

Role of Amniotic Fluid Optical Density (AFOD) and Low dose Isoxsuprine Hcl rapid infusion tocolysis for the management of PTL.

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Abstract:

Background: S. Ramet al reported: Onset of spontaneous labor occurs at completion of fetal functional maturity at AFOD value of 0.98 ± 0.27 (at 650nm). All these events together occurring at any time from 35+ wks to 42+ wks indicate individual term for each fetus^{1,2}. Preterm labors with AFOD 0.98 ± 0.27 are mature and cannot be stopped by any means, as labor cascades are already established. Babies born with AFOD < 0.40 are functionally premature^{1,2}, and we expected these premature labors would respond well for tocolysis and other methods for continuation of pregnancies as labor cascades are not fully established.

Methods: In this case series study, 22 singleton pregnant women who were in preterm labor (PTL), and who underwent CRL gestational age estimations, 5 of them PTL with membrane rupture and 17 without membrane rupture were included. USG guided amniocentesis was performed as per the ACOG guidelines, and AFOD estimations were done for fresh uncentrifuged samples. Antenatal corticosteroids, low dose Isoxsuprine Hcl rapid infusion tocolysis, and weekly 17-alpha hydroxy progesterone caproate were given. After successful tocolysis and continuation of pregnancies, AFOD estimations were repeated when women presented with labor pains again before 37w+6 days. Women were allowed to deliver if mature or near mature AFOD values were observed. AFOD estimations were also done at spontaneous labor or at caesarean sections after 38 wks. Babies were observed for functional maturity in terms of color of skin, adherence of vernix, and development of RDS. Results were presented in two tables and analyzed.

Results: In non-membrane rupture group (N=17), pregnancies could be continued for 1 to 7 wks. In membrane rupture group, in N=2/5 women leak could be stopped and pregnancies could be continued for 3 to 6 wks. Except one, in both groups all babies could attain mature or near mature AFOD values irrespective of GA and birth weight, no RDS was observed, and all babies survived.

Conclusion: With AFOD guided PTL management coupled with low dose Isoxsuprine Hcl rapid infusion tocolysis, pregnancies could be continued to completion of fetal functional maturity in 21/22 women with good neonatal outcome.

Key Words: Amniotic fluid optical density (AFOD), Low dose Isoxsuprine hydrochloride infusion, Increased drop rate, Preterm labor.

I. Introduction:

Premature birth is a global problem. It is the leading cause of neonatal mortality and long term neurological morbidity³. Preterm birth was also suggested to predispose for long term morbidities like diabetes mellitus, hypertension, obesity, and stroke³. As many as 15 million preterm births occurred worldwide in the year 2010 as per the Lancet report published in the year 2012⁴. Majority of these preterm births occurred in low resource countries of south Asia, and sub Saharan Africa. India was the leading country contributing 3.5 million preterm births to the global burden⁴. The global action report by WHO "Born too soon" says the incidence of preterm birth is progressively increasing world over⁵. In developing countries poor resources and poor infrastructure is the cause, whereas in developed countries, 80% of premature births occur due to iatrogenic late preterm births⁵.

In terms of etiopathogenesis, asymptomatic bacteriuria, bacterial vaginosis, periodontal disease, cervical shortening, and genetic factors were extensively explored³. A systemic review and meta-analysis of 95

randomized controlled trials found that compared with placebo, prostaglandin inhibitors exhibited the highest probability of delayed delivery by 48hrs with no class superior to placebo in reducing neonatal respiratory distress syndrome³. This shows that, with available scientific knowledge and modalities we are not able to continue many pregnancies beyond 48hrs or at least to achieve lung maturity. We are not able to predict, prevent or effectively treat preterm birth. All this shows that there is a gross deficiency in understanding the whole problem.

Amniotic Fluid Optical Density (AFOD) research by S. Ram et.al had given new insights in to the physiological aspects of fetal functional maturity and onset of spontaneous labor^{1,2}. Babies attain completion of functional maturity at AFOD (at 650nm) value around 0.98. At this AFOD value women go in for spontaneous labor. But this AFOD value around 0.98, completion of functional maturity and onset of spontaneous labor, that all go to gather can occur at any time from 35+ wks to 42+ wks indicating [individualized term for each fetus](#)^{6,7}. Further, [babies born with AFOD <0.40 are functionally premature](#) and develop varying degrees RDS irrespective of gestational age and birth weight¹. [A baby can be fully functionally mature](#) even at 35+ wks if the AFOD value is around 0.98. On the other hand [a baby can be functionally premature](#) and develop RDS even at 40 wks if AFOD value is <0.40 (term RDS)^{6,7}.

Preterm labors with AFOD value around 0.98 are mature and cannot be stopped by any means as labor cascades are already and fully established. On the other hand labors with AFOD <0.40 are functionally premature; and we expected these labors would respond well for tocolysis and other methods for continuation of pregnancies as the labor cascades are not fully established. In this study we analyzed the results of 22 women with PTL who underwent AFOD guided preterm labor management coupled with low dose Isoxsuprine Hcl rapid infusion tocolysis⁸

II. Methods:

In this case series study of 22 singleton pregnant women who were in preterm labor (PTL), and who underwent CRL gestational age estimations, 5 of them PTL with membrane rupture and 17 without membrane rupture were included. Women with cervical dilatation more than 3cm, rupture of membranes more than 6hrs, evidence of active infection, HT disorders of pregnancy, GDM, medical disorders complicating pregnancy, and multi fetal pregnancy were excluded. PTL was diagnosed as per the ACOG criteria 1997⁹. USG guided amniocentesis was performed as per the ACOG¹⁰ guidelines for AFOD estimations. Blood stained and meconium stained AF samples were excluded from study. AFOD estimations were done for uncentrifuged fresh AF samples with colorimeter at 650nm. The women were kept in left lateral position with foot end elevation. Intravenous antibiotics Cefotaxime and metronidazole were given. Antenatal corticosteroids, Betamethasone 12mg/daily for two days were given¹¹. Inj. 17alpha Hydroxy progesterone caproate 250mg I.M weekly was given before 24 wks of gestation, and after 24 wks, 500mg I.M weekly was given. Low dose Isoxsuprine Hcl rapid infusion tocolysis⁸ was given. All women were advised to take plenty of oral fluids. After successful tocolysis and continuation of pregnancies, AFOD estimations, and tocolysis were repeated when women presented with labor pains again before 37w+6days. Women were allowed to deliver when mature or near mature AFOD values were observed. AFOD estimations were also done for AF samples collected at spontaneous labors and at caesarean sections after 38 wks.

Babies were observed for functional maturity in terms of color of the skin, adherence of vernix caseosa on skin surface, and development of RDS at birth. Informed and written consent was obtained from all subjects who participated in this study. This study conforms to standards of declarations of Helsinki.

In membrane intact group of 17 women, Gravida, para, AFOD values at different gestational ages, mode of delivery, duration of pregnancy that could be continued, development of RDS, number of days in NICU, birth weights and neonatal outcomes were presented in **Table 1** and analyzed.

In membrane rupture group of 5 women, the details of outcome of leaking membranes, AFOD values at different gestational ages, mode of delivery, duration of pregnancy that could be continued, development of RDS, number of days in NICU, birth weights and neonatal outcomes were presented in **Table 2** and analyzed.

Techniques of sample collection: USG guided Amniocentesis was performed, under aseptic precautions without any anesthesia, from the most superficial pocket which do not contain cord or placenta, using 2ml disposable syringe fitted with 2.5 cm long 23G needle drawing 2cc of amniotic fluid.

[Sample collection at amniotomy in laboring subjects](#): Under Sims speculum examination, with good source of light membranes were visualized, and 2ml disposable syringe fitted with 2.5 cm long 23 G needle was used to pierce the membrane and draw the AF sample. Membranes were pierced when the uterus was not acting and when membranes were not under tension to avoid splashing of AF.

[Sample collection at caesarean sections](#): While doing cesarean section, careful hysterotomy was performed avoiding injury to bulging membranes. With 2ml disposable syringe fitted with 2.5 cm long 23 G needle, the membrane was pierced and the AF sample was drawn

Method of measuring AFOD: The colorimeter was set at 650 nm wave-lengths. The test tube containing distilled water (control solution) was inserted in to the cuvette holder of the machine and '0' reading was adjusted. Then the test tube containing fresh uncentrifuged A.F sample was inserted, and with a press of a button the AFOD value was directly read from the display screen of the machine.

Low dose Isoxsuprine Hcl rapid infusion tocolysis⁸: In this technique instead of usually given 40mg (4amps) of Isoxsuprine Hcl in 500ml 5% dextrose 40drops/min, we gave 10mg (1amp) of Isoxsuprine Hcl in 500ml 5% dextrose 160drops/min. This is, one fourth dose of the drug with 4times increased drop rate delivering same 200micgr of beta mimetic drug/min. Initially we ran 2 pints of this low dose Isoxsuprine Hcl infusion at the rate of 160-180drops (10ml/min). Later the drop rates were adjusted as 80drops/min or 40drops/min, or stop the drip based on the uterine activity. After 24hrs, two pints of this low dose rapid infusion tocolysis was given in bid dose for 2-3 days. The women were ambulated gradually when the uterine activity comes under satisfactory control.

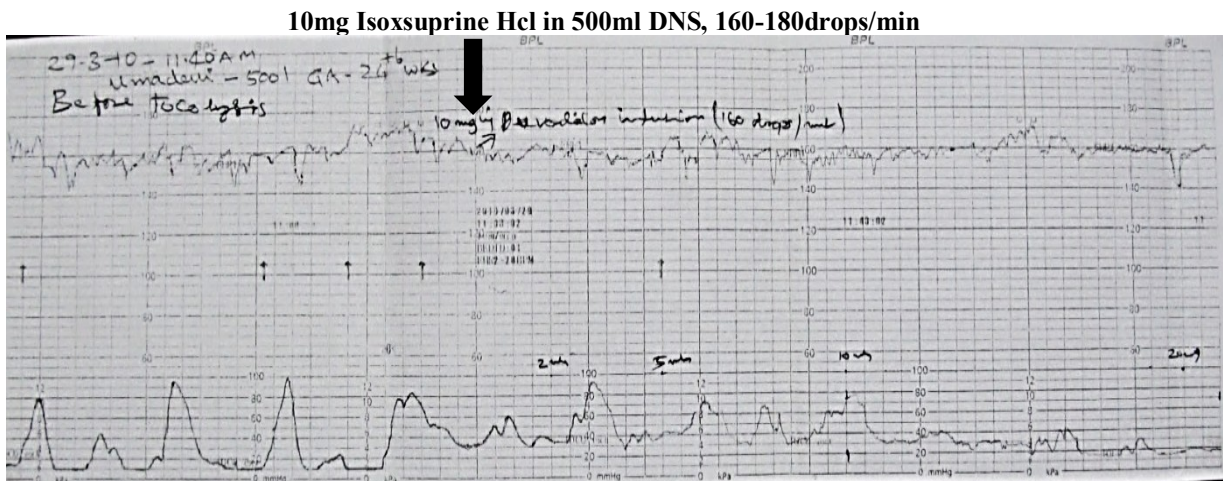


Fig 3: Satisfactory cessation of uterine activity could be achieved with 10mg Isoxsuprine Hcl infusion at the rate of 160-180drops/min within few minutes after initiation of therapy.

10mg Isoxsuprine Hcl in 500ml DNS, 160-180drops/min

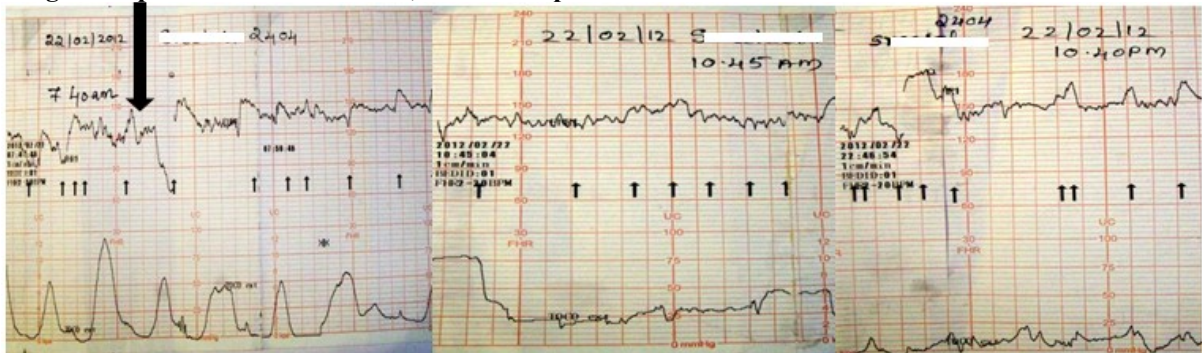


Fig 3: Pregnancies could be continued for longer periods by repeated use of 10mg Isoxsuprine Hcl rapid infusion tocolysis.

III. Results

In both groups, different babies attained mature AFOD values (0.98 ± 0.27) at different gestational ages ranging from 33wks+ 4days to 40wks +3days.

In membrane intact group of 17 women (Table.1), pregnancies could be continued for a variable period of 1wk to 7wks +3days. In all babies, completion of functionally maturity status could be achieved with AFOD values 0.98 ± 0.27 irrespective of GA and birth weight. Their skin was mature pale brown in color with very little or no vernix caseosa on skin surface. None of the babies developed RDS, and all of them survived. Babies with case Nos. 4, 12, 14, and 16 had either low birth weights or low AFOD values and they required only warmer care and feeding in NICU for a variable period of 4 to 12days. In case No.3 there was grade 2 meconium stained liquor on amniocentesis, and we took this woman for cesarean section without trial.

Table.1: Clinical details and results of AFOD guided PTL management in membrane intact group.

| SL no | Gr | P a r a | GA at PTL wk.+d | AFOD on Admn | GA at rec of PTL wk+d | AFOD at rec of PTL | GA at del wk+d | AFOD at del | Mode of del | Birth wt Kg | Preg. cont. wt wk+d | R D S | Warmar care days | Neo-natal out come |
|-------|----|---------|-----------------|--------------|-----------------------|--------------------|----------------|-------------|-------------|-------------|---------------------|-------|------------------|--------------------|
| 1 | 2 | 1 | 35+1 | 0.15 | 37+6 | 0.45 | 39+1 | 0.97 | Lscs | 2.88 | 2 + 5 | Nil | -- | good |
| 2 | 2 | 1 | 33+1 | 0.21 | -- | -- | 38+4 | 1.74 | Lscs | 2.65 | 5 + 6 | Nil | -- | good |
| 3 | 2 | 1 | 36+0 | 0.36 | -- | -- | 38+0 | Mec | Lscs | 3.10 | 1 + 4 | Nil | -- | good |
| 4 | 1 | 0 | 35+5 | 1.14 | -- | -- | 35+5 | 1.14 | ND | 2.30 | 0 + 0 | Nil | 4 | good |
| 5 | 2 | 1 | 35+1 | 0.23 | -- | -- | 37+4 | 0.66 | Lscs | 3.10 | 1 + 4 | Nil | -- | good |
| 6 | 3 | 0 | 35+1 | 0.34 | -- | -- | 38+2 | 1.15 | Lscs | 2.55 | 1 + 6 | Nil | -- | good |
| 7 | 1 | 0 | 34+6 | 0.29 | -- | -- | 37+3 | 0.91 | ND | 2.40 | 2 + 0 | Nil | -- | good |
| 8 | 2 | 1 | 35+1 | 0.24 | 37+1 | 0.27 | 38+1 | 0.67 | ND | 2.60 | 3 + 0 | Nil | -- | good |
| 9 | 1 | 0 | 35+1 | 0.24 | 36+5 | 0.69 | 37+2 | 0.89 | ND | 2.40 | 2 + 2 | Nil | -- | good |
| 10 | 2 | 0 | 35+1 | 0.56 | -- | -- | 37+1 | 1.40 | Lscs | 2.65 | 2 + 0 | Nil | -- | good |
| 11 | 2 | 0 | 33+0 | 0.18 | -- | -- | 40+3 | 1.04 | Lscs | 3.00 | 7 + 3 | Nil | -- | good |
| 12 | 1 | 0 | 33+4 | 0.89 | -- | -- | 33+4 | 0.89 | ND | 1.70 | 0 + 0 | Nil | 12 | good |
| 13 | 1 | 0 | 36+1 | 0.23 | -- | -- | 38+6 | 0.90 | Lscs | 3.30 | 2 + 3 | Nil | -- | good |
| 14 | 1 | 0 | 36+6 | 0.14 | 37+5 | 0.45 | 37+5 | 0.69 | Lscs | 2.33 | 1 + 0 | Nil | 4 | good |
| 15 | 1 | 0 | 36+5 | 0.55 | -- | -- | 38+4 | 1.20 | ND | 2.90 | 1 + 1 | Nil | -- | good |
| 16 | 2 | 0 | 35+1 | 0.84 | -- | -- | 35+1 | 0.90 | Lscs | 1.70 | 0 + 0 | Nil | 8 | good |
| 17 | 2 | 1 | 34+5 | 0.29 | -- | -- | 37+6 | 0.99 | ND | 2.50 | 2 + 2 | Nil | -- | good |

In membrane ruptured group N=5 (Table.2), pregnancies could be continued for a variable period of 2 days to 6 weeks + 2 days. In two women with case Nos. 1 & 3 leak could be stopped and pregnancy could be continued for 6 weeks, and 2 weeks + 6 days respectively.

In woman with case No.1 leaking membrane occurred at 21 weeks + 6 days. Pregnancy could be continued for up to 28 weeks + 1 day at which time second rupture of membrane occurred and the AFOD value was 0.43. The woman was referred to a tertiary care center for further management. There the woman was delivered normally, birth weight was 1.23 kg, and the baby developed mild RDS. Baby expired on 3rd neonatal day in NICU due to sepsis.

In woman with case No.2, leaking membrane occurred at 28 weeks + 4 days and the AFOD value was 0.35. Leak could not be stopped, and after 2 days the repeat AFOD value was 0.53. Baby was delivered by caesarean section, and the birth weight was 1.0 kg. The skin was premature thin shiny red in color with very little vernix (very much premature) on the surface. [Baby developed mild RDS](#) which responded well for oxygen supplementation with mask. Baby received only warmer care and feeding in NICU for 21 days and survived.

In women with case no 3, 4 and 5 mature AFOD values could be achieved, and the skin was mature pale brown in color with very little or no vernix caseosa on the surface. None of them developed RDS and all of them survived.

Table.2: Clinical details and results of AFOD guided PTL management in membrane rupture group.

| SL No | Gr | P a r a | GA at PROM wk.+d | AFOD on Adms | Status of leak after treatment | GA at delive wk.+d | AFOD at deliv | Mode of deliv | Birth wt. Kg | Preg. contd.For wk.+d | RDS | NIC U Care days | Neo-natal out com |
|-------|----|---------|------------------|--------------|--------------------------------|--------------------|---------------|-------------------|--------------|-----------------------|------|-----------------|-------------------|
| 1 | 1 | 0 | 21+6 | -- | Stopped | 28 + 1 | 0.43 | ND at ref hosp | 1.23 | 6 + 0 | mild | 3 | NND |
| 2 | 1 | 0 | 28+4 | 0.35 | Dint stop | 28+6 | 0.53 | Lscs | 1.00 | 0 + 2 | mild | 21 | Survi |
| 3 | 3 | 2 | 35+5 | 0.35 | Stopped | 38+4 | 1.51 | ND | 3.10 | 2 + 6 | nil | -- | Survi |
| 4 | 1 | 0 | 35+5 | 0.65 | Reduced | 36+2 | 0.92 | ND | 2.90 | 0 + 4 | nil | -- | Survi |
| 5 | 1 | 0 | 37+2 | 0.58 | Dint stop | 37+4 | 0.98 | ND | 2.80 | 0 + 2 | nil | -- | Survi |



Fig 3: Functionally mature baby with no vernx and RDS at 33wks+4days(left). AFOD was 0.98 ± 0.27 : case No.12 in Table1. Functionally premature baby at 39wks+2days with plenty of vernix and with RDS: AFOD was < 0.40 (right).

IV. Discussion:

Rudolf Klimek measured the functional maturity status of the newborn babies with clinical scoring system (Klimek's maturation index) and reported, some babies attain completion of functional maturity early and in some the maturation process completes late^{12, 13}. He reported babies can attain completion of functional maturity at any time from 36wks to 42wks, (i.e. over a period of 6wks) and proposed the concept of individual term^{12, 13}. Further he observed, fetal functional maturity is a separate entity and it does not depend either on size, weight or GA of the fetus^{12, 13}. For the same reason biometric measurement of fetal size and weight by ultrasound cannot give the information about the functional maturity status of the fetus.

Klimek's work assessed the functional maturity status of the baby only after birth of the baby but not before the birth. He did not have a specific marker to measure the functional maturity status of the fetus.

S. Ram et al. had shown that, spontaneous onset of labor occurs at AFOD value 0.98 ± 0.27 (at 650nm)^{1, 2}. At this AFOD value babies attain completion of functional maturity. This AFOD 0.98 ± 0.27 , completion of fetal functional maturity, and onset of spontaneous labor, that all go together occurs at any time from 35+ wks to 42+ wks indicating individualized term for each fetus^{1, 2, 6, and 7}.

This concept of individualized term for each fetus is having a significant impact on the management of PTL. A preterm baby at 35+ wks gestation can be fully functionally mature (as in case Nos. 4 and 12 in Table 1) and do not develop RDS, if the AFOD value is around 0.98 (Fig. 3). On the other hand, a term baby even at 40wks can be functionally premature and develop RDS if the AFOD value is < 0.40 (Fig. 3)^{1, 2}.

A fetus which completes maturation as early as 36wks becomes post mature or dysmature (idiopathic IUGR) by 37+ wks, if labor does not start for some reason. On the other hand a fetus destined to complete maturation by 42wks, if delivered at 40wks, it becomes premature by 2wks and develop RDS (term RDS)⁶. The definitions of preterm, term, post-term, and postdated pregnancies are made by obstetricians for clinical convenience. Nature does not have these definitions. Nature's philosophy is only to push the baby out when the baby is fully functionally mature and fit to survive outside⁶. Under the light of this new scientific information, there is every need to redefine preterm labor based on functional maturity status of the fetus (AFOD) rather than the G.A.¹⁴.

As AFOD represents the functional maturity of fetus, in our current study we used this as a marker to assess the functional maturity status of the fetus.

S. Ram et al. reported effective tocolysis and resuscitation of fetal distress in utero could be achieved with the use of low dose Isoxsuprine Hcl rapid infusion tocolysis⁸. They could achieve effective and satisfactory cessation of uterine activity within few minutes after initiation of this tocolytic therapy (Fig. 1). In our current study we repeatedly used this tocolytic technique for continuation of pregnancies (Fig. 2).

In a double-blind placebo-controlled trial, Meis PJ et al. reported a substantial reduction in the rate of recurrent preterm delivery by weekly injections of 17-alpha hydroxy progesterone caproate¹⁵. In our current study we have given Inj. 17-alpha hydroxy progesterone caproate 250mg I.M weekly before 24wks of gestation, and after 24wks 500mg I.M weekly was given till mature AFOD values were observed.

In our present study of 22 singleton pregnant women (both groups), 20 babies attained mature AFOD values (0.98 ± 0.27) at different gestational ages ranging from 33wks+4days to 40wks +3days confirming the concept of individualized term for each fetus^{6, 7} (Table. 1 & 2).

In membrane intact group of 17 women, pregnancies could be continued for a variable period of 1wk to 7wks +3days. In membrane ruptured group of 5 women, pregnancies could be continued for 2days to 6wks. In this group, in two women with case Nos.1 & 3 leak could be stopped and pregnancy could be continued for 6wks and 2wks +6d respectively (**Table.2**). These results in terms of continuation of pregnancies in preterm labor are unusually good when compared with contemporary practice.

In this study majority of babies could attain complete or near complete functional maturity status with AFOD values around 0.98 irrespective of GA and birth weight. As the babies were functionally mature, they did not develop RDS and 21/22 of them survived. Babies with case numbers 4, 12, 14, and 16 in membrane intact group, and case No2 in membrane rupture group had either low birth weights and/or lower side of mature AFOD values, and they required only warmer care and feeding in NICU for a variable period of 4days to 21 days (**Table.1**).

On follow up and observation of all these babies for a period of over 1.5years, we could not observe any neurological deficit.

AFOD estimation in preterm labor gives an idea about the functional maturity status of the fetus. With mature AFOD reading, babies can be delivered without any delay as in case of case No.4 and 12 in Table.1 and Fig.3.S. Ram et.al reported a rapid surge like raise in AFOD from a value of 0.40 to 0.98. The duration of surge was found to be around 8 to 10 days^{6, 7}. Based on this, AFOD estimation further helps to predict the number of days further required for completion of maturity. This helps us to avoid unnecessary waiting indefinitely for the onset of spontaneous labor¹⁶.

V. Conclusion:

Amniotic Fluid Optical Density (AFOD) research has given new insights into the physiological aspects of spontaneous labor and strengthened the concept of 'Individual term' by Prof. R. Klimek of yester years. It appears that, it is possible to continue pregnancies to completion or near completion of fetal functional maturity with AFOD guided PTL management coupled with effective 'Low dose Isoxsuprine Hcl rapid infusion tocolysis', and uterine sedation by weekly Injections of 17-alpha hydroxy progesterone caproate. Our study should be considered as a pilot study, and our results should be further evaluated and confirmed by multicentric studies with larger sample size.

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