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İleri Anne Yaşı Olan Spontan Gebeliklerde Olumsuz Obstetrik ve Neonatal Sonuçları Öngörebilmek İçin Anne Yaşı İçin Bir Eşik Değer Belirlenmesi

A Cut Off Value For Advanced Maternal Age In Predicting Adverse Obstetric and Neonatal Outcomes In Spontaneous Pregnancies

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ÖZ

Amaç: 40 yaşın üzerindeki spontan gebeliklerde olumsuz obstetrik ve neonatal sonuçları tahmin etmek için anne yaşı için bir eşik değer tanımlamak.

Yöntem: 40 yaş ve üzeri 359 gebelik retrospektif olarak değerlendirildi. Gebeler grup 1 (40-43) ve grup 2 (≥44) olmak üzere iki gruba ayrıldı. Çalışma gruplarının obstetrik ve neonatal sonuçları karşılaştırıldı. Ayrıca maternal yaş açısından olumsuz obstetrik ve neonatal sonuçları tahmin etmek için ROC eğrisi analizi yapıldı.

Bulgular: Obstetrik komplikasyon oranı grup 2'de (% 80.5) grup 1'den (% 36.5) anlamlı olarak daha yüksekti (p <0.001). Preeklampsi oranı da grup 2'de anlamlı olarak daha fazlaydı (p: 0.001). NICU'ya yatış oranları, grup 2'de (% 77.1) grup 1'e (% 28.7) göre istatistiksel olarak anlamlı derecede yüksekti (p <0.001). ROC eğrisi analizi, 41.5 yaşın olumsuz yenidoğan sonuçlarını ve NICU'ya ihtiyacı tahmin etmek için bir eşik değeri olarak bulundu (AUC: 0.607,0.566 sırasıyla).

Sonuç: Doktorlar ileri anne yaşı gebeliklerinin yönetiminde özellikle ≥41,5 yaş grubunda olan annelerde daha dikkatli olmalıdırlar.

Anahtar Kelimeler. İleri anne yaşı, Gebelik, olumsuz gebelik sonucu, olumsuz yenidoğan sonucu, yüksek riskli gebelik

ABSTRACT

Background: To define a cut off value for maternal age to predict adverse obstetric and neonatal outcomes in spontaneous pregnancies ≥40 years of age.

Methods: We retrospectively evaluated 359 pregnant women ≥40 years of age. Patients were enrolled into two groups as Group 1 (40-43) and Group 2 (≥44). We compared the obstetric and neonatal adverse outcomes of the study groups. We also performed ROC curve analysis to predict adverse obstetric and neonatal outcomes in terms of maternal age.

Results: Composite obstetric complication rate was significantly higher in group 2 (80.5%) than in group 1 (36.5%) (p < 0.001). Preeclampsia rate was also significantly more common in group 2 (p: 0.001). Admission to NICU was statistically significantly higher in group 2 (77.1%) compared to group 1 (28.7%) (p < 0.001). ROC curve analysis revealed 41.5 years of age as a cut-off value for predicting adverse neonatal outcomes and NICU admission (AUC: 0.607 and 0.566, respectively).

Conclusion: Physicians should be cautious in the management of advence maternal age (AMA) pregnancies especially in patients with maternal age of ≥41.5 years.

Keywords: Advanced maternal age; pregnancy; adverse obstetric outcome; adverse neonatal outcome, high risk pregnancy

INTRODUCTION

The term advanced maternal age (AMA) is commonly used for defining women who conceive at ≥35 years of age, while some studies preferred using ≥ 40 years of age (1, 2). The rate of AMA pregnancies have increased in the last decades due to life style changes, socio-economic factors and widespread application of assisted reproductive technologies (ARTs) (3-6).Nevertheless, AMA was reported to be associated with various perinatal complications like misscarriage, ectopic pregnancy, fetal karyotype abnormalities, fetal congenital anomalies, placental abnormalities, gestational diabetes mellitus (GDM), gestational hypertension, preeclampsia, preterm birth and stillbirth (7-12).Depending on various studies, the category of "very advanced maternal age" has also been proposed for women between the ages of ≥45 or ≥50 (13, 14).Women with very advanced maternal age have higher complications, multiple pregnancies, and an increase in premature birth and fetal growth restriction rates (15). Thus, physicians should be cautious in the management of AMA pregnancies in order to achieve favorable outcomes.

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There are many studies investigating the effects of AMA on perinatal and neonatal outcomes, but the results are inconsistent. Furthermore, previous studies have some limitations related to the study design, patient population and investigated variables. Higher rates of maternal chronic diseases, increased rates of ARTs, higher frequencies of multiple gestations seem to be the major risk factors for the higher rates of adverse outcomes in AMA pregnancies. Moreover, literature is still limited in terms of the direct effect of maternal age on perinatal outcomes. Additionally, as maternal age is at an increasing trend in the general population, there are on-going debates on the lower limit of AMA in the current studies (7, 16, 17). For this reason, the aim of this study is to define a cut off value for maternal age to predict adverse obstetric and neonatal outcomes in spontaneous pregnancies ≥40 years of age.

MATERIAL AND METHODS

This was a retrospective cohort study evaluating the obstetric and neonatal outcomes of spontaneous singleton pregnancies which were ≥ 40 years of age at our institution between 2014-2019. Demographic features and clinical characteristics of all eligible cases were evaluated. The required data were obtained from the electronic database of our institution.

Cases were divided into two groups based on maternal age; group 1: maternal age 40-43 and group 2: maternal age ≥ 44. Maternal age, systemic diseases, gravidity, parity, number of previous miscarriages, number of living child , BOIp (Beksac Obstetric Index pregnancy), gestational week at birth, birth weight was compared between two groups. Maternal systemic diseases were divided into 5 subgroups: 1) Endocrine diseases (diabetes mellitus, thyroid function disorders), 2) Cardiovascular diseases (hypertension, coronary artery disease, valvular heart disease) 3)Rheumatological diseases (rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus), 4) Respiratory system diseases (asthma, chronic obstructive lung disease) and 5) Neurological diseases (multiple sclerosis, epilepsy). BOI is a special obstetric index for the assessment of risk levels in pregnancies depanding on their previous obstetric histories [(number of alive children + (π / 10)) / Gravida]. The BOI value calculated in the preexisting pregnancy was defined as BOIp (18).

Additionally, pregnancy outcomes (live birth, termination of pregnancy and intrauterin exitus), composite obstetric complications (preeclampsia, fetal growth restriction, preterm birth, placenta previa), fetal chromosomal abnormalities, congenital structural abnormalities, 10th minute APGAR scores (7 or ≥7) and neonatal intensive unit (NICU) admissions were also compared between the groups.

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 22, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp., USA). The Kolmogorov–Smirnov test was used to evaluate the normal data distribution. Because data were not normally distributed, the median values together with interquartile range (IQR) values were used for continuous variables. Chi-square or Fisher exact test was used to compare categorical variables. The relevant data was summarized as median and interquartile range (IQR).

Receiver operating characteristic (ROC) curves were used to assess the performance of AMA in predicting obstetric complications and admission to NICU. ROC curves plot the true positive rate (sensitivity) against the false-positive rate (1 − specificity) for the possible cut-off values. The area under the curve (AUC) corresponds to the probability that the criterion will correctly classify a random observation. An AUC >0.5 indicates that the criterion is superior to chance. The significance level was set at p<0.05. Youden index was used in order to determine the optimal cut-off value. Written informed consent was obtained from all the patients, and the study was approved by the institutional ethics committee (GO 19/1129).

RESULTS

This study consisted of 359 pregnant women. Median maternal age was 41 (IQR:2). The demographic features and clinical characteristics were summarized in Table 1.

Table 1: Demographic features and clinical characterstics

Maternal Age	41 (IQR:2)
Gravidity	3 (IQR:2)
Parity	1 (IQR:1)
Previous Miscarriages	0 (IQR:1)
Living Child	1 (IQR:1)
Maternal Systemic Disease*	135(%37.6)
BOIp	0.25 (IQR:0.1)
Gestational week at birt	38 (IQR:1)
Birth weight	3175 (873)

*Number and rate

In our study, there was no ≥ 50 years old patient who could be considered as very advanced maternal age. There were 323 cases in group 1 (% 89.9) and 36 cases in group 2 (%10). Two groups were similar in terms of demographic features and clinical characteristics. The number of patients with maternal systemic disease was 124 (38.3%) in group 1 and 11 (30.5%) in group 2 (p: 0.213). The median gestational week at birth was 38 (IOR:1), 37 (IOR:3) and the median birth weight was 3180 (IQR:870) g, 3085(IQR:1118) g respectively for groups 1 and 2 (p: 0.158). The comparison of the demographic and clinical characteristics of the two groups is summarized in Table 2.

Table 2: Comparison of demographic features and clinical characteristics between groups

	Group 1 (40-43)	Group 2 ≥ 44	P value
Maternal systemic disease*	124 (%38.3)	11 (%30.5)	0.213
Endocrine diseases	48 (%38.7)	5 (%45.4)	
Cardiovascular disease	36 (%29)	3 (%27.3)	
Rheumatologic diseases	18 (%14.5)	1 (%9)	
Respiratory system diseases	12 (%9.6)	1 (%9)	
Neurological diseases	10 (%8)	1 (%9)	
Gravidity	3(IQR:2)	3(IQR:3)	0.227
Parity	1(IQR:1)	1(IQR:3)	0.664
BOIp	0.25(IQR:0.10)	0.26(IQR:0.11)	0.553
Previous Miscarriages	0(IQR:1)	0(IQR:1)	0.980
Living Child	1(IQR:1)	1(IQR:2)	0.695
Gestational week at birt	38(IQR:1)	37(IQR:3)	0.465
Birth weight	31801(IQR:870)	30851(IQR:1118)	0.158

*Number and rate

Live birth rate, termination of pregnancy rate and intrauterine ex rates were 93.4% (302) and 91.4% (33); 3% (10) and 5% (2); 3.4% (11) and 2.7% (1) for groups 1 and 2, respectively (p: 0.738). Composite obstetric complication rate was significantly higher in group 2 (80.5%) compared to group 1 (36.5%) (p < 0.001). Preeclampsia was significantly more common in group 2 (p: 0.001). Fetal chromosomal abnormality rates, fetal congenital structural abnormality rates and 10th minute APGAR scores were similliar between the groups (p: 0.920, p: 0.285 and p: 0.618 respectively). Admission to NICU was statistically significantly higher in group 2 (77.1%) compared to group 1 (28.7%) (p < 0.001). The obstetric and neonatal outcomes were summarized in Table 3.

Table 3: Obstetric and neonatal outcomes

	40-43	≥ 44	P value
Pregnancy outcome			
live birth	302 (%93.4)	33 (%91.6)	0.738
termination	10 (%3)	2 (%5)	
intrauterin ex	10 (%3)	1 (%2.7)	
Obstetric complications	118 (%36.5)	29 (%80.5)	**< 0.001**
GDM	52(%16)	10(%27.7)	0.790
Preeclampsia	20(%6.1)	8(%22.2)	**0.001**
Intrauterine growth retardation	10(%3)	10(%8.3)	0.111
Preterm birth	7(%2.1)	2(%5.5)	0.217
Placenta previa	5(%1.5)	2(%5.5)	0.990
Intrauterin ex	10(%3)	1(%2.7)	0.916
Abnormal karyotype	7 (%2.1)	1 (%2.7)	0.920
Fetal anomaly	36 (%11.1)	4 (%11.1)	0.285
10th minute APGAR score			0.618
< 7	27 (%8.6)	5 (%14.2)	
≥ 7	286 (%91)	30 (% 83.3)	
NICU admission	90 (%28.7)	27 (%77.1)	**< 0.001**

Results of the ROC curve analysis for assessing the performance of AMA in predicting obstetric complications and rate of admission to NICU are shown in Table 4,

Table 4: ROC curve analysis for assessing the performance of AMA in predicting obstetric complications and percentages of admission to NICU

Obstetric complications	Cut-off value for	Sensitivity	Specifity	P value			
AUC: 0.607							
(95% CI: 0.546-0.669)							
	41.5	52.8	72.7	<0.001			
Percentages of admission to NICU							
AUC: 0.566							
(95% CI: 0.496-0.635)							
	41.5	56.6	69.8	<0.047			

and ROC curves are shown in Figure 1 and 2.

Figure 1: ROC curves for obstetric complications

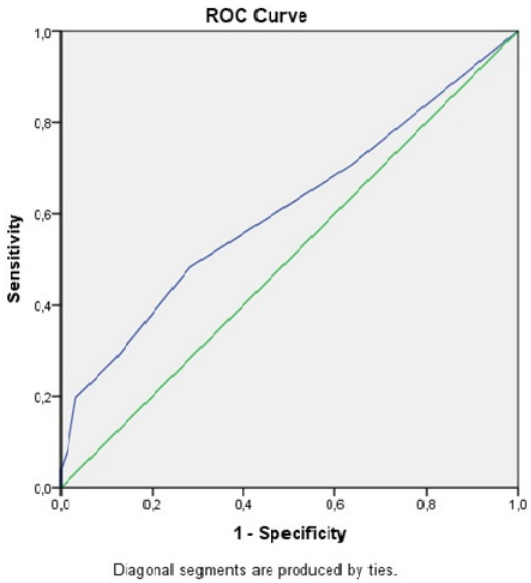
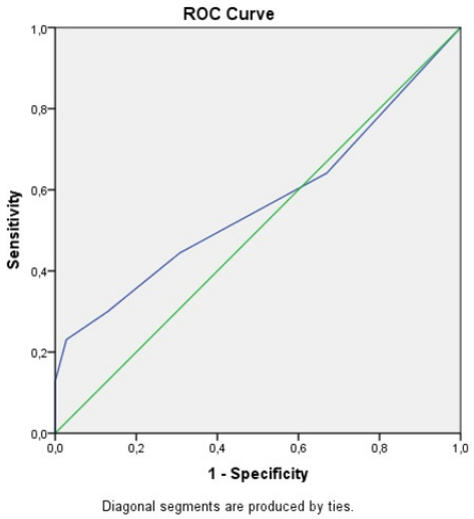


Figure 2: ROC curves for NICU admission



AUC values were 0.607 (95% CI: 0.546–0.669) and 0.566 (95% CI: 0.496–0.635) for obstetric complications and rate of admission to NICU, respectively. As a result, maternal age of 41.5 (52.8% sensitivity, 77.7% specificity) and 41.5 (56.6% sensitivity, 69.8% specificity) was determined to be the cutoffs for obstetrics outcomes and admission to NICU, respectively, with highest sensitivity and specificity.

DISCUSSION

Higher rates of obstetric complications and NICU admissions were observed in pregnancies with maternal age of ≥44 in this study. Furthermore, a cut-off value of 41.5 was found for predicting increased rates of both composite obstetric complications and NICU admissions. Although ,the association between AMA pregnancies and adverse pregnancy outcomes have been known for many years, the optimal cut-off value for advanced maternal age has not been clearly determined yet (19-24). As many factors like increased rates of maternal systemic diseases, ART procedures, multiple pregnancies and decreased oocyte quality may all affect the outcome of pregnancy in these group of patients, it is challenging to define a cut-off value for AMA (19-23). However, studies evaluating merely the effect of maternal age on the obstetric outcomes may be useful for the physicians. For this reason, singleton spontaneous pregnancies with AMA were evaluated in this study.

Favilli et al. conducted a matched retrospective cohort study of 630 patients comparing pregnant women aged 40 years or more with a control group aged 20 to 30 years. Increased rates of preterm delivery due to higher frequencies of GDM and pregnancy induced hypertension was reported in older patients. However, similar rates of preeclampsia and placenta previa were found in both groups (21).

Schimmel et al. compared spontaneously-conceived singleton births of AMA mothers (≥35 years) with spontaneously-conceived singletons of mothers aged 24–27 years in their retrospective single-center study including 24 579 eligible women. Incidence of GDM and hypertension were significantly higher in the AMA group. Moreover, large for gestational age neonates were more common in the AMA group (22).

Haslinger et al. retrospectively compared the outcome of pregnancies in very AMA patients with controls aged 30 years at time of delivery. They also found high rates of gestational hypertension, preeclampsia and gestational diabetes in very AMA pregnancies (15).

Hollenbach et al. retrospectively evaluated the data of 724,802 pregnancies and they divided the patients into different age categories: 1)

35, 2) 35-39, 3) 40-44, 4) 45-49 and 5) ≥50. The authors found increased rates of obstetric complications with increased maternal age (20).

Lean et al. conducted a systematic review and meta-analysis including 63 cohort studies and 12 case-control studies. The authors concluded that the risk of stillbirth, FGR, neonatal death, GDM and NICU admission was increased in AMA pregnancies (23).

Kanmaz et al. categorized 26937 patients into 4 groups in their single center retrospective study: 1) group 1 (25-35), 2) group 2 (35-40), 3) group 3 (40-45), and 4) group 4 (45 years). The authors reported increased rates of prenatal complications in the AMA groups (19).

The findings of this study was generally consistent with the current literature. However, to the best of our knowledge, no study in the literature investigated merely the effect of maternal age on pregnancy outcomes (19-23). In our opinion this is the main strength of our study. On the other hand, retrospective design, relatively small number of cases and single center experience were the main limitations.

CONCLUSION

Physicians should be cautious in the management of AMA pregnancies, especially in patients with maternal age of ≥41.5 years. Further studies in larger populations are necessary in order to confirm our results.

Conflict of Interest

The authors state that they have no conflict of interest in this study.

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