOL (OR 44.200, 95% CI 12.378–157.831, $p < 0.001$) followed by TVL (OR 10.857, 95% CI 3.816–30.887) and BS (OR 5.261, 95% CI 1.845–15.004) (Table 3).

In our study, the median time from induction to onset of active labor and delivery was 8 h and 14 h when phIGFBP-1 level was > 7.8 µg/l. Using correlation coefficient, the increase in the levels of phIGFBP-1 was positively correlated with BS and inversely with TVL, thus indicating that higher levels of phIGFBP-1 are associated with cervical ripeness (Table 4).

Discussion

In this study, the levels of phIGFBP-1 were determined using IGFBP-1 ELISA kit (Biovendor Czech Republic). ROC curve was constructed to determine the optimal cutoff level of phIGFBP-1 (7.8 µg/l) for prediction of successful IOL. As far as we know, other international studies done on the role of phIGFBP-1 in IOL used a commercially

Table 2 Performance characteristics of phIGFBP-1, TVL and BS for prediction of successful IOL

Prediction criteria	Sensitivity	Specificity	PPV	NPV	+ LR	− LR	Youden index
phIGFBP-1 (> 7.8 µg/l)	0.87	0.87	0.89	0.85	6.76	0.15	0.74
TVL (≤ 3.5 cm)	0.84	0.67	0.75	0.79	2.53	0.23	0.51
BS (≥ 3)	0.49	0.85	0.79	0.59	3.18	0.60	0.34

PPV positive predictive values, *NPV* negative predictive values, + LR positive likelihood ratio, − *LR* negative likelihood ratio

Table 3 Logistic regression analysis with a reduced model produced by forward stepwise conditional elimination for likelihood of successful induction of labor

Characteristic	Univariate analysis		Multivariate analysis	
	Odds ratio estimate (95% CI)	*p* value	Odds ratio estimate (95% CI)	*p* value
phIGFBP-1				
> 7.8 µg/l	44.200 (12.378–157.831)	< 0.001	44.200 (12.378–157.831)	< 0.001
BS				
≥ 3	5.261 (1.845–15.004)	0.002		
TVL				
≤ 3.5 cm	10.857 (3.816–30.887)	< 0.001		

Table 4 Correlation of phIGFBP-1 levels with BS and TVL

Characteristic	BS (*p* value)	TVL (*p* value)
phIGFBP-1	0.275 **(0.011)**	− 0.254 **(0.020)**

p value <0.05 is considered significant in this study and has been highlighted in bold

available kit (Actim Partus kit) with a detection limit of 10 µg/l [18–22]. In our study, phIGFBP-1 was found to have a higher sensitivity and specificity (0.87 each) for prediction of successful IOL at levels > 7.8 µg/l, when compared to studies done by Katarzyna and Vallikkannu on a similar subset of population, i.e., nulliparous females (0.67–0.48 and 0.81–0.59 respectively). Though the PPV was comparable to the study done by Vallikkannu et al. (0.89 vs 0.82), it was much higher than the study done by Katarzyna et al. (0.89 vs 0.64). The NPV was found to be the highest in our study as compared to the studies done by Katarzyna et al. and Vallikkannu et al. (0.56 and 0.58 respectively). Also, the positive LR was the highest (6.76) when compared to the studies done by Katarzyna et al. (0.56) and Vallikkannu et al. (0.58) (Table 5) [18, 22].

Cheung et al. found a positive correlation between phIGFBP-1 levels and successful IOL which is consistent with our study. However, it reports that BS and TVL combined with maternal characteristics was a better predictor of successful IOL than either of them alone. Also the inclusion of phIGFBP-1 did not further improve the outcomes of their study. This is in sharp contrast to our study in which phIGFBP-1 was found to be the best independent predictor of successful IOL. This difference could be because of different study cohort. This study included both nulliparous and multiparous females, while our study was done exclusively on nulliparous females [20].

Riboni et al. proposed that IGFBP-1 and BS were found to be strong independent predictors of successful IOL compared to TVL. This result was in concordance with our study as phIGFBP-1 was found to be a strong independent predictor of successful IOL in our study. However, conflicting results were obtained for BS and TVL since our study reports better predictive ability of TVL than BS [21].

Dogl et al. reported that IGFBP-1 and TVL were the best predictors of successful IOL in post-term pregnancy, similar to this study. He also demonstrated that the presence of phIGFBP-1 in cervical secretions is associated

Table 5 Comparison of test characteristics of phIGFBP-1 in predicting successful vaginal delivery in nulliparous women after induction of labor (IOL) among various studies

Study	Sensitivity	Specificity	PPV	NPV	+ LR	− LR
Present study (cutoff level 7.8 µg/l)	0.87	0.87	0.89	0.85	6.76	0.15
Katarzyna et al.	0.67	0.48	0.64	0.56	1.28	0.69
Vallikkannu et al.	0.81	0.59	0.82	0.58	2.0	0.31

with shorter induction to delivery time. On comparison of induction to delivery time between the two, it can be inferred that induction to delivery time was higher at the cutoffs recommended in our study (phIGFBP-1 > 7.8, BS ≥ 3 and TVL ≤ 3.5 cm) [19]. On the other hand, although increased phIGFBP-1 did show reduced induction to delivery interval, this correlation was not found to be significant in our study [19].

Additionally, higher levels of phIGFBP-1 correlated with higher BS and lower TVL, i.e., with ripe cervix ($p = 0.011$ and 0.020, respectively) in this study. This was in concordance with the study done by Vallikkannu et al. and Nuutila et al. [22, 24].

For a predictive tool to be of value, it should have a high sensitivity, specificity, PPV and NPV. phIGFBP-1 fulfils all the above-mentioned criteria and is found to be a strong independent predictor of successful IOL in this study. However, the sensitivity and specificity of phIGFBP-1 need to be further analyzed on a larger subset of population as only one multicentric study done till now does not show any significant advantage in terms of sensitivity and specificity, which further limits its routine clinical application [21].

Although phIGFBP-1 is not a relatively new marker to predict successful IOL, its retrieval from the cervical secretions, preservation and chemical analysis requires special expertise and equipment which enhances the cost and makes it difficult to use in primary and secondary centers. This limits its role as a routine screening test in low resource settings.

The strength of this study is that it is possibly, the first Indian study to determine the minimum cutoff value of phIGFBP-1 required for the prediction of successful IOL in prolonged pregnancy. Our cohort was a homogeneous group of women of Indian ethnicity. Our study population included only Primigravida with singleton pregnancy beyond 41 weeks gestation and thus controlling many known confounding factors.

Conclusion

phIGFBP-1 is a strong independent predictor successful IOL as compared to TVL and BS in primigravida with prolonged pregnancy. It can be used for screening purpose, though its high price could be a constraint for its routine use in low resource settings. Further studies for validation of phIGFBP-1 as a marker for prediction successful IOL is required in a larger sample of Indian population in different clinical settings.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent Informed consent was obtained from all individual participants.

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About the Author

Aayushi Rathore She has completed her postgraduation in obstetrics and gynecology from UCMS & GTB Hospital, Delhi and is currently practicing as a senior resident at VMMC & Safdarjang Hospital, Delhi.

Affiliations

Aayushi Rathore[1] · Richa Sharma[1] · Rajarshi Kar[2] · Anupama Tandon[3] · Amita Suneja[1] · Kiran Guleria[1]

Richa Sharma
gautamdrricha1@gmail.com

Rajarshi Kar
rajarshi.kar@gmail.com

Anupama Tandon
anupamatandon@hotmail.com

Amita Suneja
amita_suneja@yahoo.co.in

Kiran Guleria
kiranguleria@yahoo.com

[1] Department of Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi, India

[2] Department of Biochemistry, UCMS & GTB Hospital, Delhi, India

[3] Department of Radio-Diagnosis, UCMS & GTB Hospital, Delhi, India