## Original Article

# Outcomes of induction of labor with mature and premature amniotic fluid optical density (AFOD): A preliminary case control study

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**ABSTRACT**

**Background:** Onset of spontaneous labor occurs on completion of fetal functional maturity at amniotic fluid optical density (AFOD) value $0.98 \pm 0.27$ (Mean $\pm$ SD). All three events occurring together at any time from 35 to 42 weeks indicate individual term for each fetus. Babies born with AFOD $\leq 0.40$ are functionally premature and develop varying degrees of respiratory distress syndrome (RDS). In this study, we tested the hypothesis, labors with AFOD $0.98 \pm 0.27$ are functionally mature with well-established labor cascades and may respond well to induction. On the other hand, labors with AFOD $\leq 0.40$ are functionally premature with poorly established labor cascades and may not respond well to induction.

**Methods:** In this gestational age and parity-matched case control study, cases consisted of 36 uncomplicated singleton laboring women who delivered normally with premature ($\leq 0.40$) AFOD values. Controls consisted of 36 similar laboring women who delivered normally with mature AFOD ($0.98 \pm 0.27$) values. Uncentrifuged fresh AF samples collected at amniotomy were used for OD measurement with colorimeter at 650 nm. Women were assigned to groups based on AFOD values. In both groups, labor was induced with vaginal T. Misoprostol 25 mcg 6 hourly up to 4 doses. Labor outcome measures; Bishop score at induction, induction- delivery intervals (IDI), induction failures, number of T. Misoprostol required, presence of fetal distress, RDS, and NICU admission days were recorded in both groups and compared.

**Results:** Median Bishop scores at induction in cases and controls were 5.0 (IQR 4.25--6), 7.0 (IQR 6--8), respectively. Median IDI in cases and controls were 18 h (IQR 12.25--21.5 h) and 7.0 h (IQR 5--9.5 h), respectively. Number of induction failures in cases and controls were 8 and 0, respectively.

Outcomes of Induction of labor with....

Statistically significant differences observed in all these outcomes between groups ($P = 0.00$) favoring inductions with mature AFOD.

**Conclusion:** Labor induction with mature AFOD value was successful in all women with shorter IDI and with better perinatal outcomes.

**Key words:** Induction of labor; mature amniotic fluid optical density; premature amniotic fluid optical density.

## Introduction

In developing countries, up to 25% of all deliveries at term now involve induction of labor, but in some developing countries the rates are generally low.[1,2] Induction of labor is

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done for different indications like postdated pregnancy, PIH, GDM, and selected cases of scanty liquor. Failure to progress in labor is one of the commonest indications for cesarean section (CS) in current obstetrics. No progress in labor creates anxiety for the parturient and her bystanders, resulting in request or demands for CS. Threat of adverse outcomes and litigation around CS create stress to obstetrician, which results in increased CS rates.

The concept of "individualized term for each fetus," based on amniotic fluid optical density (AFOD) by Samartha Ram *et al* has given new insights into the physiology of spontaneous labor. Spontaneous onset of labor occurs at AFOD value 0.98 ± 0.27 (Mean ± SD), which coincides with completion of fetal functional maturity.[3]

All these three events occurring together at any time from 35+ weeks to 42+ weeks indicate "individual term for each fetus."[4-7] There are early maturing fetuses which attain completion of functional maturity as early as 35--36 weeks, and there are late maturing fetuses that attain completion of maturity as late as 41--42 weeks.[4-7]

### Hypothesis
Labors with AFOD value 0.98 ± 0.27 are functionally mature with well-established labor cascades and may respond well to induction. On the other hand, labors with AFOD ≤0.40 are functionally premature with poorly established labor cascades, and may not respond well to induction. This hypothesis is tested in this case control study by comparing the labor outcome measures between induced labors with premature and mature AFOD values.

## Methods

In this gestational age and parity-matched case control study, cases group consisted of 36 uncomplicated singleton laboring women who delivered normally with premature (≤0.40) AFOD values. Controls group consisted of 36 similar laboring women who delivered normally with mature (0.98 ± 0.27; Mean ± SD) AFOD values. Women were selected for these groups after AFOD estimation after AF sample collection at amniotomy. Labor induction was done for different indications like postdated pregnancy, PIH, GDM, and selected cases of scanty liquor in both groups. Cervical ripening by modified (Burnett's) Bishop score was recorded in both groups before induction. Labor was induced with vaginal Tab. Misoprostol 25 mcg 6 hourly up to 4 doses in both groups. Misoprostol doses were skipped when the uterine action was clinically adequate. If the labor was not progressing well after this trial, labor was reassessed clinically and by cardio tocography (CTG). If this assessment suggests fitness

for further trial, oxytocin infusion with 2.5 units in 500 ml dextrose saline was given. Fresh uncentrifuged AF samples were used for AFOD measurement with colorimeter at 650 nm. Multifetal pregnancies, malpresentations and positions, hydramnios, post-cesarean pregnancies, and cases with meconium stained liquor were excluded.

Labor outcome measures; induction-delivery intervals (IDI), induction failures, number of Tab. Misoprostol required, fetal distress, neonatal respiratory distress (NRD), and the NICU admission days required were recorded in both groups. Prophylactic antibiotic Cephazolin 1 g IV 12 hourly was given in cases of prolonged labor.

### Induction was considered "Failed"
When no significant cervical dilatation and descent of the presenting part was observed after 4 doses of misoprostol.

### Neonatal respiratory distress (NRD)
Respiratory grunting, labored breathing, intercostal recession, and transient tachypnea within 1 h after birth were considered as neonatal respiratory distress.

### Fetal distress was defined
Persistent fetal bradycardia, recurrent late decelerations, variable decelerations, and persistent fetal tachycardia (FHR >160) were considered as fetal distress.

### AF sample collection at amniotomy
After 4 cm of cervical dilatation, under good source of light, Sims speculum was applied and the membrane was visualized. AF sample was drawn using 2.5 cm long 23 G needle fitted with 2 ml disposable syringe.

### Method of measuring AFOD
The colorimeter was set at 650 nm wavelength. The test tube containing distilled water (control solution) was inserted into the cuvette holder of the machine and the "0" reading was adjusted. Then this control test tube was removed from cuvette holder, and the test tube containing fresh uncentrifuged AF sample was inserted. With the press of enter button, the AFOD value can be read directly from the display screen.

Informed and written consent was obtained from all the subjects who participated in this study. This study confined to the standards of declarations of Helsinki.

### Statistical analysis
Statistical analysis was done using SPSS Windows Version 20.0. Armonk, NY. As the distribution was non-Gaussian, we presented the median with interquartile range for continuous

variables, and percentage for categorical variables. Chi-square test was used to compare the outcomes of categorical variables by groups. Mann--Whitney test was used to compare the average of outcome measures of the two groups. The cutoff point for statistical significance was set at α-level of 5%. Logistic regression analysis and ROC curve analysis was done for Bishop scores at induction, IDI, induction failures, and NRD.

## Results

The median maternal age in cases was 23 years (IQR 20--25 years), and in controls it was 24 years (IQR 20--25 years). The median parity in cases was 1.5 (IQR 1--2), and in controls it was 1.5 (IQR 1--2). The median CRL GA at induction in cases was 38.6 weeks (IQR 37.7--40.0 weeks), and in controls it was 39.0 weeks (IQR 38.4--39.8 weeks). No statistically significant differences were observed in these parameters between cases and controls, with *P* values 0.599, 0.653, and 0.431, respectively [Table 1].

In 36 women of control group, the median AFOD value was 1.00 (IQR 0.80--1.15). These mature AFOD values were observed at different gestational ages ranging from 36 weeks to 42 weeks. In 36 women of cases group, the median AFOD value was 0.38 (IQR 0.24--0.48). These premature AFOD values were observed at different gestational ages ranging from 36 weeks to 40.6 weeks [Table 1].

The median Bishop score at induction in cases was 5.0 (IQR 4.25--6), and in controls it was 7.0 (IQR 6--8). This difference is statistically significant, *P* < 0.000 [Table 1].

The median IDI in cases was 18.0 h (IQR 12.25--21.5 h), and in controls it was 7.0 h (IQR 5--9.5 h). This difference is statistically significant, *P* < 0.000 [Table 1].

The total number of T. Misoprostol required in cases group was 96 (Median 3.0: IQR 2--3), and in controls group it was 56 (Median 1.5: IQR 1--2). This difference is statistically significant, *P* < 0.000 [Table 1].

The total number of NICU admission days required in cases was 39 (Median 1.0: IQR 0--1), and in controls it was 8 (Median 0.0: IQR 0--0). This difference is statistically significant, *P* < 0.000 [Table 1].

As per the defined criteria, none of the women had induction failure in controls group (0%), whereas in cases group, inductions failed in 8 (22.22%) women. This difference is statistically significant, *P* < 0.000 [Table 1].

In cases, 17 babies (47.2%) developed NRD, whereas in controls none of the babies (0%) developed NRD. This difference is statistically significant, *P* < 0.000 [Table 1].

In cases, 13 babies (36.9%) developed fetal distress, where as in controls 3 babies (8.3%) developed fetal distress. This difference is statistically significant, *P* < 0.005 [Table 1].

### Logistic regression analysis
#### Bishop score at induction
We categorized Bishop score into two groups. A score of >5 was considered as favorable and <5 was considered as unfavorable. Logistic regression analysis showed regression coefficient −3.601 and the odds ratio 0.027. For an additional increase of AFOD by 0.01, the odds of Bishop score being unfavorable reduces by 0.973%. *P* =0.000 [Table 2].

#### Induction-delivery interval
We classified IDI in to either normal (for primygravida <12 h, and for multigravida <8 h) or prolonged. Logistic regression

**Table 1: Comparison of labor outcome measures between 'Cases group' and 'Controls group'**

| Variable | Pre mature AFOD. Cases group, *n*: 36, Median (I.Q.R) | Mature AFOD. Controls group, *n*: 36 Median (IQR) | Statistical test used | Significance *P* |
|---|---|---|---|---|
| Maternal Age | 23 (20-25) | 24 (20-25) | Mann-Whitney | 0.599 |
| Para | 1.5 (1-2) | 1.5 (1-2) | Mann-Whitney | 0.653 |
| CRL. GA at induction | 38.6 (37.7- 40.0) | 39.0 (38.4-39.8) | Mann-Whitney | 0.431 |
| AFOD at ARM | 0.38 (0.24-0.45) | 1.00 (0.80-1.15) | -- | -- |
| No of T. Misopr. used | 3.0 (2-3) | 1.5 (1-2) | Mann-Whitney | <0.000 |
| Induct. del. interval | 18.0 (12.25-21.5) | 7.0 (5-9.5) | Mann-Whitney | <0.000 |
| NICU days | 1.0 (0-1) | 0.0 (0-0) | Mann-Whitney | <0.000 |
| Induction failures | 8 (22.22%) | 0 (0%) | Chi-square | <0.000 |
| NRD | | | Chi-square | |
| No | 19 (52.8%) | 36 (100%) | | <0.000 |
| Yes | 17 (47.2%) | 0% | | |
| Fetal. distress | | | | |
| No | 23 (63.9%) | 33 (91.7%) | Chi-square | 0.005 |
| Yes | 13 (36.1%) | 3 (8.3%) | | |

AFOD, Amniotic fluid optical density; NRD, Neonatal respiratory distress

analysis showed regression coefficient −4.479 and the odds ratio 0.011. For an additional increase of AFOD by 0.01, the odds of prolonged IDI reduces by 0.989%, $P$ = 0.000 [Table 2].

### Neonatal respiratory distress (NRD)
Logistic regression analysis showed regression co efficient −6.731 and the odds ratio 0.001. For an additional increase of AFOD by 0.01, the odds for developing NRD reduce by 0.991%, $P$ = 0.002 [Table 2].

### Induction failure
Logistic regression analysis showed regression coefficient −11.500 and the odds ratio 0.000. For an additional increase of AFOD by 0.01, the odds of induction failure reduce by 1%, $P$ = 0.012 [Table 2].

### ROC Curve analysis
ROC curves were constructed for Bishop score at induction, IDI, NRD, and induction failures [Figures 1 and 2]. From the ROC curve, the optimized cutoff AFOD value was determined as 0.41. All the ROC curves for these variables were very well above the 45° line, indicating that there is a very significant

relationship between AFOD and these outcome variables. The sensitivity, specificity, and the area under ROC curve to predict the outcomes at this cutoff AFOD value are shown in Table 3.

## Discussion

Onset of spontaneous labor occurs on completion of fetal functional maturity at AFOD value 0.98 ± 0.27 (Mean ± SD). All these three events occur together at any time from 35 weeks to 42 weeks indicating individual term for each fetus. There are early maturing fetuses which attain completion of functional maturity as early as 35--36 weeks, and there are late maturing fetuses that attain completion of maturity as late as 41--42 weeks.[4-7] Babies born with AFOD value ≤0.40 are functionally premature and develop varying degrees of respiratory distress, irrespective of gestational age and birth weight.

Rising levels of amniotic fluid lecithin during third trimester induces progressive and rapid detachment of vernix from fetal skin surface, which gets mixed with amniotic fluid, results in rapid change of color in liquor before the onset of spontaneous labor.[4,8] The color of liquor to start with looks watery, then changes to milky, buttermilk like, and then to curd like. There is a slow and prolonged rise in AFOD till a value around 0.40 is reached. After this value is attained, the AFOD rises rapidly like a surge, which coincides with the onset of spontaneous labor.[4,8] The duration of surge, that is, the number of days required for AFOD rising from 0.40 to 0.98 is around 8–10 days.[4]

**Table 2: Results of logistic regression analysis are shown**

| Variable | B (L.R co efficient) | (Log B) odds ratio | Percentage change in odds | $P$ |
|---|---|---|---|---|
| Bishop score at induction | −3.601 | 0.027 | 97.3 | 0.000 |
| Induction Delivery Interval | −4.479 | 0.011 | 98.9 | 0.000 |
| NRD | −6.731 | 0.001 | 99.1 | 0.002 |
| Induction failures | −11.500 | 0.000 | 100 | 0.012 |

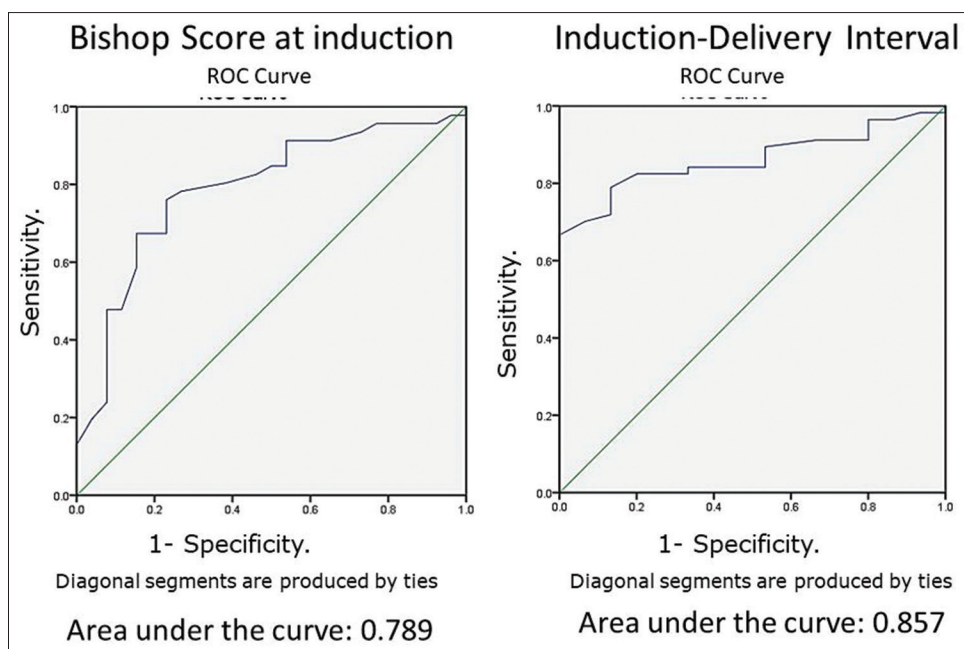NRD, Neonatal respiratory distress



Figure 1: ROC Curves of Bishop score at induction and induction-delivery interval
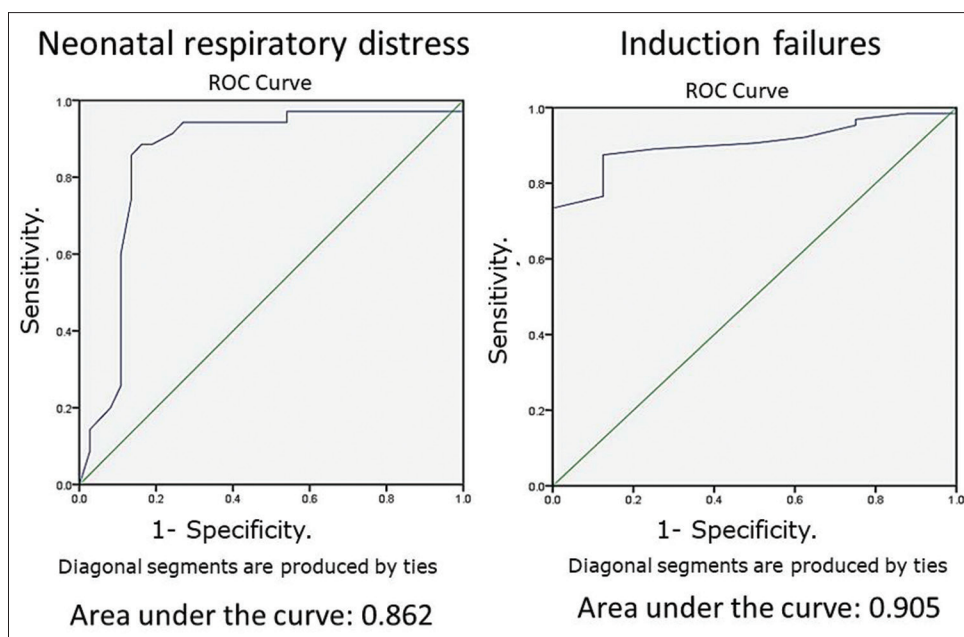
**Figure 2: ROC Curves of neonatal respiratory distress and Induction failures**

**Table 3: The sensitivity, specificity and area under ROC curve to predict the outcomes at a cut-off AFOD value of 0.41 are shown**

| Outcome | Sensitivity (%) | Specificity (%) | Area under curve (95% CI) |
| --- | --- | --- | --- |
| Unfavorable Bishop score | 82.6 | 54.8 | 0.789 |
| Prolonged induction-delivery intervals | 94.3 | 54.1 | 0.857 |
| NRD | 82.5 | 80.0 | 0.862 |
| Induction failures | 76.6 | 87.5 | 0.905 |

NRD, Neonatal respiratory distress

Human amniotic fluid cells can produce prolabor cytokines like IL6, IL8, IL1 beta, and EGF, which can trigger the expression and production of uterine activation proteins (UAPs) and prostaglandins.[9,10] During this phase of AFOD surge, the released uterine activation proteins and prostaglandins produced by the detached vernix cells induce changes (preparations) in cervix, uterus, and vagina for the onset of spontaneous labor.[4]

In this study, in 36 women of controls group, mature AFOD values (median: 1.00, IQR 0.80 --1.15) were observed at different gestational ages ranging from 36 weeks to 42 weeks. All these babies were fully functionally mature and none of them developed NRD, irrespective of gestational age and birth weight (concept of individual term for each fetus).

In 36 women of premature AFOD group, premature values (median: 0.38, IQR 0.24--0.48) were observed at different gestational ages ranging from 35.7 weeks to 40.6 weeks. All these babies were functionally premature, and 17 of them developed NRD. These babies are delayed maturers and might have attained completion of functional maturity in due course of time.

More favorable Bishop scores at induction, shorter IDIs, and lesser number of Tab. Misoprostol required, and lesser induction failures were observed in mature AFOD group when compared with premature AFOD group [Table 1]. These results indicate the preparations for onset of spontaneous labor had taken place in mature AFOD group when compared with premature AFOD group. Results of regression analysis and ROC curve analysis also showed inductions of labors with mature AFOD values are having better labor outcomes when compared with labors with premature AFOD values.

Number of babies that developed fetal distress, and the NICU admission days required were also less in mature AFOD group. All these observations indicate that induction of labor with premature AFOD values result in iatrogenic prematurity and adverse maternal and perinatal outcomes when compared with inductions with mature AFOD values.

As primary CS rates are increasing steeply, repeat sections are also rising in geometrical proportions. Most of these sections are done electively without confirming fetal functional maturity. This results in iatrogenic prematurity

and increased NICU admissions. ACOG and RCOG guidelines recommend confirmation of lung maturity before elective termination of pregnancies before 38 completed weeks of gestation to prevent respiratory morbidity.[11,12] The only way to confirm lung maturation is by L/S ratio estimation, which needs amniocentesis. Instead of costly, cumbersome, and delayed L/S ratio estimation, AFOD estimation can be done. USG-guided amniocentesis at term is a simple and safe procedure, as many amniotic fluid pockets are available superficially, and can be accessed within a depth of 2.5 cm.

If AFOD value is premature, decision for induction or CS can be postponed. If AFOD value is known, it is also possible to predict the number of days required for completion of fetal functional maturity. Based on this, it is possible to program elective CS or induction of labor. A course of steroids may also be given to hasten foetal functional maturity whenever needed.

The incidence of meconium stained liquor prior to spontaneous labor was found to range between 6 and 11%.[13] Amniocentesis before induction also helps to pick up these women. Elective CS can be done to avoid induction on already distressed fetus to prevent intrapartum fetal distress, foetal death, and meconium aspiration syndrome.

## Conclusion

Inductions guided by AFOD result in delivery of babies at optimal maturity, and significantly reduce prolonged labor, induction failures, respiratory morbidity, NICU admissions, and CS rates. Further research in this area should be directed to find out noninvasive alternatives to AFOD by imaging technologies to avoid invasive amniocentesis. Further studies are needed to confirm our observations with larger sample size.

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Nil.

### Conflicts of interest
There are no conflicts of interest.

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