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Sonographic Identification and Measurement of the Epiphyseal Ossification Centers in the Prediction of Fetal Lung Maturity in Pregnant Egyptian Women

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Abstract

Background: Respiratory distress syndrome is a major cause of neonatal mortality and morbidity. Lung maturity is important in high-risk pregnancies. The strongest predictor of lung maturity is gestational age and also, can be assed by ultrasonographic markers as epiphyseal osscification centers.

Aim of Study: This study was to evaluate the distal femoral, proximal tibial and proximal humeral ossification centers as predictive tools of fetal lung maturity.

Patients and Methods: This study was prospective comparative study was carried out on 100 pregnant women attended Obstetric and Gynecological Clinic of Damanhour Teaching Hospital.

All cases in this study will subjected to: (1) History taking; (2) Complete clinical examination; (3) Investigations.

After approval of local ethics committee, all patients were informed well about the procedure and had an informed written consent before carrying the procedure.

Data were analyzed using IBM SPSS software package version 20.0. Data were collected, tabled then analyzed were *p*-values 0.05 were considered significant.

Results: Our results revealed non-significant difference between women regarding demographic data, signs and symptoms, past-history. Ultrasonographic examination revealed significant reduction of respiratory distress with increased osscification centers number and Also, ICU admission decrewased significantly with increased osscification centers number. In addition, occification centers number significantly increased with increased gestational age.

Conclusion: This study can concluded that the size and appearance of the proximal humeral epiphysis will be helpful to determine the gestational age and viability of the fetus in normal as well as medico legal cases.

Key Words: *Gestational age – GA – Last menstrual period – LMP – Respiratory distress syndrome – RDS.*

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Introduction

THE most common cause of mortality and neonatal morbidity in preterm and early term fetuses is lung immaturity. Respiratory distress syndrome (RDS) is a major cause of neonatal mortality and morbidity where the lung cannot provide sufficient oxygen **[1].**

Prediction of lung maturity is important in the management of high-risk pregnancies. The strongest predictor of lung maturity is gestational age. Thus, infants who are born at less than 39 weeks have significantly higher rates of neonatal morbidity when compared with infants born at a gestation of 39 weeks or longer **[2].**

There are various methods of determination of fetal lung maturity, such as, clinical methods like menstrual history and Last menstrual period (LMP), per abdomen examination and date of quickening **[3].**

Per abdominal examinations can also give erroneous results in cases such as polyhydrominos or multiple gestation or IUGR. So, to avoid the drawbacks of clinical methods, additional help of ancillary methods like amniocentesis, radiography and ultrasonography is required to assess the fetal maturity. Amniocentesis is an invasive technique and use of X-rays is hazardous to fetus **[4].**

Fetal lung maturity can be assessed indirectly by ultrasonographic marker of fetal lung maturity. Over the last 30 years, the prediction of lung maturity by noninvasive ultrasound methods has been extensively explored **[5].**

Earlier studies comparing fetal lung echogenicity with the placenta, **[6,7,8]** fetal gut, **[9]** or liver **[10,11]** demonstrated ultrasonographic changes as-

sociated with fetal lung maturation. Other studies used free floating particles in amniotic fluid as a method to evaluate fetal lung maturity by ultrasound **[12]**.

The epiphyseal ossification centers of long bones, which can be reliably identified and measured sonographically, may be a useful marker of fetal lung maturity **[15]**.

The measurement of epiphyseal ossification centers of long bones as markers of gestational age using radiography was first described 50 years ago. These studies were based on the findings of maternal abdominal X-rays carried out during pregnancy and on X-rays of neonatal extremities. However, the fear of exposing the fetus to radiation and the large variability in the figures obtained led to the discontinuation of this method for determination of gestational age **[14]**.

The advent of ultrasonography solved most of the technical problems encountered with radiography and eliminated the fear of fetal radiation. Moreover, ultrasound is able to identify each ossification center at a much earlier stage, as long as the diameter is at least 1mm. The main ossification centers appear ultrasonically as egg shaped echo rich areas. The ossification centers of Distal Femoral and Proximal tibial Epiphysis can be seen at the level of knee joint whereas the proximal humeral epiphysis is seen at shoulder joint **[14]**.

Patients and Methods

This is prospective comparative study was carried out on 100 pregnant women at Damanhour Teaching Hospital From Feb. 2021 – Feb. 2022.

The following females (1) Age from 16-45 years, (2) Singleton pregnancy at 35-40 GW, (3) Living fetus, (4) Delivering within 72 hours after scan; all were included in the study. Women with (1) Pregnant <35 WG; (2) Multiple gestations; (3) Uncertain gestational age; (4) Severe medical condition leading to termination of pregnancy; (5) Cases with major congenital anomalies, hydrops fetalis, premature rupture of membranes, umbilical cord prolapse and placental abruption; (6) Polyhydramnios and oligohydramnios; and (7) Intrauterine growth restriction, macrosomic fetuses, or presence of meconium stained amniotic fluid were excluded from this study.

All cases signed a well-informed written consent to declare their agreement to be enrolled in the study as agreed upon by the ethical committee.

All cases in this study will subjected to: (1) history taking "personal, present, past, menstrual, obstetric histories"; (2) Complete clinical "general, local and gynecological examination including pelvic and rectal" examination; (3) Investigations "routine and ultrasonographic examination to assess last menstrual period and gestations age by detection of osscifications centrs of bones".

After approval of local ethics committee, all patients included in the study or their relatives were informed well about the procedure and had an informed written consent before carrying the procedure.

Data were analyzed using IBM SPSS software package version 20.0 (Belmont, Calf, 2013). Data were collected in tables then analyzed in regarding to Chi square (x^2) and *p*-value less than 0.05 were considered significant.

Results

Table (1) showed the demographic data of the women included in the study.

Table (2), representing the presenting signs and symptoms of women of the study that included vaginal discharge, pelvic discomfort, pruritis, dysparunia and post-coital bleeding with any significance of them on the others.

Past-history revealed that 10% of women complaining of DM, 9% complaining of hypertension, 4% complaining of heart diseases, 2% had rheumatic disease and 11% of them underwent previous operations without any significant factor in the past-history (Table 3).

Ultrasonographic examination determine that 42% of cases had gestational age 35-37 W and 58% of them had gestational age of 38-40 ws without significance of any group (p=0.231). Also, U/S examinations revealing the presence of <3 centers in 12% of cases, 3-4 osscifications centers in 3-%; 4-6 osscification centers in 45% of cases and >6 osscifications centers in 13% of cases with significance of the group of 4-6 osscification centers (p=0.0214), (Table 4).

Demographic data of fetus showed that most of babies were delivered through CS (70%) while 30% delivered by normal vaginal delivery; 54% of babies were males and 46% were females without difference regarding gender; also there were no difference between babies regarding APGAR score whether after 2 or 5min. Finally most babies delivered without respiratory distress (93%) and

reflecting on ICU admission which present only in 9% of babies (Table 5).

Statistical analysis revealed that osscification centers were statistically low in babies with respiratory distress syndrome (p=0.001). Also, whenever the ICU admission of babies were increased there were a significant decrease in the number of osscification centers (p=0.0001); while there was no significant relation between the number of osscification centers and the mode of deliver of babies (p=0.170) (Table 5).

Correlating gestational age of the fetus and the epiphyseal osscification centers revealed that Mean Epiphyseal Ossification Centers was significantly increase with increasing gestational age (p=0.0001), (Table 6).

Table (1): Distribution of the studied maternal group regarding their demographic data.

Variable	Number	Percent
Maternal age:		
<25	44	44.0
25-30	40	40.0
30+	16	16.0
Mean ± S.D.	25.35±3.75	
Consanguinity:		
Yes	8	8.0
No	92	92.0
BMI:		
Normal weight	31	31.0
Over weight	52	52.0
Obese	17	17.0
Mean ± S.D.	32.85±4.33	
Gestational age:		
35-37	43	43.0
38-40	57	57.0
Mean ± S.D.	37.82±1.74	
Gravidity:		
1	22	22.0
2-3	36	36.0
4-5	42	42.0
Mean ± S.D.	3.08±1.47	
Parity:		
0	24	24.0
1-2	36	36.0
3-4	40	40.0
Mean ± S.D.	2.00±1.47	
Previous abortion:		
No	8	8.0
Yes	92	92.0
Number of living children:		
No	26	26.0
1-2	36	36.0
3-4	38	38.0
Mean ± S.D.	1.92±1.52	

Table (2): Sign and symptoms among the studied patients group.

	Number	Percent
Vaginal discharge	6	6.0
Pelvic discomfort	7	7.0
Purities	13	13.0
Dysparunia	10	10.0
Post coital bleeding	10	10.0

Table (3): Distribution of the studied patients group regarding past medical history.

Past medical history	Number	Percent
D.M.	10	10.0
Hypertension	9	9.0
Heart disease	4	4.0
Rheumatic disease	2	2.0
Previous operation	11	11.0

Table (4): Ultrasound findings in the studied group.

Variable	Number	Percent
GA (U/S):		
35-37 W	42	42.0
38-40 W	58	58.0
Mean ± S.D.	38.01±1.65	
Mean Epiphyseal Ossification Centers:		
<3	12	12.0
3-4	30	30.0
4-6	45	45.0
>6	13	13.0
Mean ± S.D.	4.53±1.22	

Table (5): Distribution of the studied group regarding mode of delivery.

	Number	Percent	p
Mode of delivery:			
Normal vaginal delivery	30	30.0	0.170 (NS)
C.S.	70	70.0	
Gender:			
Male	54	54.0	
Female	46	46.0	
APGAR Score 2 min:			
5.00	29	29.0	0.024 (S)
6.00	27	27.0	
7.00	29	29.0	
8.00	15	15.0	
APGAR Score 5 min:			
5.00	3	3.0	0.024 (S)
6.00	6	6.0	
7.00	15	15.0	
8.00	23	23.0	
9.00	30	30.0	
10	23	23.0	
RDS:			
No	93	93.0	0.001 (S)
Yes	7	7.0	
ICU admission:			
No	91	91.0	0.0001 (S)
Yes	9	9.0	

Table (6): Relation between mean Epiphyseal Ossification Centers and gestational age.

Gestational age GA (Ws)	Mean ± S.D
35 W	2.72±0.22
36 W	3.42±0.17
37 W	3.85±0.15
38 W	4.54±0.33
39 W	5.24±0.16
40 W	6.12±0.44
ANOVA	24.872
p	0.0001 (S)

Discussion

Prediction of lung maturity is important in the management of high-risk pregnancies. The strongest predictor of lung maturity is gestational age. Thus, infants who are born at less than 39 weeks have significantly higher rates of neonatal morbidity when compared with infants born at a gestation of 39 weeks or longer **[2]**.

There are various methods of determination of fetal lung maturity, such as, clinical methods like menstrual history and Last menstrual period (LMP), per abdomen examination and date of quickening **[3]**.

Fetal lung maturity can be assessed indirectly by ultrasonographic marker of fetal lung maturity. Over the last 30 years, the prediction of lung maturity by noninvasive ultrasound methods has been extensively explored **[5]**.

The advent of ultrasonography solved most of the technical problems encountered with radiography and eliminated the fear of fetal radiation. Moreover, ultrasound is able to identify each ossification center at a much earlier stage, as long as the diameter is at least 1mm. The main ossification centers appear ultrasonically as egg shaped echo rich areas. The ossification centers of Distal Femoral and Proximal tibial Epiphysis can be seen at the level of knee joint whereas the proximal humeral epiphysis is seen at shoulder joint **[14]**.

The measurement of epiphyses ossification centers (EOCs) of long bones as markers of gestational age using radiography was first described 50 years ago. These studies were based on the findings of maternal abdominal X-rays carried out during pregnancy 1-4 and on X-rays of neonatal extremities **[15]**.

The advent of ultrasonography, however, solved most of the technical problems encountered with radiography and eliminated the fear of fetal radiation. 8 Moreover, whereas radiography is only able to measure EOCs of at least 3mm, ultrasound is able to identify each EOC at a much earlier stage, as long as the diameter is at least 1mm **[16]**.

Ultrasound has become routine in antenatal care, and measurement of the EOCs of long bones involves very little more time than that normally required for an ultrasonographic examination of the fetus. These facts motivated us to examine the usefulness of the identification and measurement of epiphyses ossification centers at different gestational ages during the last trimester of pregnancy and to test the hypothesis that the sum of the diameters of the three EOCs could be more precise than each EOC diameter considered individually.

The aim of this thesis was to evaluate the distal femoral, proximal tibial and proximal humeral ossification centers as predictive tools of fetal lung maturity.

This study was conducted at Obstetrics and Gynecology department, Damanhur Teaching Hospital, and will include a sample of 100 pregnant women. The mean age of mother in our study was 25.35±3.75 years, the mean BMI was 32.85±4.33. The mean gestational age by U/S was 38.01±1.65 weeks, the mean epiphyseal ossification centers was ranged from 2.4-6.8 with a mean of 4.53±1.22, the epiphyseal ossification centers was parallel to gestational age.

DFE was detectable by ultrasonography in 71% at 32 weeks. Where in 72% of our 32 week study DFE was not visible by ultrasound, yet. In hisstudy DFE was detectable in 100% of fetuses at 37 weeks gestation, just as ours.

In line with the results of this study, it has previously shown that the DFE is not visualized before 28 weeks gestation in american population and the mean age at DFE appearance is 32 to 33 weeks gestation 4. If a DFE is not visualized, the fetus is most likely less than 34 menstrual weeks gestation as the DFE is observed in 94% of fetuses at 34 weeks gestations **[16]**.

Moreover, a DFE of 3 mm or more is associated with a gestational age of greater than 37 weeks in 84% of fetuses. It is comparable with the mean gestational age 36.71 in this study **[17]**.

Wu ad his colleagues, **[18]**, has also reported that, 29 weeks gestation for first appearance of

DFE in Chinese. However the DFE was detectable in 100% of fetuses at the end of 34 week, compared with 37 weeks in this study **[18]**.

Gentili and his coworkers, **[19]**, reported that the fetal ossific centers become visible sonographically at different gestational ages; before 24 weeks, they are not detectable; the calcaneal ossification center is detectable at 24 weeks; the talar ossification center from 26 weeks, the distal femoral epiphyseal ossification center from 32 weeks; and the proximal tibial epiphyseal ossification center from 36 weeks **[19]**.

The measurement of epiphyses ossification centers of long bones as markers of gestational age using radiography was first described 50 years ago. These studies were based on the findings of maternal abdominal X-rays carried out during pregnancyand on X-rays of neonatal extremities **[20]**.

However, the fear of exposing the fetus to radiation, the technical problem involved in visualizing the epiphyses ossification centers, and the large variability in the figures obtained led to the discontinuation of this method for determination of gestational age. The advent of ultrasonography, however, solved most of the technical problems encountered with radiography and eliminated the fear of fetal radiation **[14]**.

Ultrasound is able to identify each epiphyses ossification center at much earlier stage, as long as the diameter is at least 1mm **[16]**.

Another similar results by Donne and his colleagues, (2005), who enrolled women with singleton pregnancies of 30-40 weeks gestation in prospective study. The distal femoral, proximal tibial, and proximal humeral ossification centers were identified and measured **[14]**.

A nomogram of fetal bone development was created using the sum of the three diameters. Gestational age correlated well with the diameters of the DFE & PTE centers but even better with the sum of the three ossification centers. Positive predictive values of the fetus having gestational age of at least 37 weeks when the sum of the three centers was 7, 11, and 13mm were 82%, 94%, and 100%, respectively.

In our study, it was found that 7 cases had neonatal respiratory distress syndrome, and it was found that the mean Epiphyseal Ossification Centers was significantly low in neonatal with respiratory distress syndrome (p<0.05).

Also in this study it was found that 9 cases admitted to ICU, and the neonatal ICU admission show a low epiphyseal ossification centers (p<0.05). It was found that there was a positive significant correlation between mean epiphyseal ossification centers and APGAR score at 5min.

Assessment of fetal lung maturation is one of the most important steps while deciding in birth of the fetus. The objective should be protection of the fetus from risks such as sequelae of respiratory distress syndrome (RDS), necrotizing enterocolitis, intraventricular hemorrhage, patent ductus arteriozus and neonatal sepsis as much as possible. However, the main point in deciding birth is the clinical condition of the mother and the fetus **[21]**.

Saba and his colleagues, (2014), in their study concluded that ultrasound appearance and size of epiphyseal ossification centers of femur, tibia and humerus can be useful in prediction of gestational age (GA) during the third trimester of pregnancy, a period in which standard fetal biometric estimates of gestational age are least accurate. This technique appears to identify GA <33wks or >33 wks based on the presence or absence of the distal femur epiphysis (DFE) **[22]**.

Ultrasound visualization of proximal tibia epiphyseal (PTE) ossification is a strong indicator of GA (36) wks, where appearance of proximal humerus epiphseal (PHE) ossification virtually confirms the maturity of the fetus.

Saba and his colleagues, **[22]**, who found that the proximal humeral epiphysis (PHE) was not observed before 36 week and was observed in a small proportion of fetuses 14% at the 36th week of GA, and this percentage increased to 25% at the 37th, 66% at the 38th, and 100% at the 39th and 40th weeks, respectively. And the visualization of proximal humeral epiphysis also implies that fetus has attained maturity.

Similar findings are found in the study of Mahony and his coworkers, **[16]**, study which showed that all fetuses with a visible proximal humeral epiphysis (PHE) had a mature amniocentesis, a good indicator of fetal lung maturity based on L/S ratio and phosphatidyl glycerol in amniotic fluid.

Similar findings are also found in the study of Kumari and his colleagues, **[23]**, who found that during ultrasonography for proximal humeral epiphysis not seen with the gestational age below 35 weeks. And also similar results are in the same line with our results in the study of Mongolli and his coworkers, **[24]**, who reported confirmation of

fetal maturity may also be obtained by examining the ossification centers. The distal femoral epiphysis appears at a mean age of 32-33 weeks' gestation. Its size increases linearly with gestational age. Ultrasound detection of the proximal humeral epiphysis has been correlated with a mature amniocentesis lung profile.

The ossification centers appeares after 31st week gestation. The order of appearance is DFE, PTE and PHE as first, second and third respectively. At first the average size of Distal Femoral Epiphysis was more than Proximal Tibial and Proximal Humeral Epiphysis but on reaching at a menstrual age of 38-39 weeks, the size of epiphysis become almost same.

This shows that the proximal humeral epiphysis is growing at a faster pace as compared to proximal tibial and distal femoral epiphysis. So, the size and appearance of these epiphyseal centers will be helpful to determine the gestational age and viability of the fetus in normal as well as medico legal cases.

It can also be drawn from the conducted studies that the identification and measurement of these ossification centers may be less affected by fetal growth restriction or excessive growth than other anthropometric ultrasonographic measurements like Crown Rump Length, Abdominal Circumference, etc. **[23].**

Conclusion:

From this study we can concluded that the size and appearance of the proximal humeral epiphysis will be helpful to determine the gestational age and viability of the fetus in normal as well as medico legal cases.

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التعرف وقياس مراكز التعظم بالموجات فوق الصوتية للتنبؤ بنضوج رئة الجنين فى السيدات الحوامل المصريات

الخلفية العلمية : متلازمة الضائقة التنفسية هى سبب رئيسى لوفيات واعتلال حديثى الولادة. نضج الرئة مهم فى حالات الحمل عالية الخطور. أقوى مؤشر على نضج الرئة هو عمر الحمل وأيضاً، يمكن تصنيفه بواسطة علامات الموجات فوق الصوتية كمراكز تعظم المشاش.

الهدف من البحث : هدفنا هو تقييم مراكز التعظم الفخذى البعيد والظنبوب القريب والعضد القريب كأدوات تنبؤية لنضج رئة الجنين.

المرضى وطرق البحث : أجريت هذه الدراسة المقارنة على ١٠٠ امرأة حامل التحقن بعيادة أمراض النساء والتوليد فى مستشفى دمنهور التعليمى.

وستخضع جميع الحالات فى هذه الدراسة لأخذ التاريخ، الفحص السريرى الكامل، التحقيقات.

بعد موافقة لجنة الأخلاقيات المحلية، تم إبلاغ جميع المرضى جيداً بالإجراء وكان لديهم موافقة خطية مستنيرة قبل إجراء الإجراء.

تم تحليل البيانات باستخدام حزمة برامج IBM SPSS الإصدار ٢٠.٠. تم جمع البيانات وجدولتها ثم تحليلها كانت قيم p 0.05 تعتبر مهمة.

النتائج : كشفت نتائجنا عن اختلاف غير كبير بين النساء فيما يتعلق بالبيانات الديموغرافية والعلامات والأعراض والتاريخ الماضى. كشف الفحص بالموجات فوق الصوتية عن انخفاض كبير فى الضائقة التنفسية مع زيادة عدد مراكز التعظم وأيضاً، انخفض القبول فى وحدة العناية المر كزة بشكل كبير مع زيادة عدد مراكز التعظم. بالإضافة إلى ذلك، زاد عدد مراكز occification بشكل كبير مع زيادة عمر الحمل.

الخلاصة : يمكننا أن نستنتج أن حجم ومظهر المشاش العضد القريب سيكون مفيداً لتحديد عمر الحمل و قابلية الجنين للبقاء فى الحالات القانونية العادية وكذلك الطبية.