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Ultrasonographic Measurement of Distal Femoral and Proximal Tibial Epiphyseal Ossification Centers in the Third Trimester and their Correlation to Gestational Age

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ABSTRACT

Background: Sonographic estimations are derived from calculations based on fetal measurements and thus, serves as an indirect indicator of maturity and GA. **Objective:** This study aimed to measure the distal femoral (DFOC) and proximal Tibia (PTOS) epiphyseal ossification centers in the 3rd trimester and correlate them to BPD, HC, AC, FL and GA to increase the ultrasound accuracy of gestational age (GA) estimation and thus avoiding iatrogenic prematurity.
MethodS: A prospective observational cohort study. A total of 150 low risk pregnant women. The Distal Femoral and the Proximal Tibia epiphyseal ossification centers were measured and correlate them to BPD, HC, AC, FL and GA.
Results: The best cut-off of DFOC in prediction of maturity (GA ≥ 37th weeks' gestation) was ≥ 4.4 mm with area under curve 0.88 (CI: 0.83 to 0.94) with sensitivity 82.8%, specificity 79.3%, positive predictive value (PPV) 95%, negative predictive value (NPV) 49% and overall accuracy 80% (p<0.001), the best cut-off of PTOC in prediction of maturity (GA ≥ 37th weeks' gestation) was ≥ 2.5 mm with area under curve 0.887 (CI: 0.83 to 0.95) with sensitivity 82.8%, specificity 74.4%, positive predictive value (PPV) 95%, negative predictive value (NPV) 44% and overall accuracy 76% (p<0.001). **Conclusion:** There was a strong positive correlation between DFOC, PTOC and GA.
Keywords: Ultrasound, Gestational age, Distal femoral, Proximal tibia, Ossification centers.

INTRODUCTION

Accurate gestational age estimation is one of the most important factors needed for optimum obstetrical management. Neonatal respiratory distress syndrome is the most leading one for neonatal mortality and morbidity. Lack of accurate gestational age estimation, particularly in some geographical regions at greatest risk of these conditions, means that preterm delivery and small for gestational age rates are mere approximations in many parts of the world [(1)].

Respiratory distress syndrome is a major cause of neonatal morbidity and mortality that is most commonly caused by a deficiency in lung surfactant in premature infants. Therefore, laboratory tests were developed to measure the presence and concentration of lung surfactant in amniotic fluid in order to estimate maturity of the fetal lung. Although these tests were once widely employed, their utilization by physician has decreased in last years. Several studies have shown that demonstration of a mature fetal index by antenatal testing does not improve neonatal outcomes. Reduced respiratory and non-respiratory morbidities are highly correlated with gestational age of the fetus. Fetal lung maturity testing may have passed the point of being clinically useful [(2)]. Unusual methods like amniocentesis, radiography and ultrasound are required to assess the fetal maturity. Amniocentesis is an invasive technique and use of X-rays is hazardous to fetus [(3)].

Evidence suggested that gestational age estimation using ultrasound measurements is clinically superior to using menstrual dating with or without ultrasound, providing ultrasound is performed with quality and accuracy [(4)]. Pregnant women are frequently unsure of the date of their last menstrual period and when this is combined with late booking for antenatal care, determination of gestational age becomes a real challenge even with ultrasonography [(5)].

Non-traditional ultrasound measurements as secondary epiphyseal ossification centers in late gestation may assist in determining accurate gestational age and appropriate fetal lung maturity [(1)]. Adding of new ultrasound measurements as distal femoral and proximal tibia ossification centers in 3rd trimester to the traditional measurements, may increase the ultrasound accuracy in gestational age estimation, diagnosis of intrauterine growth restriction, prediction of fetal lung maturity and avoiding iatrogenic prematurity [(1)].

METHODS

A prospective observational cohort study was conducted in Department of Obstetrics & Gynecology, Faculty of Medicine, Zagazig University in the period from August 2021 to January 2022. A total of 150 pregnant women; singleton pregnancy, completed 28th weeks' gestation based on last regular sure menstrual period and /or 1st trimester ultrasound dating. Low risk and uncomplicated pregnancies.

Exclusion criteria: Pregnancies with medical complication as diabetes mellitus and hypertension, obstetric complication as oligohydramnios, polyhydramnios and intrauterine growth restriction, and/or fetal congenital anomalies.

All women in this study were subjected to full history, clinical examination. investigations [CBC, Rh factor, FBS, PPBS, kidney and liver function tests and clotting and bleeding time]. Trans-abdominal ultrasound. The distal femoral and the proximal tibia epiphyseal ossification centers were measured using Mindary DC-70EXP ultrasound.

Trans-abdominal ultrasound using a 5 MHZ convex array transducer probe. GA was calculated by measuring BPD, HC, AC, and FL. Fetal condition,

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amniotic fluid, fetal heart rate, placenta, and the presence of any fetal anomalies were assessed. The DFOC appeared as a slit like ovoid or globular or egg shaped echogenic structure or hyperechoic rich eras centrally placed within the hypo echogenic epiphyseal cartilage of the femur at its distal extremity. It can be imaged at 1mm (shape, brightness and size). Its exact detection was made by guiding the transducer along the largest axis of the femoral diaphysis avoiding oblique sectioning. Ultrasonically, the PTOC appeared as a slit like isolated echogenic ovoid or globular or egg shaped formation centrally positioned within the proximal hypo echogenic epiphyseal cartilage. It can be imaged at 1mm (shape, brightness and size). Measurements of the epiphysis were taken from the outer to outer margins in an axial plane (anteroposterior) along the Medio-lateral surface at level of knee joint. Each measure was made from a separate scan image, at least 3 measurements were taken and the largest one of the 3 measures was considered as the current diameter. Attention, the overlapping of membranes between the transducer and the fetal knee produce acoustic shadows that made visualization of the ossification centers unavailable.

DFOC and PTOC were correlated to the BPD, HC, FL, AC and GA, then correlated to each other. The gestational age at which the DFOC and PTOC first appeared (can be identified on ultrasound), and that at which the ossification center appeared in 100% of the cases were determined. Also, the rate of growth of the ossification center was assessed. The data were collected at the end of each examination on a form specially designed for this study. From completed 28^{th} weeks' gestation to $\geq 37^{th}$ weeks' gestation, the DFOC and PTOC were measured for each week of gestational age, pregnant women were divided to groups each group was 2 weeks' gestation as 29^{th} – 30^{th} weeks' gestation, 31^{st} – 32^{nd} weeks' gestation and so on. A norm- gram with the values of mean DFOC and PTOC was constructed for each week of gestational age by adjusting the data using multiple linear regression and controlling for GA.

Ethical approval: The Institutional Review Board of Faculty of Medicine, Zagazig University gave its approval to the study protocol (#9282-30-1-2022). A written informed consents were taken from included cases. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were collected throughout history, basic clinical examination, laboratory investigations and outcome measures then coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data qualitative were represented as number and percentage and quantitative continues groups were represented as mean ± SD. The following tests were used to test differences for significance: Difference and association of qualitative variable by Chi square test (X^2), differences between quantitative independent multiple by ANOVA and correlation by Pearson's correlation. The significance level was set at 0.05. P value ≤ 0.05 for significant results & ≤ 0.001 for high significant result.

RESULT

The minimum DFOC was detected by 29^{th} -30^{th} weeks' gestation. It was detected in all participant by 33^{rd} -34^{th} weeks' gestation with minimal diameter of completed 37^{th} weeks' gestation was 3 mm. The minimum PTOC was detected by 31^{st} -32^{nd} weeks' gestation. It was detected in all participant by 37^{th} -38^{th} weeks' gestation with minimal diameter of completed 37^{th} weeks' gestation was 1.9 mm (table1). There was a statistically significant positive correlation between DFOC, PTOC & PTOC/DFOC ratio and gestational age (Table 2). The DFOC grew up every 2 weeks' gestation 1mm from 34^{th} weeks' gestation to ≥37 weeks' gestation. The PTOC grew up every 2 weeks' gestation 1mm from 34^{th} weeks' gestation to ≥ 37 weeks' gestation. Mean ratio PTOC/DFOC at ≥ 37^{th} weeks' gestation was 0.5. The best cut-off of DFOC in prediction of maturity (GA ≥ 37 weeks) is ≥4.4mm with area under curve 0.88 (CI: 0.83 to 0.94) (Table 3). The best cut-off of PTOC in prediction of maturity (GA ≥ 37 weeks) was ≥ 2.5 mm with area under curve 0.89 (CI: 0.83 to 0.95) (figure 1). There was statistically significant very strong positive correlation between DFOC and femur length among studied females (figure 2). At ≥ 37 weeks' gestation, FL was 70 mm and DFOC was 5.2 ± 1.2 mm with ratio near 7% (figures 3-6).

Table (1): Ultrasonically detection of DFOC and PTOC by gestational age

Gestational age (weeks)	Number	DFOC Number (%)	Range(mm)	PTOC Number (%)	Range (mm)
29-30	150	75 (50%)	0-2.8	0(0%)	0
31-32	150	127(85%)	0-4.6	30(20%)	0-2.3
33-34	150	150(100%)	1.4-4.3	75(50%)	0-2.9
35-36	150	150(100%)	2-6.1	146(97%)	0-3.8
37-38	150	150(100%)	3-7.5	150(100%)	1.9-7.1
39-40	150	150(100%)	4-8.6	150(100%)	2.4-8

Table (2): Correlation between DFOC & PTOC among 150 participants

Gestational age (weeks)	DFOC (mean ± SD)	PTOC (mean ± SD)	Ratio PTOC/DTOC
29-30	2±0.4		
31-32	2.8±0.8	1.9±0.4	0.56±0.14
33-34	2.9±o.7	2±0.8	0.63±0.03
35-36	4±1	2.6±0.6	0.68±0.14
37-38	5.2±1.2	3.9±1.3	0.77±0.21
39-40	6.3±1.5	5.2±1.2	0.83±0.8
r	0.79	0.67	0.34
p	0.001**	0.001**	0.001**

**p≤0.001 is statistically highly significant

Table (3): Ultrasound Biometry of the studied participants

n	GA (weeks)	FL(mm) Mean ± SD	BPD(mm) Mean ± SD	HC(mm) Mean ± SD	AC(mm) Mean ± SD	DFOC(mm) Mean ± SD	PTOC(mm) Mean ± SD
30	**29-30**	58 ± 10	76 ± 9	295 ± 13	290±9.8	2 ± 0.4	
30	**31-32**	62 ± 19	79 ± 19	305 ± 20	305 ± 34	2.8 ± 0.8	1.9 ± 0.4
30	**33-34**	65 ± 20	85 ± 23	312 ± 19	314 ± 56	2.9 ± 0.7	2 ± 0.8
30	**35-36**	69 ± 19	89 ± 26	323± 32	320 ± 46	4 ± 1	2.6 ± 0.6
30	**37≥**	70 ±20	91 ± 26	335 ± 45	334 ± 67	5.2 ± 1.2	3.9 ± 1.3

**p≤0.001 is statistically highly significant

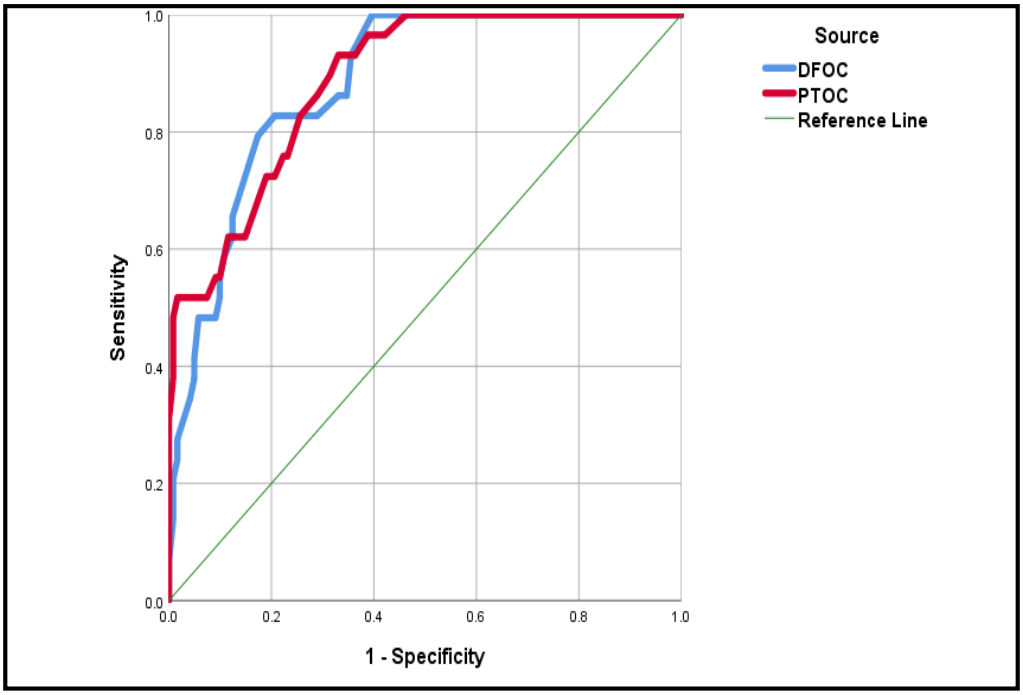

Fig. (1): Curve showing diagnostic performance of DFOC and PTOC in assessment of gestational age.

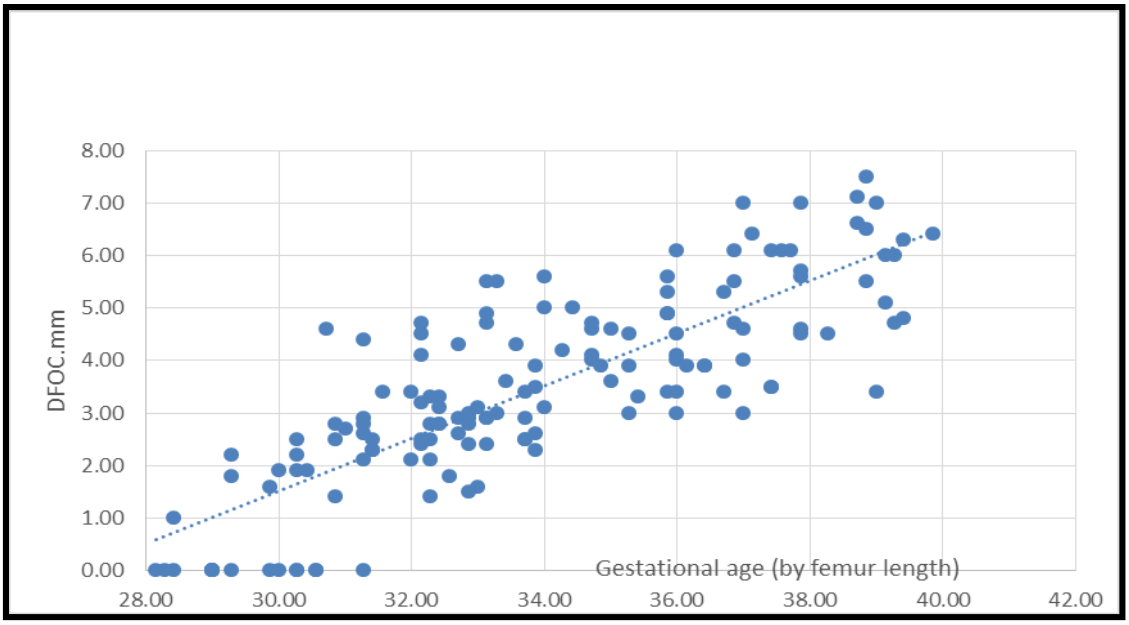

Fig. (2): Scatter dot graph showing significant positive correlation between DFOC and gestational age assessed by femur length.

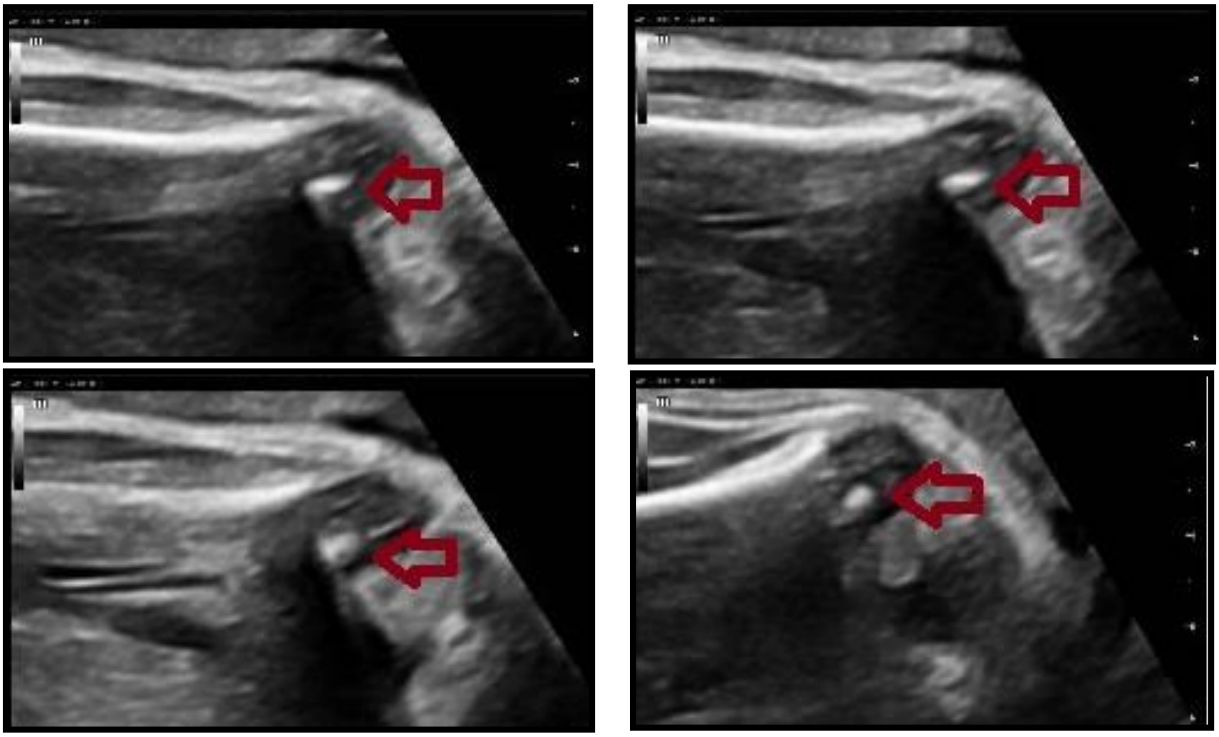

Fig. (3): DFOC=2.8mm was detected by 32 weeks' gestation.

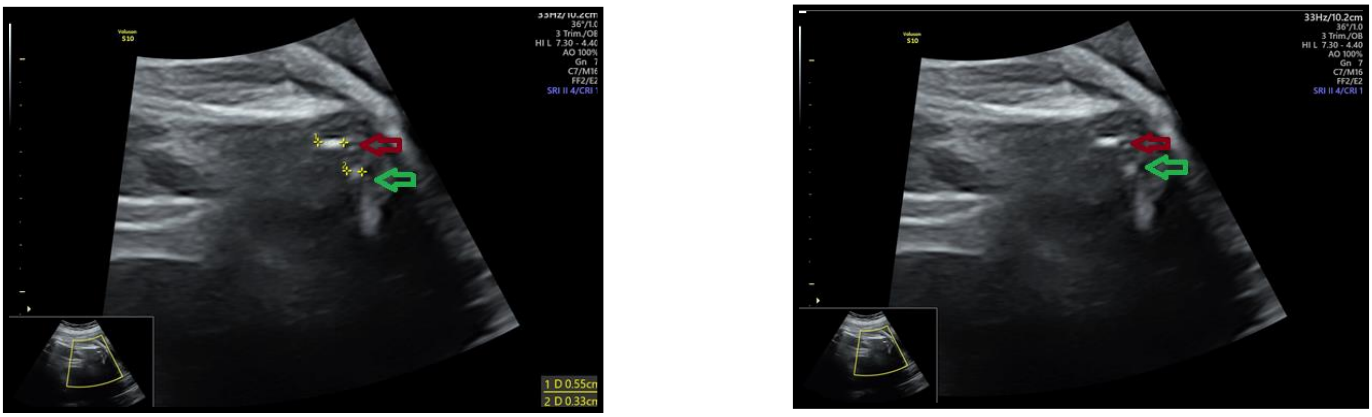

Fig. (4): DFOC was measured 5.5 mm and PTOC was measured 3.3 mm by 35weeks and 6 days GA.

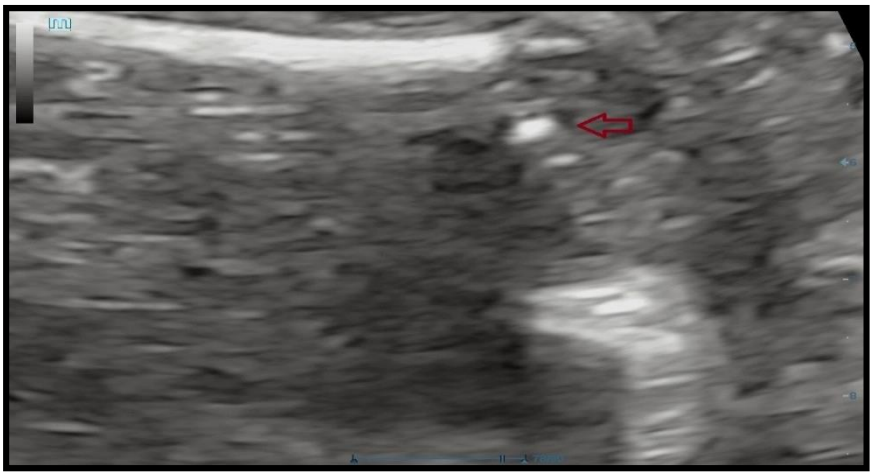

Fig. (5): DFOC=2.8mm by 31weeks'gestation.

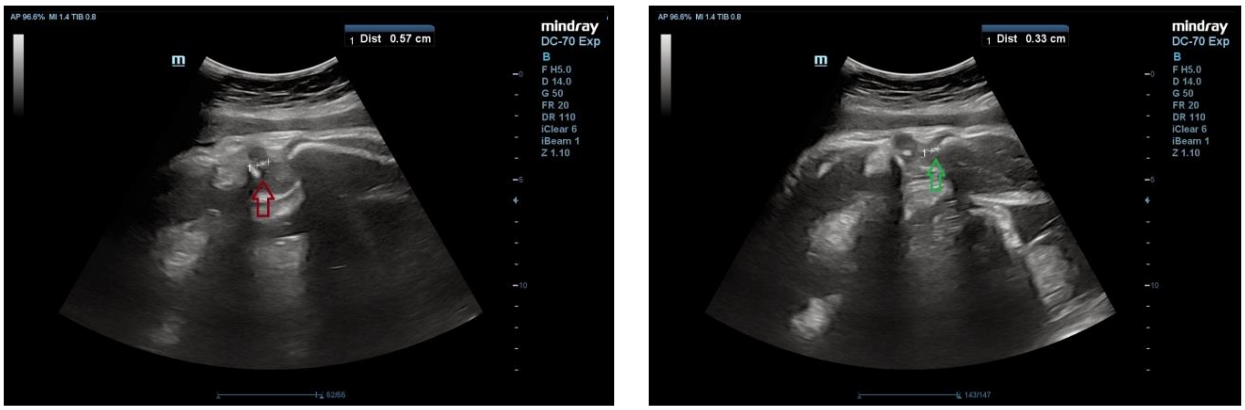

Fig. (6): Measurement OF DFOC was 5.7mm and PTOC was 3.3mm by 37 weeks'gestation.

DISCUSSION

Our results showed that the mean DFOC diameters increased linearly as GA increases. DFOC showed a very strong positive relationship (r = 0.80) with GA. This is in line with a study conducted by **Birang *et al.*** [6] on Iranian population that showed a correlation coefficient of 0.8 between DFOC and GA.

The DFOC was not visualized before the 29th week of gestation in our population. DFOC was also not visualized before the 29th week in a study conducted by **Mohney *et al.*** [7], on American population, with the mean age of DFOC appearance being 32–33 weeks. **Udoh *et al.*** [8] also reported 29 weeks' gestation for the first appearance of DFOC among Chinese population. At term, the DFOC was seen in 100% of fetuses and ranged between 4.00 and 9.00 mm.

A positive strong correlation was found between the DFOC diameter and PTOC diameter and gestational age in weeks at ≥ 37th weeks' gestation at a correlation coefficient value (CI:0.83-0.94). and (CI:0.83-o.95) respectively indicating that the epiphyseal ossification center of each of the two bones studied varied greatly, as is seen in the case of other anthropometric indicators [BPD, HC, AC and FL], but their presence or absence can be useful in drawing some specific and critical decisions with regard to gestational age. If none of the two epiphyseal ossification centers was detected on ultrasound examination, there was a very high possibility that the fetus has not yet reached 34th weeks' gestation (P<0.001). If only the distal femoral was visualized, and particularly if it is less than 2.8 mm in diameter, the fetus very probably did not yet reach 34th weeks 'gestation (P≤0.001). On the other hand, if the DFOC and PTOC were visible, the fetus has certainly completed at least 36th weeks 'gestation.

The DFOC was detected in 50% at 30th weeks 'gestation, 85% at 32th weeks 'gestation and 100% at 34th weeks 'gestation. The PTOC was detected in 50% at 34th weeks 'gestation, 97% at 36th weeks' gestation and 100% at 37th weeks' gestation. Similar results are obtained by a study done by **Bitrus *et al.*** [1] who reported that DFOC detection by ultrasound increased dramatically to 56% at 33th weeks' gestation, reaching 94% at 36th weeks' gestation and 100% at 37th weeks' gestation. Gestational age was correlated well with the diameters of the distal femoral and the proximal Tibia epiphyseal ossification centers.

The DFOC and PTOC can also be useful as a marker of completed 37 weeks' gestation. Our study showed that fetuses of at ≥ 37 weeks' gestation, the DFOC mean diameter was 5 mm ranged (3mm-7.5mm) and PTOC mean diameter was 4 mm with ranged (2mm-7mm). This is in line with a study carried by **Bitrus *et al.*** [1], in which they reported that the agreement with the DFOC diameters were 84% (3 mm), 94% (4 mm) and 100% (5 mm) respectively.

The best cut-off of DFOC in prediction of maturity (GA≥37 weeks) was ≥ 4.4 mm with area under curve

0.88 (CI: 0.83 to 0.94) with sensitivity of 82.8%, specificity of 79.3%, positive predictive value (PPV) of 95%, negative predictive value (NPV) of 49% and overall accuracy of 80% ($p<0.001$).

The best cut-off of PTOC in prediction of maturity (GA ≥ 37 weeks) was ≥ 2.5 mm with area under curve 0.887 (CI: 0.83 to 0.95) with sensitivity of 82.8%, specificity of 74.4%, positive predictive value (PPV) of 95%, negative predictive value (NPV) of 44% and overall accuracy of 76% ($p<0.001$). This is in agreement with the study of **Elsaeed *et al.* [9]** who reported that the distal femoral epiphysis was not visualized in all cases (in Nigerian) until the 29th weeks of gestation, and at this age, it was visualized in only 15% of the fetuses, and this proportion increased drastically to 61% at GA of 32 weeks and 100% at GA of 37 weeks.

The DFOC diameter increases with GA ($r = 0.85$, $P < 0.02$) of the fetuses in all age groups, .at term, the DFOC was seen in 100% of fetuses and ranged between 4.00 and 9.00 mm. This is in agreement with a study done by **Bitrus *et al.* [1],** which concluded that each of the 2 epiphyseal ossification centers was a useful indicator for gestational age in 3rd trimester. **Mwagirus *et al.* [10]** reported similar results in Kenyan peoples where DFOC wasn't detected before 30th weeks' gestation but was observed in 72% of fetuses at 33th weeks' gestation, in 86% at 35th weeks' gestation and in 100 % at 37th weeks' gestation. The PTOC was seen for the 1st time at 31th weeks' gestation and in 50% of the fetuses at 35th weeks' gestation, 83 % at 38th weeks' gestation and 100 % at term. The DFOC at 37th weeks' gestation was ≈ 4 mm. The PTOC at 37th weeks' gestation was 2.7 mm. DFOC and PTOC had a high positive predictive value for estimating GA in last trimester. They used the diameter of DFOC and PTOC for drafting reference charts of GA.

There was statistically significant association between detection of DFOC and GA detected by FL. DFOC was first detected at 29th – 30th weeks' gestation, FL was 58 ± 10 mm and DFOC was 2 mm. At ≥ 37th weeks' gestation FL was 70 ± 20 mm and DFOC was 5 mm with ratio of 7 %, (CI: 0.83 to 0.95) with sensitivity of 82.8%, specificity of 79.3%, positive predictive value (PPV) of 95%, and overall accuracy of 80% ($p<0.001$) ($r=0.82$). Also, **James *et al.* [11]** reported that DFOC is 7% of length of femur.

This study did not propose substituting other anthropometric measurements, such as bi- parietal diameter, abdominal and head circumference, or femur length. By the diameters of the 2 DFOC & PTOC we would like to draw attention to the possibilities offered by this simple marker of fetal development as a good indicator of fetal lung maturity.

The identification and measurements of the epiphyseal ossification centers may be less influenced by fetal growth restriction or excessive growth than other anthropometric measurements, whereas a deficit in calcium metabolism may occasionally delay the appearance of the 2 epiphyseal ossification centers **[12].**

CONCLUSION

There was strong positive correlation between DFOC & PTOC and GA. The diameter of the DFOC and PTOC is a useful method for determining fetal maturity and gestational age in 3rd trimester. Therefore, future studies may focus on chart for our people as United States of America, Canada and some other countries. Future studies may focus on showing the relationship between gestational age and secondary epiphyseal ossification centers [DFOC and PTOC] in complicated pregnancies.

Conflict of interest: The authors declared no conflict of interest.

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