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ORIGINAL ARTICLE

Does Advanced Maternal Age Increase the Risk of Adverse Perinatal Outcomes?

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ABSTRACT

Objective: To compare the perinatal outcomes of advanced maternal aged women (≥ 35 years) to the controlgroup (20-35 years) in a tertiary hospital.
Material and methods: This study was conducted on 2152 women who gave birth between 1st January and 31st December 2011. The 'study group' was comprised 537 pregnant women aged ≥35 years and the 'control group' was comprised 1615 pregnant women aged between 20-35 years. The maternal and fetal outcomes of two groups were compared statistically.
Results: The incidence of preterm delivery was significantly higher in the advanced maternal aged women group (14.5% vs 6.6%, p<0.001). Low birth weight, very low birth weight babies and intrauterin growth restriction were also significantly higher in this group (7.1% vs 4.6%, p= 0.01, 5.2% vs 0.9%, p<0.001, and 8.2% vs. 4.8% p=0.003, respectively). Although cesarean section rate was significantly higher in the study group (34.8% vs. 26.6%, p<0.001), emergency cesarean section rate was significantly higher in the control group (29.4% vs 40%, p=0.01). Pregnancy induced hypertension and gestational diabetes mellitus were significantly higher in the older women compared to control group (p<0.001, OR: 2.2, 95% Cl:1.5-3.5 and p=0.01 OR: 1.89, 95% Cl:1.2-2, respectively).
Conclusion: Pregnancies with advanced maternal age have higher risk of maternal and fetal complications. The most crucial risks for older pregnancies are pregnancy induced hypertension and gestational diabetes mellitus. The cesarean section rates are also higher in older pregnant women.

Key words: Maternal age; Pregnancy complications; Cesarean section

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Introduction

Traditionally, women giving birth at ages ≥35 years are termed as 'advanced maternal age'(AMA). Such women are likely to encounter several problems during early and late pregnancy [1]. Early complications include spontaneous miscarriage, fetal aneuploidy and congenital anomalies [2]. Due to the increase in concomitant medical and surgical diseases with age perinatal complications are more common in pregnancies of women older than 35 years. During pregnancy, the most common antenatal problems of older women are hypertensive diseases, diabetes (both gestational and overt) and placental pathologies (previa and abruption) [3-5]. Maternal age and parity are independent risk factors for placenta previa [6].

Additionally, babies of older women are at risk of being premature and small for gestational age [2,6,7]. According to the findings of the World Health Organization (WHO) Multicountry Survey, published in 2014, the risk of maternal and perinatal mortality is higher in older pregnant women [8]. In the United States, the maternal mortality for women aged 35 to 39 years is more than twice that of women aged 25 to 29 years (21 versus 9 per 100.000 live births) [9]. Although, by WHO definition pregnant women aged >35 years have increased risks for pregnancy complications, most of the data in literature is focused on the analysis of developed countries [8]. In the last National Vital Statistics of United States, during 1961-2011, the total birth rates were reported to have decreased for all reproductive aged women. Although this decrease was more prominent (9% decrease) in women aged 25-29 years, from 1996 until 2006, the ratio of giving birth among women aged >35 years increased from 12% to 20% [9,10]. The

reasons for this increase in the developed world are wider opportunities for higher education and career advancement, second marriages and the availability of better contraceptive choices [11]. But data from developing countries like Turkey are limited; In this retrospective cohort study, we aim to compare the perinatal outcomes of pregnant women aged ≥ 35 years to the control group in our hospital, representative of Central Anatolia, in Turkey.

Material and Method

This retrospective cohort study was conducted on women who gave birth at Etlik Zubeyde Hanım Women's Health Training and Research Hospital, a tertiary referral hospital, between 1st January 2011 and 31st December 2011. In this period there were 16230 deliveries in our hospital. We investigated all the pregnant women aged ≥ 35 years as AMA after the exclusion criteria was applied in this period. The 'study group' comprised of 537 pregnant women aged ≥ 35 years. Using a 1: 3 ratio for cases: controls, the control group consisted of 1615 women aged between 20 and 34 years, who were randomly selected. This study was approved by the local ethics committee and performed in accordance with the ethical standards for human research established by the Declaration of Helsinki.

Patients who had terminated their pregnancy prior to 24 weeks, due to congenital or chromosomal anomalies, were excluded from the study. Furthermore, patients who had any concomitant systemic illness, presence of the history of previous preeclampsia or gestational diabetes mellitus (GDM), used artificial reproductive technologies or multiple pregnancies were also excluded from this study because these conditions induce worse perinatal outcomes [12].

The gestational age was calculated as the gestational weeks from the first day of the last menstrual period (LMP) to the delivery. When this gestational age was inconsistent ultrasound measurement of the first trimester was used for correction. All data were retrieved from our patients' medical records and the hospital's computerized database.

The demographic data reviewed were as follows: the age, gravidity, parity, number of miscarriages and the presence of a smoking habit. Nulliparity was defined as not having any previous history of deliveries greater than 20 gestational weeks. Multiparity was defined as a previous history of ≥1 delivery greater than 20 gestational weeks. The clinical data reviewed were as follows: body mass index (BMI: weight (kg)/height^2 (m^2)) of the women on after birth, antenatal complications of the pregnancy, the type of delivery, birth weight of the baby and gestational age on birth. Obstetric complications such as placenta previa, placental abruption, hypertension, preeclampsia, gestational diabetes mellitus, preterm delivery, low birth weight (LBW), very low birth weight (VLBW), intrauterin growth restriction (IUGR) and fetal demise were recorded for each patient. LBW was defined as a birth weight of ≤2500 g, VLBW ≤1500 g and macrosomia ≥4000 g. IUGR was defined as an estimated fetal weight below the 2 standard deviations measured by ultrasound according to gestational age [13].

For all of the other babies, birth weights between 2500 g and 3999 g were defined as normal birth weight (NBW). Preterm delivery was defined as any delivery before 37 completed weeks of pregnancy [14]. Stillbirth was defined as any intrauterine death after 24 weeks of gestation.

Women were diagnosed as having pregnancy induced hypertension (PIH) if either of two systolic blood pressure measurements obtained at least six hours apart were ≥140 mm/Hg or if both diastolic pressures were ≥90 mm/Hg. Preeclampsia was defined as the new onset of hypertension and proteinuria (≥0.3 gr in a 24-hour urine specimen or protein: creatinin ratio ≥0.3) or presence of end-organ dysfunction (platelet count <100.000/microliter, serum creatinine >1.1 mg/dL or doubling of the serum creatinine, elevated serum transaminases to twice normal concentration) after the 20th gestation week in a previously normotensive woman. In 2013 the American College of Obstetricians and Gynecologists removed proteinuria as an essential criterion for diagnosis of preeclampsia [15]. GDM screening was carried out in all pregnant women with a glucose challenge test in 24-28th gestational weeks. Here, the blood glucose level was measured one hour after drinking a beverage containing 50 g of glucose. Patients with positive results (>140 mg/dl) then underwent a 100 gr oral glucose tolerance test for confirmation of GDM. Postpartum haemorrhage (PPH) was defined as estimated blood loss ≥500 mL after vaginal delivery, and ≥1000 mL after caesarean delivery.

In this study, cesarean sections were divided into three groups: elective, emergency or unscheduled c-section. Elective c-section was arranged by the obstetricians as close to the estimated date of delivery.

Indications for an elective c- section included previous c-section, breech presentation, the presence of any contraindication to normal delivery or concomitant medical problems. Our clinic has 16500 deliveries per annum and we give appointment for cesarean section to pregnants with the history of previous uterin surgery. As a result, vaginal birth is not performed on patients with history of cesarean section. In our clinic we usually prefer c-section for breech presentation [16]. At the same time, patients who applied to the hospital with active labor or had any abnormality in the fetal monitor were directly referred to the labor ward. If labor did not progress within a reasonable time (1.5 cm/hour in multiparous, 1.2 cm/hour in primiparous in the active phase of labor) oxytocin augmentation and amniotomy were performed. A cesarean section was performed when the labor did not progress as required, if cephalopelvic disproportion (CPD) occured or breech presentation in active labor or macrosomia was present. This group was classified as 'unscheduled c- section'. All cesarean sections performed in cases of suspected fetal distress, umblical cord prolapsus, placental ablation and preclampsia were classified as 'emergency c- section'. Fetal distress was defined as the presence of recurrent late or variable decelerations or bradycardia or absent baseline fetal heart rate variability on nonstress test (NST).

For the statistical analysis of this study, continuous variables were expressed as mean±standard deviation (SD), and categorical variables as number and percentage. The Kolmogorov-Smirnov test was used to assess normal data distribution. Student t-test and Chi Square test were used to compare groups. Odds Ratio (OR) and its respective confidence interval at 95% were computed. P values were considered significant at the 0.05 level. All of the statistical analysis was performed using SPSS Statistics version 21.0 software.

Results

After the exclusion criteria were applied, a total of 2152 women giving birth between 1st January 2011and 31st December 2011 were included in the study. The mean age BMI values were 37.7±2.3 years and 26.6±4.3 kg/m^2 for the study group; and 30.9±4.05 years vs 29.7±2.9 kg/m^2 for the control group. The differences of mean age and BMI between groups were statistically significant (p<0.001 and p<0.001, respectively). The percentage of multiparous patients in the study and control groups were 88.7% and 82.9%, respectively (p <0.001). There was no significant difference between groups in terms of smoking habitus (p=0.1). All patients were married and living with their families. The mean gestational age and birth weight were lower in the study group when compared to the control group (37.1±3.4 vs. 37.8±2.4 weeks, respectively; p<0.001 and 3162.6±694.2 vs. 3280.9±520.9 g, respectively; p <0.001). The study group had a significantly higher risk for both PIH and GDM than the control group (p<0.001, OR: 2.24; 95% CI 1.19-4.21 and p<0.01, OR: 1.89; 95% CI 1.05-3.39, respectively). The perinatal outcomes and antenatal complications of the pregnancies are shown in Table 1.

Table 1. Perinatal outcomes and antenatal complications in the groups

	AMA*(n, %) (n=537)	Control (n, %) (n=1615)	p value	OR (CI%95)
LBW[1]	38 (7.1)	72 (4.6)	0.01	1.6 (1.1-2.4)
VLBW[2]	28 (5.2)	14 (0.9)	<0.001	6.2 (3.3-12.3)
IUGR[3]	44 (8.2)	77 (4.8)	0.003	1.9 (1.2-2.6)
Stillbirth	7 (1.3)	17 (1.1)	0.41	1.1 (0.4-3.6)
Preterm delivery	78 (14.5)	106 (6.6)	<0.001	2.4 (1.7-3.3)
PIH[4]	37 (6.9)	51 (3.2)	<0.001	2.2 (1.5-3.5)
Preeclampsia	15 (2.8)	21 (1.3)	0.01	2.1 (1.1-4.2)
GDM[5]	38 (7.1)	63 (3.9)	0.01	1.9 (1.2-2.8)
PPH[6]	17 (3.2)	34 (2.1)	0.14	1.6 (0.8-2.7)

*Advanced maternal aged, [1]Low birth weight, [2]Very low birth weight, [3]Intrauterin growth restriction, [4]Pregnancy induced hypertension, [5]Gestational diabetes mellitus, [6]Post partum hemoragia.

Table 2. Delivery mode of the groups

	AMA* (n=537)	Control (n=1615)	p value	OR (CI%95)
Vaginal delivery	350 (65.2%)	1185 (73.4%)	<0.001	0.7 (0.6-0.8)
Cesarean section	187 (34.8%)	430 (26.6%)	<0.001	1.4 (1.2-1.8)
Elective c- section	60 (11.2%)	93 (5.7%)	<0.001	2.1 (1.2-2.9)
Emergency c- section	55 (10.2%)	172 (10.6%)	0.4	0.9 (0.7-1.3)
Unscheduled c-section	72 (3.4%)	165 (10.2%)	0.04	1.4 (1.1-1.8)

*Advanced maternal aged

There was a significantly increased risk of cesarean section in the study group (34.8% vs. 26.6%, p<0.001) (Table 2). Furthermore, the rate of elective c-section was 11.2% in the AMA group vs. 5.7% in the control group (p<0.001). The indications of c-sections are shown in Table 3.

Discussion

AMA is well known to increase the risk for perinatal complications and adverse pregnancy outcomes when compared to younger women. In this study, we found that LBW, VLBW, IUGR and preterm delivery were higher in the AMA when compared to

Table 3. Indications of cesarean sections in AMA and control group

	AMA* (n, %) (187, 34.8)	Control (n, %) 430, 26.6)	p v alue	OR (CI%95)
Elective c-section	**60 (32)**	**93 (22)**		
Previous cesarean delivery	53 (88.5)	69 (75)	0.03	2.6 (1.7-6.6)
Placenta previa (uncomplicated)	2 (3.08)	6 (6.3)	0.4	0.5 (0.9-2.5)
Previous uterine surgery	3 (4.6)	6 (6.3)	0.7	0.7 (0.2-3.7)
Presentation anomalies	2 (3.3)	12 (12.9)	0.05	0.2 (0.1-1.1)
Emergency c-section	**55 (29.4)**	**172 (40)**		
Suspician of fetal distress	42 (76.4)	124 (72.1)	0.5	1.2 (0.6-2.5)
Umblical cord prolapsus	2 (3.7)	18 (10.7)	0.1	0.3 (0.1-1.4)
Placental ablation	3 (6.1)	8 (4.3)	0.8	1.2 (0.3-4.6)
Preeclampsia	8 (12.2)	22 (12.3)	0.7	1.2 (0.5-2.8)
Unscheduled c-section	**72 (38.5)**	**165 (38.4)**		
CPD**	30 (41.7)	73 (44.2)	0.7	0.9 (0.5-1.6)
Fetal Macrosomia	21 (29.3)	35 (21.2)	0.2	1.5 (0.8-2.9)
Presentation anomalies	6 (10.5)	33 (20)	0.06	0.5 (0.2-1.2)
Labor arrest	7 (12.2)	24 (14.6)	0.4	0.8 (0.3-2.1)
Primigravid age	8 (14)	–	–	–

*Advanced maternal aged, ** Cephalopelvic disproportion

controls. Also PIH, GDM and cesarean section rate were higher in the AMA study group.

In literature, adverse outcomes, such as macrosomia, stillbirths and preterm delivery, are reported more frequently in older women, when compared to controls [17,18]. In a large cohort study from the United Kingdom (UK), scholars argued that older mothers are at an increased risk of adverse pregnancy outcomes compared to their younger peers [19]. Furthermore, Delpisheh et al. showed that in older women, the rate of LBW infants was 8.85%, compared to 6.35% in the younger control group [20]. Increasing age can cause vascular problems in the placenta, resulting in higher rates of LBW and VLBW. The present retrospective study also confirmed the increased risk of perinatal complications in a tertiary hospital in Turkey: the rate of LBW and VLBW babies were significantly higher in older women compared to the controls (7.1% vs 4.6%, p= 0.01, OR:1.6:1.1-2.4 and 5.2%vs 0.9%, p<0.001, OR: 6.2:3.3-12.3, respectively). In his study Baser et al found the risk of IUGR as 9.5% in the >40y women group [17]. In our study, IUGR rate in the AMA group was 8.2% (p<0.003).

The risk of iatrogenic preterm delivery increases for AMA patients with concomittant problems [18, 21]. Aging is known to increase the incidence of chronic hypertension. In literature, older women are reported to be 1.5 times more likely to develop preeclampsia, compared to women under 35 years of age [22]. The vascular impairment resulting from age increases susceptibility to PIH and preeclampsia [23]. In our study PIH and preeclampsia incidence were higher in the study group (6.9% vs. 3.2%, p<0.001, OR:2.2, 95% CI:1.5-3.5 and 2.8% vs. 1.3%, p= 0.01, OR:2.1, 95% CI:1.1-4.2, respectively). Similar to previous studies, preterm delivery rate was also higher in the AMA group than control group [7,24]. In our study the risk of preterm delivery in AMA group was 2.4 times more than control group (14.5% vs. 6.6%, p<0.001, OR: 2.4, 95%CI: 1.7-3.3). In our study, the main indication for iatrogenic preterm delivery was PIH.

Furthermore, the rate of GDM was also higher in the AMA group compared to the control group (7.1% vs 3.9%, p=0.01, OR: 1.89, 95% Cl: 1.2-2.8). This could be explained by the association between aging and progressive vascular endothelial damage. Fulop et al. reported a reduction in insulin sensitivity with age [25]. In the study group, the higher BMI and impaired glucose tolerance could be the causes of GDM. Szoke etal. showed pancreatic β cell dysfunction and impaired glucose tolerance got worse with age [26].

In a study from the United States, Mularz et al. reported that the highest adjusted OR for cesarean delivery was in primiparous women of AMA (1.97, 95% CI: 1.95-2) [27]. Additionally, Lamminpää et al. reported that c-section was found to be twice as likely in women of AMA [22]. In another study, the c-section rate for primiparous women over 35 years and over 40 years were reported as 38% and 50%, respectively [28]. In primiparous women, the relationship between maternal age and delivery by emergency c-section was identified as linear. This suggests a biological effect of AMA on labor performance, rather than simply obstetrician or maternal preference [10]. Although elective c-section for primiparous older pregnancies were not a routine procedure in our antenatal care practice, in this study, 14% of all primiparous older women delivered by unscheduled c-section. The cesarean indications of those primiparous women in the study group were the 'primigravid age' without any other indication for c-section. The elective c-section in the AMA group relates to previous cesarean section deliveries with the rates of 88.5%. Although primary cesarean rates were similar in both groups, the ratio of elective cesarean rate was significantly higher in the study group compared to the control group (p=0.006, OR: 1.7, 95% CI: 1.2-2.5). The most common emergency c- section indication in both groups was suspicion of fetal distress. However there was no statistical difference between groups according to CPD, the presentation anomalies were significantly higher in control. We expected these indications higher in the study group as a result of decreased contractility and aging uterine myometrium, but this situation was controversial.

AMA patients have multiple problems during pregnancy [29]. The presence of concomitant diseases, aging uterine myometrium, decreased contractility, presentation anomalies and placental pathologies, such as previa and abruption, may be contributing factors to CPD and the increased c- sections in older women [6,30]. In our study, 1.5% of women with AMA had placental pathologies and one fetus died because of total placental abruption. But there was no significant difference between the groups in terms of stillbirths (1.3% vs 1.1%, p= 0.41, OR:1.1, 95%CI: 0.4-3.6) Perinatal deaths affect 0.8% of all pregnancies of women over the age of 35 years.

The exact mechanism underlying the pathogenesis of adverse pregnancy outcomes and perinatal mortality in older mothers is unclear. It has been suggested that pre-pregnancy obesity and lower socio-economic factors contribute to the increased rates of adverse outcomes for women over 35 years of age [31]. However, in the present study, there was no difference between the two groups in terms of perinatal mortality. In the study group, perinatal deaths were computed as 1.3 %. It can be argued that increased mortality could be due to increased cardiovascular diseases, pre-pregnancy obesity and socio-economic factors. However, this study cannot expand on this due to the lack of information about pre-pregnancy obesity and the socioeconomic status of the patients.

The patients of this study were from a tertiary maternity hospital. This hospital generally treats women with a low socioeconomic status living in Central Anatolia. The AMA pregnancies we encounter are rarely due to higher/further education resulting in delayed fertility; instead AMA pregnancies are generally the result of multiparity, sociocultural factors and, sometimes, infertility.

Although this study did not find an increase in perinatal mortality, it demonstrated that pregnancies with AMA have a higher risk of developing maternal and fetal complications. The LBW, VLBW, IUGR and preterm delivery rates were higher in the AMA. Also in older pregnancies, the higher risk of preeclampsia and GDM and increased cesarean rate are important. As a final word, we suggest providing more careful and specialized prenatal care by the health services of developing countries in order to decrease the antenatal complications of older pregnant women.

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