

Cervical insulin-like growth factor binding protein-1 (IGFBP-1) to predict spontaneous onset of labor and induction to delivery interval in post-term pregnancy

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Key words

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Abstract

Objective. To evaluate whether insulin-like growth factor binding protein-1 (IGFBP-1) assessed in cervical secretion can predict successful induction and spontaneous onset of labor in post-term pregnancy, compared to ultrasound measurement of cervical length and Bishop score. **Design.** Cohort study, originating from a randomized controlled trial. **Setting.** Obstetric department of a university and tertiary referral hospital, Norway. **Population.** Five hundred and eight post-term women who had been randomized to induction of labor or expectant management 1 week beyond estimated day of delivery (289 [±2] days of gestation). **Methods.** Time to delivery was related to presence of IGFBP-1 in cervical secretion, Bishop score and ultrasound measurement of cervical length recorded at inclusion. **Main outcome measures.** Spontaneous onset of labor and delivery within 3 days in the expectant management, and delivery within 24 hours of induction in the induction group. Test characteristics (sensitivity, specificity and negative and positive values and likelihood ratios) for IGFBP-1, Bishop score and cervical length were calculated. Logistic regression and Cox regression were used to account for parity and body mass index. **Results.** With expectant management, IGFBP-1 predicted spontaneous labor onset and delivery within 72 hours with low sensitivity and high specificity (0.45 and 0.80, respectively), as did Bishop score (0.24, 0.92). Cervical length was more sensitive (0.67, 0.58). IGFBP-1 predicted successful induction within 24 hours with low sensitivity and high specificity (0.30, 0.85), such as Bishop score (0.06, 1.00) and cervical length (0.45, 0.76). Parity enhanced successful induction. **Conclusion.** IGFBP-1 predicts both spontaneous labor onset and successful induction in post-term pregnancy. Bishop score and cervical length performed equally well.

Introduction

Contradictory opinions exist regarding management of the uncomplicated post-term pregnancy. It is a matter of debate whether to follow the development expectantly with serial antenatal surveillance or to induce labor. Induction may increase operative vaginal delivery rates, cesarean delivery rates and the incidence of excessive uterine activity with abnormal fetal heart rate patterns (1–3). A Cochrane review recommends that induction of labor should be offered to low-risk women at 41 completed weeks, and thereby reduce the risk

of perinatal death (4). Clinical tools for prediction of time to delivery or the induction-to-delivery interval would indeed be helpful in weighing the benefits and risks of different management.

A bedside test for phosphorylated isoforms of insulin-like growth factor binding protein-1 (IGFBP-1) has been suggested to predict success of labor induction (5). Phosphorylated isoforms of IGFBP-1, different from those found in amniotic fluid, are produced by decidual cells and are presented in the cervical secretion of women with intact fetal membranes. When the cervix matures, the decidua and

chorion will detach, causing proteins to leak into the cervical canal (5). Studies of IGFBP-1 and cervical ripeness in post-term pregnancies are lacking. In the clinical setting of post-term assessment, it would be useful to be able to predict imminent spontaneous onset of labor, or conversely identify cases where induction of labor will fail.

The aim of this study was to compare the diagnostic performance of IGFBP-1 test with the Bishop score and vaginal ultrasound scanning, with respect to time to spontaneous onset of labor and delivery in expectant management, and the time to delivery interval with induction in post-term pregnancy.

Material and methods

This study originated from a randomized controlled trial of post-term pregnancy management at St. Olav's University Hospital between September 2002 and July 2004. In Norway, pregnancies are dated by the 18-week ultrasound scan, and the duration of pregnancy is defined as 282 days. Detailed information about inclusion criteria, induction methods and study design has been published elsewhere (6). In brief, women were invited for a post-term follow-up 1 week after the estimated day of delivery (at 289 [± 2] days of gestation). All participants were informed and gave written consent. Women were randomly allocated to either immediate induction of labor (within 24 hours of randomization) or serial antenatal monitoring every third day until spontaneous delivery. The study included women with singleton pregnancies, fetus in cephalic presentation and no pre-labor rupture of membranes. The study showed that both expectant management and induction of labor led to equally good outcomes for the neonate as well as and the parturient.

A cervical assessment was done at the time of randomization, including IGFBP-1-test, transvaginal ultrasound measurements of the cervical length and a digital examination to assess the Bishop score (7). For the IGFBP-1-test (Actim Partus Test, Medix Biochemica, Kauniainen, Finland), a cervical secretion sample was obtained using a sterile dacron swab that was left in the cervix for 10–15 seconds. The swab was swirled in a test extraction solution for 10 seconds, and a dipstick in the solution indicated positive test if two blue lines appeared. The women were examined by transvaginal ultrasound in the dorsal lithotomy position. Cervical length was measured according to the method described by Valentin et al. (8). Cervical length < 26 mm was considered a 'short' cervix.

When the cervix was unfavorable (Bishop score ≤ 5), 50- μ g misoprostol was placed at 6-hourly intervals in the posterior fornix for induction of labor. Dinoprostone 0.5 mg intracervically every 12 hours was used when the uterus was scarred. Women who had a favorable cervix (Bishop score ≥ 6) were induced by amniotomy, followed by oxytocin infusion.

The clinical trial was approved by the Committee for Medical Research Ethics of Health Region IV (19.06.02, 106-01), Norway, and was registered in the Clinical Trial Registration (ClinicalTrials.gov, NCT00385229). Computerized randomization without stratification was used.

For the purpose of this study, we defined two cohorts. For parturients who were randomized to expectant management, we considered spontaneous onset of labor and delivery within 72 hours (3 days) as the outcome of interest. Among the induced parturients, we considered delivery within 24 hours after induction. The diagnostic information of the IGFBP-1 test, Bishop score and cervical length were related to the outcome in these cohorts.

Descriptive results are reported as median (range). Pearson's chi-squared test was used to compare categorical outcomes, and the Mann-Whitney U-test to analyze continuous variables. The diagnostic performance of each procedure was determined according to the usual definitions of sensitivity, specificity, positive and negative predictive value and likelihood ratio (9). Mc Nemar's test was used for paired comparison of test characteristics. Cases with missing values on one or more item were excluded from the respective analyses. A Kaplan-Meier plot with log-rank test was used to visualize and assess the respective time courses. Logistic regression was employed to investigate the impact of parity and body mass index (BMI) with respect to spontaneous onset of labor and delivery within 72 hours. Cox regression analysis was used to investigate the additional impact of parity and BMI regarding induction to delivery. Cesarean section and delivery after 24 hours were considered censored.

No power analysis was performed for this study specifically. Regarding the precision of test characteristics (such as sensitivity), the length of the confidence intervals varied between 0.10 and 0.20 given that approximately 50–100 observations were available for analysis (Tables 2 and 4).

A p -values < 0.05 were considered to indicate statistical significance and all tests were two-tailed. SPSS (SPSS Inc., Chicago, IL, USA) version 15, and the statistical software R were used for statistical analyses (10).

Results

Baseline characteristics of the study population are shown in Table 1. In the expectant management group, 59 (23%) of 254 women were induced due to medical reasons, one

Table 1. Baseline characteristics of the study population ($n = 391$).

| | |
|--------------------------|------------|
| Caucasian (n , %) | 382 (97.7) |
| Para 0 (n , %) | 168 (43.0) |
| Daily smoking (n , %) | 43 (11.0) |
| Age (mean, SD) | 30.1 (4.7) |
| BMI (mean, SD) | 30.1 (4.0) |

Note: SD, standard deviation; BMI, body mass index.

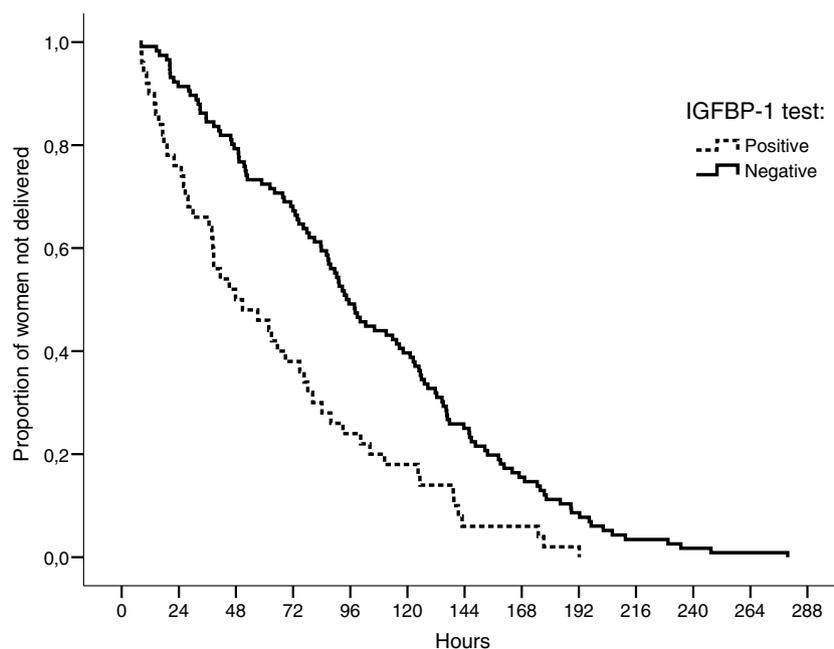


Figure 1. Expectant management group. Kaplan-Meier curves showing the remaining proportion of women in the monitoring group with spontaneous onset of labor delivering different hours after inclusion for positive and negative results of IGFBP-1 test.

woman declined to participate, two had cesarean delivery and 19 were induced according to the protocol at gestational day 300. Thus, a cohort of 173 women was available for analysis of time to delivery, but as IGFBP-1 test results were missing for seven women and Bishop score was missing in one, 166 and 172 women were available for analysis. In the induction group, 35 (14%) women progressed to spontaneous labor before the scheduled appointment for induction, and one woman had a cesarean delivery. Thus, a cohort of 218 women was available for analysis of time to induced delivery, but as IGFBP-1 test results were missing in nine women, the Bishop score in one and cervical length two women, 209, 217 and 216 cases were available for analysis, respectively.

In the expectant management group, 50 (30%) of 166 women had positive IGFBP-1 test results at inclusion. The median gestational age at delivery was 291 days (range 287–297) for IGFBP-1 test positive women compared with 293 days (range 289–301) for test negative IGFBP-1 women ($p < 0.001$). The Kaplan-Meier plots of time to spontaneous onset of labor and delivery after inclusion according to test result are shown in Figure 1. Time to delivery was significantly shorter for women with a positive IGFBP-1 test result (log-rank test, $p < 0.001$).

In the expectant management group, 25 (15%) of 172 women had Bishop score ≥ 6 at inclusion. The median gestational age at delivery was 290 (range 288–297) versus 293 days (range 287–301) for women with Bishop score ≥ 6 and ≤ 5 , respectively ($p = 0.001$). Cervical length shorter than 26 mm at inclusion was found in 91 (53%) of 173 women. Median gestational age at delivery was 292 (range 287–298)

versus 293 days (range 289–301) for women with a short and long cervix, respectively ($p = 0.002$).

Test characteristics with respect to spontaneous onset of labor and delivery within 72 hours of inclusion are shown in Table 2. A positive IGFBP-1 test had higher sensitivity than the Bishop score ($p = 0.007$), but lower than cervical length measurements ($p < 0.001$). The specificity for delivery within 72 hours was highest for Bishop score ≥ 6 compared with IGFBP-1 and cervical length ($p = 0.022$ and $p < 0.001$, respectively). The specificity for positive IGFBP-1 was higher than for cervical length < 26 mm ($p = 0.002$) (Table 2). Analyzing women who were randomized to induction but proceeded to spontaneous labor before induction was actually done (data not shown), led for all three assessment methods to a modest improvement in sensitivity and positive predictive value, but unaltered specificity and a slightly lower negative predictive value. In a stepwise logistic regression analysis, only IGFBP-1 test and cervical length predicted spontaneous onset of labor and delivery within 72 hours; neither Bishop score, parity nor BMI had significant impact (Table 3).

In the induction group, 59 (28%) of 209 women had positive IGFBP-1 test results at inclusion. The median induction to delivery time was 9 hours (range 2–59) for IGFBP-1 test positive women compared with 13 (range 2–58) among the negatives ($p < 0.001$). At inclusion 11 (5%) of 218, women had Bishop score ≥ 6 . The median induction to delivery time was 6 hours (range 2–17) versus 12 (range 3–59) for women with Bishop score ≥ 6 and ≤ 5 , respectively ($p = 0.005$). Cervical length shorter than 26 mm was found in 93 (43%) of 216 women at inclusion. Median induction to delivery time

Table 2. Spontaneous onset of labor and delivery with 72 hours in the expectant management group. Test characteristics for IGFBP-1 test, Bishop Score and cervical length.

| | Sensitivity | Specificity | PPV | NPV | PLR | NLR |
|----------------------------|--------------|---------------|--------------|---------------|------|------|
| IGFBP-1 test | (31/69) 0.45 | (78/97) 0.80 | (31/50) 0.62 | (78/116) 0.67 | 2.29 | 0.68 |
| 95% CI | (0.34–0.57) | (0.72–0.87) | | | | |
| Bishop score ≥ 6 | (17/72) 0.24 | (92/100) 0.92 | (17/25) 0.68 | (92/147) 0.63 | 2.95 | 0.83 |
| 95% CI | (0.15–0.34) | (0.86–0.96) | | | | |
| Length of cervix < 26 mm | (49/73) 0.67 | (58/100) 0.58 | (49/91) 0.54 | (58/82) 0.71 | 1.60 | 0.57 |
| 95% CI | (0.56–0.77) | (0.48–0.67) | | | | |

Note: PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; PLR: positive likelihood ratio; NLR: negative likelihood ratio.

Table 3. Expectant management group. Parameter estimates and *p*-values from logistic regression analysis with respect to spontaneous onset of labor and delivery within 72 hours.

| | Odds ratio estimate | | <i>p</i> -value |
|------------------|---------------------|-------------|-----------------|
| | Point estimate | 95% CI | |
| IGFBP-1 | | | 0.015 |
| Negative | 1.00 | Reference | |
| Positive | 1.51 | (1.19–5.30) | |
| Bishop score | | | 0.130 |
| ≤ 5 | 1.00 | Reference | |
| ≥ 6 | 2.24 | (0.79–6.39) | |
| Length of cervix | | | 0.037 |
| ≥ 26 mm | 1.00 | Reference | |
| < 26 mm | 2.14 | (1.05–4.37) | |
| Parity | | | 0.969 |
| Nulliparous | 1.00 | Reference | |
| Parous | 1.01 | (0.50–2.05) | |
| BMI | | | 0.812 |
| ≥ 30 | 1.00 | Reference | |
| < 30 | 1.09 | (0.81–1.51) | |

was 11 hours (range 2–36) versus 12 (range 3–59) for women with a short and long cervix ($p = 0.01$). In the survival analysis, 37 women were censored, 20 because of delivery beyond 24 hours and 17 because of cesarean section. There were three women with a positive IGFBP-1 test in each of these groups. Kaplan-Meier plots of the time from induction to delivery according to test results are shown in Figure 2. Time to delivery was significantly shorter for women with a positive IGFBP-1 test result (log-rank test, $p < 0.001$).

Test characteristics for induction to delivery within 24 hours are given in Table 4. The most sensitive test for predicting delivery within 24 hours was cervical length < 26 mm, compared with IGFBP-1 test and Bishop score ($p = 0.005$, $p < 0.001$). A positive IGFBP-1 test was more sensitive for delivery within 24 hours than Bishop score ≥ 6 ($p < 0.001$).

The Cox regression analysis of time to delivery after induction showed that multiparity, Bishop score ≥ 6 , positive

IGFBP-1 test and cervical length < 26 mm predicted earlier delivery (Table 5). BMI did not contribute.

Discussion

We found the IGFBP-1 test to be an independent predictor for successful induction within 24 hours in post-term pregnancies, performing equally well as cervical length and Bishop score, but with rather low sensitivity. In this population, we found high positive predictive values for induction to delivery within 24 hours with a positive IGFBP-1, similar to Bishop score ≥ 6 and cervical length < 26 mm. The IGFBP-1 test was as good as Bishop score and cervical length in predicting induction to delivery in post-term pregnancies. To predict spontaneous onset of labor and delivery within 3 days, the IGFBP-1 test was found to have low sensitivity and high specificity.

A possible limitation of the study is that separate parity was only considered in the multivariate models. We did indeed find inducibility to be associated with parity, in accordance with other studies, but parity was not associated with spontaneous onset of labor and delivery within 72 hours. We refrained from further sub-analyses (sensitivity etc.), as the study was not stratified by design.

Strengths of the study are the relatively large sample size, uniform dating of pregnancy by ultrasound scan and that only a few persons were involved in the examination of the participants (85% of the examinations were done by Runa Heimstad).

The IGFBP-1 test is quick and easy to use and may be less uncomfortable for the women compared with traditional methods such as the Bishop score or transvaginal ultrasound. It is, however, doubtful whether a new test could be recommended on economic considerations, as the test implies more expenses without adding further information.

In the clinical setting of post-term follow-up, the ability to predict spontaneous onset of labor within 72 hours is warranted. Our findings of positive predictive values of Bishop score and cervical length are in agreement with the study of Rozenberg et al. However, their study was based on a

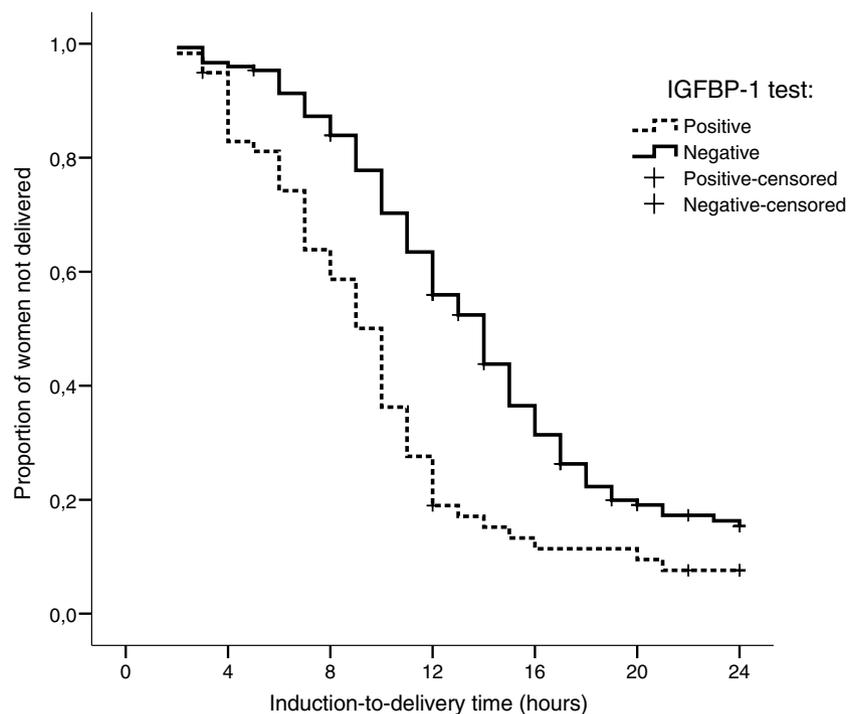


Figure 2. Induction group. Kaplan-Meier curves showing the remaining proportion of women in the induction group not delivered within 24 hours according to IGFBP-1 test. Cases with Cesarean section and delivery >24 hours were censored.

population of gestational week 39–40, and their predictive cutoff was 7 days (11).

We found short cervical length, a high Bishop score and a positive IGFBP-1 test to be associated with a lower gestational age at delivery, but only short cervical length and positive IGFBP-1 test were associated with spontaneous onset of labor. The comparative literature is conflicting. Both cervical length and Bishop score have been found to predict time to spontaneous onset of labor in prolonged pregnancies (12,13). Strobel et al. found Bishop score and cervical length to predict spontaneous onset of labor both within 24 hours and 48 hours. Within 96 hours, only the Bishop score was found to be an independent predictor in nulliparous women. In parous women, neither Bishop score nor cervical length could be used to predict onset of labor within 96 hours (13).

Vankayaalapati et al. found cervical length to be a significant independent predictor in nulliparous women (14).

The results of this study are in accordance with the study of Rane et al. in which cervical length, Bishop score and parity were found to be independent predictors of delivery within 24 hours after induction in prolonged pregnancies (15). Pandis et al. found that parity, cervical length and Bishop score provided independent information with respect to delivery within 24 hours of induction, using multivariable Cox regression analysis (16). Their study included women with pregnancies from 37 to 42 weeks of gestation and not only post-term pregnancies.

In conclusion, the IGFBP-1 test could be used to assess inducibility, but compared to established procedures as Bishop score and vaginal ultrasound measurements of

Table 4. Test characteristics for IGFBP-1 test, Bishop Score and cervical length for induction to delivery within 24 hours.

| | Sensitivity | Specificity | PPV | NPV | PLR | NLR |
|-------------------------|---------------|--------------|--------------|---------------|------|------|
| IGFBP-1 test | (56/189) 0.30 | (17/20) 0.85 | (56/59) 0.95 | (17/150) 0.11 | 1.98 | 0.83 |
| 95% CI | (0.23–0.37) | (0.62–0.97) | | | | |
| Bishop score ≥ 6 | (11/196) 0.06 | (21/21) 1.00 | (11/11) 1.00 | (21/206) 0.10 | NA | 0.94 |
| 95% CI | (0.03–0.10) | (0.77–1.00) | | | | |
| Length of cervix <26 mm | (88/195) 0.45 | (16/21) 0.76 | (88/93) 0.95 | (16/123) 0.13 | 1.89 | 0.72 |
| 95% CI | (0.38–0.52) | (0.52–0.92) | | | | |

Note: PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; PLR: positive likelihood ratio; NLR: negative likelihood ratio; NA: not available.

Table 5. Cox regression analysis of time to vaginal delivery within from induction, as observed in the induction group. Time beyond 24 hours and Cesarean section were censored.

| | HR | 95% CI | <i>p</i> -value |
|------------------|------|-------------|-----------------|
| IGFBP-1 | | | <0.001 |
| Negative | 1.00 | Reference | |
| Positive | 2.06 | (1.47–2.89) | |
| Bishop score | | | 0.039 |
| <6 | 1.00 | Reference | |
| ≥6 | 2.03 | (1.04–3.97) | |
| Length of cervix | | | <0.001 |
| ≥26 mm | 1.00 | Reference | |
| <26 mm | 1.88 | (1.36–2.59) | |
| Parity | | | <0.001 |
| Nullipara | 1.00 | Reference | |
| Multipara | 2.48 | (1.79–3.43) | |
| BMI | | | 0.82 |
| ≥30 | 1.00 | Reference | |
| <30 | 1.31 | (0.97–1.76) | |

Note: HR, hazard ratio.

cervical length, the test adds no further information. The IGFBP-1 test and cervical length are the best predictors of spontaneous onset of labor within 72 hours in post-term pregnancy.

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