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SONOGRAPHIC IDENTIFICATION AND MEASUREMENT OF THE EPIPHYSEAL OSSIFICATION CENTERS IN THE PREDICTION OF FETAL LUNG MATURITY IN EGYPTIAN WOMEN

By

Amr Awad Amin Abd El-Hady, Ismail Mohammed Abd El-Azeam Mira, and Farid Ahmed Kassab

Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University

E-mail: Amrsamon@gmail.com

ABSTRACT

Background: 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.

Objective: Evaluating the distal femoral, proximal tibial and proximal humeral ossification centres as predictive tools of fetal lung maturity.

Patients and methods: This study was conducted at Obstetrics and Gynecology Department, Damanhur Teaching Hospital, from May 2019 to January 2020 and included 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, and the epiphyseal ossification centres were parallel to gestational age.

Results: The results of this study showed that the relation between Mean Epiphyseal Ossification Centers and neonatal Respiratory distress syndrome. The mean Epiphyseal Ossification Centers were significantly low in neonatal with respiratory distress syndrome ($p < 0.05$). It was found that there was a positive significant correlation between mean epiphyseal ossification centers and APGAR score at 5 min. It was found that the Mean Epiphyseal Ossification Centers were significantly increased with increasing gestational age.

Conclusion: The distal femoral, proximal tibial and proximal humeral ossification centers have good predictive values of fetal lung maturity.

Keywords: Sonographic, Epiphyseal Ossification Centers, Fetal Lung Maturity.

INTRODUCTION

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 *(Palacio et al., 2012).*

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 *(Misra et al., 2016).*

Ancillary methods like amniocentesis, radiography and ultrasonography are required to assess the foetal maturity. Amniocentesis is an invasive technique and use of X-rays is hazardous to fetus *(Beck et al., 2015).*

Foetal lung maturity can be assessed indirectly by ultrasonography marker of fetal lung maturity. The prediction of lung maturity by non-invasive ultrasound methods has been extensively explored *(Butt and Lim, 2014).* Other studies used free floating particles in amniotic fluid as a method to evaluate fetal lung maturity by ultrasound *(Keikhaie et al., 2017).*

The measurement of epiphyseal ossification centres 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 *(Kumari et al., 2015).*

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 1 mm. 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 *(Birang et al., 2013).*

The aim of 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 conducted at Obstetrics and Gynecology Department, Damanhur Teaching Hospital, from May 2019 to January 2020 and included 100 pregnant women. Informed verbal consents were obtained from all patients in the study.

Inclusion criteria:

Age: 16-45. Singleton pregnancies at 35 – 40 weeks. Living fetus and delivering within 72 hours from scan.

Exclusion criteria:

Pregnant women less than 35 weeks of gestation. Multiple gestations. Uncertain gestational age. Severe medical condition leading to termination of pregnancy. Cases with major congenital anomalies, hydrops fetalis, premature rupture of membranes, umbilical cord prolapse and placental abruption. Polyhydramnios and oligohydramnios and intra-uterine growth restriction, macrosomic fetuses, or presence of meconium stained amniotic fluid.

Methods:

All included women after informed consent was subjected to:

1. **History taking** included personal history, menstrual history, obstetric history, present history included: gynecological symptoms, urinary symptoms, and past history.
2. **Examination** included general examination, abdominal examination and vaginal examination.

3. **Investigations:** Routine investigations and ultrasound scan to assess the gestational age and to detect any abnormality.
4. **Interventions:** Gestational age was determined by last menstrual period or ultrasound in the first trimester. Abdominal ultrasound was done using a 2.5 - 7.5 MHz trans-abdominal probe with the women in the recumbent position. Fetal condition, gestational age, the presence of any fetal or uterine anomalies, the placenta and the amniotic fluid were assessed. The main ossification centres appeared ultrasonically as egg shaped echo rich areas. The ossification centres of distal femoral and proximal tibial epiphysis were seen at the level of knee joint whereas the proximal humeral epiphysis was seen at shoulder joint. Measurements of the epiphysis were taken from the outer to outer margins in an axial plane along the axial plane along the medio-lateral surface. Each measure was made from a separate scan image. At least, three measurements were taken, and the mean values of the three measures were considered as the current diameter.

Statistical analysis:

The data were collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 21) software.

The statistical tests used as follows:

Arithematic mean, standard deviation, for normally distributed data, comparison between two independent populations were done using independent t-test, while more than two populations were analyzed using F-test (ANOVA). For categorized parameters, Chai square test was used. To study the association between each two variables, person correlation coefficient was used. The level of significant was 0.05.

RESULTS

The ultrasound findings in the studied group were recorded and the range, mean and S.D were calculated **(Table 1)**.

Table (1): Ultrasound findings in the studied group

Parameters	Number	Percent
GA (U/S)		
35-37	42	42.0
38-40	58	58.0
Range	35.14-40.3	
Mean	38.01	
S.D.	1.65	
Mean Epiphyseal Ossification Centers		
<3	12	12.0
3-4	30	30.0
4-6	45	45.0
>6	13	13.0
Range	2.4-6.8	
Mean	4.53	
S.D.	1.22	

The main ossification centers appeared ultrasonically as egg shaped echo rich areas. The ossification centers of distal femoral and proximal tibial epiphysis were seen at the level of knee joint **(Figures 1, 2** and **4)**. Whereas the proximal humeral epiphysis was seen at shoulder joint **(Figure 3)**. Measurements of the epiphysis were taken from the outer to outer margins in an axial plane along the axial plane along the medio-lateral surface **(Figures 5 and 6)**.

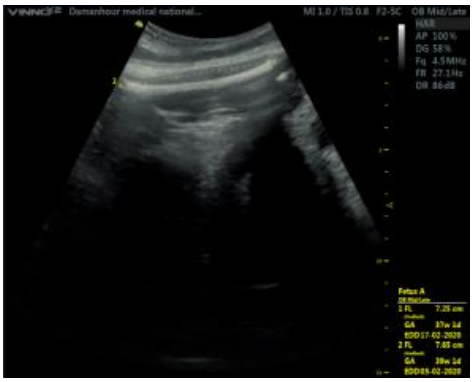

Figure (1): Fetal knee showing distal femoral epiphysis (DFE)

Figure (2): Fetal knee showing both distal femoral epiphysis (DFE) and the proximal tibial epiphysis (PTE)

Figrue (3): Ultrasound image of proximal humeral epiphysis

Figrue (4): Fetal knee showing distal femoral epiphysis (DFE)

Figrue (5): Ultrasound image of distal femoral epiphysis of 36-week fetus

Figrue (6): Distal femoral epiphysis at 39 weeks

The mean epiphyseal ossification centers significantly low in neonatal with respiratory distress syndrome **(Table 2)**.

Table (2): Relation between mean Epiphyseal Ossification Centers and neonatal respiratory distress syndrome

Neonatal Respiratory distress syndrome / Mean Epiphyseal Ossification Centers	No "n=93"	Yes "n=7"	Total
Range	2.40-6.80	2.60-3.60	2.40-6.80
Mean	4.64	3.10	4.53
S.D.	1.20	0.37	1.22
P	0.001*		

The neonatal ICU admission showed a low epiphyseal ossification center **(Table 3)**.

Table (3): Relation between mean epiphyseal ossification centers and NICU admission

ICU admission / Mean Epiphyseal Ossification Centers	No "n=91"	Yes "n=9"	Total
Range	2.40-6.80	2.60-3.60	42.40-6.80
Mean	4.68	3.06	4.53
S.D.	1.18	0.37	1.22
p	0.0001*		

There was a positive significant correlation between mean epiphyseal ossification centers and APGAR score at 5 min **(Table 4)**.

Table (4): Correlations between epiphyseal ossification centers and APGAR score at 1 and 5 min

Parameters		Mean Epiphyseal Ossification Centers	Neonatal APGAR score 1 min	APGAR score 5 min
Mean Epiphyseal Ossification Centers	Pearson Correlation	1	.096	.205
	P value		>0.05	<0.05
Neonatal APGAR score 1 min	Pearson Correlation	.096	1	.226
	P value	>0.05		<0.05
APGAR score 5 min	Pearson Correlation	.205	.226	
	P value	<0.05	<0.05	

The mean epiphyseal ossification centers were significantly increased with increasing gestational age **(Table 5)**.

Table (5): Relation between mean epiphyseal ossification centers and gestational age

Mean Epiphyseal Ossification Centers / G.A.	Minimum	Maximum	Mean	S.D.	Number of cases
35	2.40	3.20	2.72	0.22	14
36	3.10	3.60	3.42	0.17	11
37	3.50	4.10	3.85	0.15	17
38	4.10	5.00	4.54	0.33	17
39	5.00	5.50	5.24	0.16	16
40	5.60	6.80	6.12	0.44	25
Total	2.40	6.80	4.53	1.22	100
p	0.0001*				

The post for test with ANOVA for multiple comparisons

DISCUSSION

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 were ranged from 2.4-6.8 with a mean of 4.53±1.22, and the epiphyseal ossification centers were parallel to gestational age.

In agreement with our study, *Birang et al. (2013)* showed that ultrasonographic visualization of the epiphysis ossification centers may be a useful marker of fetal gestational age. Distal Femur Epiphysis (DFE) appeared in a small proportion of the fetuses (17%) as early as the 29th week compared with 35 weeks in this study.

Distal Femur Epiphysis (DFE) was detectable by ultrasonography in 71% at 32 weeks where in 72% of our study DFE was visible by ultrasound at 35 weeks. DFE was detectable in 100% of fetuses at 37 weeks gestation.

In line with the results of this study, it has previously shown that the distal femur epiphysis is not visualized before 28 weeks gestation and the mean age at DFE appearance is 32 to 33 weeks gestation. If a DFE is not visualized, the fetus was most likely less than 34 menstrual week's gestation as the DFE is observed in 94% of fetuses at 34 weeks gestations *(Elsaeed et al., 2017).* Moreover, a DFE of 3 mm or more was associated with a gestational age of greater than 37 weeks in 84% of fetuses. It was comparable with the mean gestational age 36.71 in this study *(Birang et al., 2013).*

The fetal ossification 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 taller ossification center from 26 weeks, the distal femoral epiphyseal ossification center from 32 weeks; and the proximal tibial epiphyseal ossification center from 36 weeks. Ultrasound is able to identify each epiphyses ossification center at much earlier stage, as long as the diameter is at least 1 mm *(Elsaeed et al., 2017).*

The distal femoral, proximal tibial, and proximal humeral ossification centers were identified and measured. A nomogram of fetal bone development was created using the sum of the three diameters. Gestational age correlated well with the diameters of the distal femur and proximal tibia epiphyseal 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 13 mm were 82%, 94%, and 100%, respectively *(Wafa et al., 2018).*

In our study, it was found that 7 cases had neonatal respiratory distress syndrome, and it was found that the mean epiphyseal ossification centers were significantly low in neonatal with respiratory distress syndrome. Also, it was found that 9 cases were admitted to NICU, and the neonatal ICU admission shows a low epiphyseal ossification center. It was found that there was a positive significant correlation between mean epiphyseal ossification centers and APGAR score at 5 min.

Assessment of fetal lung maturation is one of the most important steps while deciding the birth of the fetus. The

objective was protection of the fetus from risks such as sequelae of respiratory distress syndrome (RDS), necrotizing enterocolitis, intraventricular hemorrhage, patent ductus arteriosus and neonatal sepsis as much as possible. However, the main point in deciding birth is the clinical condition of the mother and the fetus *(Kars et al., 2011).*

Suhail et al. (2013) 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 appeared to identify GA<33weeks or>33 weeks based on the presence or absence of the DFE. They also 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. The visualization of proximal humeral epiphysis also implies that fetus has attained maturity.

Ultrasound visualization of proximal tibial epiphyseal (PTE) ossification is a strong indicator of GA 36 weeks, where appearance of proximal humeral epiphysis (PHE) ossification virtually confirms the maturity of the fetus. *Kumari et al. (2015)* found that during ultrasonography for proximal humeral epiphysis not seen with the gestational age below 35 weeks. *Abd EL-Fattah et al. (2018)* reported that 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 appear after 31st week gestation. The order of appearance is Distal Femoral Epiphysis (DFE), Proximal Tibial Epiphysis (PTE) and Proximal Humeral Epiphysis (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. So, the proximal humeral epiphysis is growing at a faster pace as compared to proximal tibial and distal femoral epiphysis. Thus, 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 *(Kumari et al., 2015).*

CONCLUSION

From the results of this study it was concluded that the distal femoral, proximal tibial and proximal humeral ossification centers have a good predictive value of fetal lung maturity.

Conflicts of interest: No conflicts of interest were encountered.

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التعرف وقياس مراكز التعظم بالموجات فوق الصوتية للتنبوء بنضوج رئة الجنين في السيدات المصريات

عمرو عوض أمين عبد الهادى، إسماعيل محمد عبد العظيم ميرة، فريد أحمد كساب

قسم التوليد وأمراض النساء، كلية الطب، جامعة الأزهر

خلفية البحث: يعتبر عدم نضج الرئة من الأسباب الأكثر شيوعًا للوفيات والمراضة الوليدية في الأجنة قبل الأوان ومتلازمة الضائقة التنفسية سبب رئيسي لوفيات ومراضة حديثي الولادة حيث لا تستطيع الرئة توفير الأكسجين الكافي. ويمكن تقييم نضج رئة الجنين بشكل غير مباشر عن طريق الموجات فوق الصوتية وعلى مدى السنوات الثلاثين الماضية.

الهدف من البحث: التعرف علي وقياس مراكز التعظم بالموجات فوق الصوتية للتنبؤ بنضوج رئة الجنين فى السيدات المصريات.

المريضات وطرق البحث: تم إجراء هذه الدراسة في قسم أمراض النساء والولادة بمستشفى دمنهور التعليمي والتى تضمنت عينة من 100 امرأة حامل.

نتائج البحث: كانت متوسط مراكز التأرجح المشاشية منخفضة بشكل ملحوظ في حديثي الولادة المصابين بمتلازمة الضائقة التنفسية. وقد وجد أن قبول وحدة العناية المركزة لحديثي الولادة تظهر مراكز تعظم منخفضة للمشاشية. ووجد أنه لا توجد علاقة ذات دلالة إحصائية بين طريقة الولادة ومتوسط مراكز التعظم المشاشية. وجد أن هناك علاقة ارتباطية موجبة بين مراكز التعظم المشاشية ورقم أبجار في 5 دقائق. ووجد أن متوسط مراكز التعظم المشاشية زادت بشكل ملحوظ مع زيادة عمر الحمل.

الاستنتاج: مراكز التعظم بالموجات فوق الصوتية للتنبوء بنضوج رئة الجنين لها قيمة تنبئية جيدة لنضج رئة الجنين.