Prenatal and Maternal Outcomes in Advanced Maternal Age, a Comparative Study

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Background: The increased maternal age is associated with many prenatal and perinatal complications including stillbirth, preterm birth and cesarean delivery.
Objectives: This study was carried out to investigate the prenatal and maternal outcomes among mothers older and younger than 35 in Fars province, Iran.
Patients and Methods: This study included 1962 singleton deliveries. The prenatal and neonatal outcomes were recorded retrospectively and compared between mothers aged older and younger than 35 years. A designed questionnaire was used for data collection of parity, gravida (gravidity and parity are two terms that refer to the number of times a female has been pregnant and carried the pregnancies to a viable gestational age), outcomes of the pregnancy, labor, and neonatal outcome. Data were analyzed using SPSS, version 15, and the $P < 0.05$ was considered significant.
Results: The mean age of 978 mothers < 35 years-old and 984 of those aged $\geq$ 35 years was 31.6 ± 6.8 years. Mothers aged $\geq$ 35 years experienced higher risk of preeclampsia ($P < 0.001$), gestational diabetes mellitus ($P < 0.001$), placental abruption ($P = 0.003$), cesarean delivery ($P < 0.001$), low Apgar at 1 minute ($P = 0.001$) and low Apgar at 5 minutes ($P = 0.001$) compared to those aged less than 35 years.
Conclusions: Women should be alerted by the higher risks for prenatal and maternal morbidity associated with delayed pregnancy. Health care providers should be aware of the impact of delayed childbearing on the health care resources.

Keywords: Prenatal; Pregnancy; Neonatal

1. Background

The modern pattern of life is associated with increase in marriage age and the tendency of married couple to seek employment, postpone childbearing until the fourth or fifth decades of life (1, 2). The late childbearing has become a common phenomenon in developed countries and its prevalence is increasing in developing countries like Iran (3). Several factors including social, educational and economic aspects contribute to delayed pregnancies. Previous studies have shown that the maternal age has increased by approximately one year (from 28.8 to 29.6 years) between 1995 and 2003 in developed countries (4). Currently the mean age of the first-time mothers is relatively high in Sweden (mean age 28.3 years), the Netherlands (28.7 years) and the United States (24.9 years) (4).

The increased maternal age is associated with many prenatal and perinatal complications including stillbirth, preterm birth, and cesarean delivery (5). Chromosomal abnormalities and spontaneous abortions are also more common in mothers aged more than 35 years. Although some studies have conflicting results regarding the pregnancy outcome beyond 40 years of age (6, 7), most indicate that these pregnancies are at higher risk for adverse outcomes including preterm delivery, prolonged labor, low birth weight, perinatal morbidity and mortality, and cesarean section (1-4, 8). In this regards Hung et al. (8) performed a systematic review of pregnancy outcome in mother older than 40 years of age, and demonstrated that stillbirth increases significantly by increasing maternal age. Also Ziadeh et al. showed that women older than 40 are at increasing risk for developing operative vaginal delivery, gestational diabetes, preeclampsia, and placenta praevia (9). Significantly higher incidences of malpresentation, abnormal labor patterns, special care baby unit admission (SCBU), and low 1-minute Apgar score were observed in nulliparous mothers aged more than 40 years-old. These mothers were also at higher risk for birth asphyxia, premature rupture of membranes, and antepartum vaginal bleeding (9). A study in Iran also revealed that the incidences of preeclampsia, gestational hypertension, cesarean delivery, placenta abruption, preterm delivery, and low Apgar scores are higher in mothers older than 40 years of age (10).

2. Objectives

The objective of this study was therefore to study the association between advanced maternal age and adverse perinatal and maternal outcomes of women in southern Iran.

3. Patients and Methods

3.1. Study Population

This study was carried out at Hafez and Zeinabieh Hospitals, affiliated with Shiraz University of Medical Sciences, Iran, during a 12-months period from March 2012 to April 2013. The study included 1962 singleton deliveries without significant fetal anomalies, carried beyond 24 weeks as determined by gestational age which was calculated according to the regular last menstrual period and further confirmed by early gestation ultrasonography. The study protocol was initially approved by the institutional review board (IRB) of Shiraz University of Medical Sciences and approved by the Ethics Committee. All the participant mothers and their spouses gave their informed written consent.

3.2. Study Protocol

This was a retrospective study carried out at Hafez and Zeinabieh teaching hospitals, and reviewing the medical records of the mothers delivered during the study period in the foregoing hospitals. A designed questionnaire sheet was used for data collection. All subjects with complete outcome information were divided into two age groups including women older and younger than 35 years of age at the time of the delivery.

The strategy used was the association between advanced maternal age and prenatal and maternal outcomes comprising demographic data considering age, parity and gravida, descriptive statistics of pregnancy complication, adverse perinatal outcome, the neonatal outcome, the frequency of cesarean delivery and its indications in each group.

The outcomes of the pregnancy included prenatal complications referred to antepartum hemorrhage, hypertension (HTN), diabetes mellitus, preterm delivery, preterm labor, labor performance involving induction of labor, mode of delivery, neonatal outcome encompassing birth weight, and Apgar scores. The incidence of antepartum hemorrhage was also recorded which was defined as vaginal bleeding caused by placental abruption, placenta previa, extra uterine causes and hemorrhage of unknown origin. The preterm labor was defined as true uterine contractions before completing 34 of gestation, presented as at least 4 contractions at 20-minute intervals. The criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP) was used for diagnosis of the preeclampsia (11). Accordingly preeclampsia was defined as sustained pregnancy-induced blood pressure accompanied by proteinuria. The HTN was defined as blood pressure higher than 140/90 mmHg measured in supine position in two distinct episodes with an interval of at least six hours. The proteinuria represented ≥ 30 mg/dL protein concentration (or 1 + on a urine dipstick) in the two or more random spot urine sample collected at an interval of at least four hours apart. Severe preeclampsia was defined as blood pressure values higher than 160/110 mmHg accompanied by more than 500 mg proteinuria in a 24 hour period or 3 + or 4 + proteinuria on a dipstick in random spot urine sample. Other indications of severe preeclampsia include blood pressure ≥ 160/110 mmHg with epigastric pain, diplopia, headache, oliguria, seizures, thrombocytopenia, and pulmonary edema, rising liver enzymes and creatinine and fetal growth restriction. Oral glucose tolerance test (OGTT) was performed in all the pregnant women via the hospital's screening program in 26 - 28 weeks of gestation. The Gestational Diabetes Mellitus (GDM) was diagnosed according to the WHO criteria (12). The Intrauterine Growth Restriction (IUGR) was defined as Estimated Fetal Weight (EFW) less than tenth percentile or the Abdominal Circumference (AC) with less than two SDs for gestational age determined by ultrasonography. Also low birth weight was described as the birth weight less than 2500 grams.

The neonatal outcome included the Apgar score, birth weight, frequency of Neonatal Intensive-Care Unit (NICU) admission, and recorded neonatal mortality. The prenatal, perinatal and neonatal outcomes were compared between the aforementioned mothers.

3.3. Statistical Analysis

The statistical analysis of data was conducted using software package SPSS for Windows, version 15.0 (SPSS, Chicago, IL, USA). The independent t-test was used to compare the results obtained from those aged ≥ 35 years and < 35 years, and the ^{2} test to compare proportions. Data were reported as Mean ± SD or proportions as appropriate. A two-tailed P < 0.05 was considered statistically significant.

4. Results

The present study comprised 1962 women with singleton deliveries, of whom 978 (49.8%) aged less than 35 years old and 984 (50.2%) aged 35 years old or older. The mothers' age ranged from 15 to 53 years old, with mean age of 31.6 ± 6.8 years old. The mean age of mothers aged ≥ 35 and those less than 35 years-old were 37.4 ± 2.5 and 25.8 ± 4.3 years, respectively. Among the participants 601 (30.6%) were primigravida and 674 (34.3%) were nulliparous (never having given birth to a child). The prevalence of abortion and stillbirth were 353 (18.1%) and 58 (2.9%), respectively. Recurrent pregnancy loss was reported in 16 (0.8%) subjects. Table 1 summarizes the demographic and baseline characteristics of the study population.

Overall, mothers aged ≥ 35 years experienced higher

Table 1. Baseline Characteristics of Participants [a]

Variables	≥ 35 Years (n = 984)	< 35 Years (n = 978)	P Value
Age, y	37.4 ± 2.5	25.8 ± 4.3	
Gravidity			
Primigravida	204 (20.7)	397 (40.6)	0.050
Multigravida	780 (79.3)	581 (59.4)	0.332
Parity			
Nulliparous	227 (23.1)	447 (45.7)	0.049
Multiparous	757 (76.9)	531 (54.3)	0.061
Abortion			
No abortion	758 (77.1)	851 (87.1)	0.851
One previous abortion	152 (15.4)	101 (10.3)	0.190
Two previous abortions	61 (6.2)	23 (2.3)	0.336
≥ Three previous abortions	13 (1.3)	3 (0.3)	0.623
Stillbirth			
No stillbirth	941 (95.6)	963 (98.4)	0.142
One previous stillbirth	29 (2.9)	10 (1.1)	0.136
Two previous stillbirth	14 (1.5)	5 (0.5)	0.886

[a] Data are presented as Mean ± SD or No. (%).

Table 2. Prenatal and Neonatal Outcome of Mothers Aged ≥ 35 and < 35 Years [a, b]

Variables	≥ 35 Years (n = 984)	< 35 Years (n = 978)	P Value
Age, y	37.4 ± 2.5	25.8 ± 4.3	
Preeclampsia	55 (5.6)	17 (1.7)	<0.001
Gestational DM	71 (7.2)	23 (2.4)	<0.001
Placental abruption	52 (5.3)	27 (2.8)	0.003
Placenta previa	19 (1.9)	12 (1.2)	0.142
Preterm delivery	62 (6.3)	48 (4.9)	0.107
IUGR	19 (1.9)	12 (1.2)	0.142
Route of delivery			
NVD	480 (48.8)	578 (59.1)	< 0.001
Cesarean section	504 (51.2)	400 (40.9)	< 0.001
LBW	134 (13.6)	109 (11.1)	0.055
Low Apgar at 1 minute	164 (16.7)	113 (11.6)	0.001
Low Apgar at 5 minutes	53 (5.4)	24 (2.5)	0.001
Still Birth	12 (1.2)	9 (0.9)	0.336
Chromosomal anomaly	4 (0.4)	2 (0.2)	0.346
Fetal anomaly	25 (2.5)	25 (2.6)	0.548

[a] Abbreviations: DM: Diabetes Mellitus, IUGR: Intrauterine Growth Restriction, LBW: Low Birth Weight.
[b] Data are presented as Mean ± SD or No. (%).

risk of preeclampsia (P < 0.001), gestational diabetes mellitus (P < 0.001), placental abruption (P = 0.003), cesarean delivery (P < 0.001), low Apgar at one minute (P = 0.001) and low Apgar at five minutes (P = 0.001) compared to those aged less than 35 years old. There were no statistically significant differences between the two groups regarding the frequency of placenta previa (P = 0.142), preterm delivery (P = 0.107), IUGR (P = 0.142), low birth weight (LBW), (P = 0.055), still birth (P = 0.336), chromosomal aberrations (P = 0.346) and fetal anomalies (P = 0.548). All the prenatal and neonatal outcomes were compared between the two age groups of mothers (Table 2).

5. Discussion

Childbearing age is being postponed to later ages because of belated marriage, higher education, career pursuit, increased life expectancy, and advanced contraception. In this regards the conception after 35 years of age has increased from 5% in 1970 to 13% of all live births in 2000. The number of pregnant women ≥ 35 years has increased by approximately 10 fold compared the previous decade (11). Up to now several studies have investigated the complication and adverse effects of advanced maternal age; however there is as yet no consensus about the definition of the advanced maternal age in the literature. It is well known that pregnancies ≥ 35 years are associated with several complications. However some studies have shown that there is no difference between mothers aged ≥ 35 years and younger (6, 7).

We found that women of advanced maternal age are more likely to have pregnancy complications and adverse perinatal outcomes which are consistent with most previous studies. We found that 35 years-old and older mothers experienced higher prevalence of preeclampsia, GDM, placental abruption, cesarean delivery, low Apgar at one minute and five minutes compared to those aged less than 35 years. However, the two groups did not differ regarding the incidence of placenta previa, preterm delivery, IUGR, LBW, still birth, chromosomal aberrations and fetal anomalies.

During the pregnancy the increased blood volume and heart rate result in increased cardiac output and decreased mean arterial blood pressure (3, 4). These changes are contrary to those during the aging that is associated with difficult adaptation of the cardiovascular system. Some factors associated with pregnancies in advanced age include the gradual loss of vascular compliance, decline in vascular responsiveness to endothelium-dependent vasodilators, loss of myocardial compliance, and less aortic flow during diastole (13). Also, HTN prevalence increases by aging (14). It has been shown by several studies that approximately 17% of all pregnancies ≥ 35 years are complicated with pre-eclampsia (8-10, 15). The risk of pre-eclampsia in nulliparous ≥ 40 years is even higher. In the same way the risk for preeclampsia in those with a history of preeclampsia in past pregnancy increases in those beyond 35 years of age (16). Preexisting HTN is the cause of high prevalence of preeclampsia in mother's ≥ 35 years old (17). Jacobsson et al. (14) reviewed the birth

certificates of 31,662 mothers aged between 40 to 44 and 1205 aged ≥ 45 years. They found that the severe preeclampsia risk increased by advancing maternal age while the risk for mild preeclampsia decreased slightly.

The risk of GDM increases with increasing maternal age which is explained by progressive vascular dysfunction leading to decreased -cell mass of pancreases and increased rates of obesity with advancing age that result in insulin resistance (15). It has been shown that women ≥ 35 years-old had a six-fold increase in risk of developing GDM compared with the younger women. Gilbert et al. (18) showed that the incidence of GDM is four-fold higher in both older nulliparous and multiparas women compared to matched controls. This finding suggests that maternal age and not parity is the risk factors for increased prevalence of GDM.

The placental abruption and placenta previa cause the bleeding complications of the pregnancy which assume to be more prevalent in older women. The premature disruption and separation of the placenta is the result of both HTN and senile degeneration of uterine vessels (15). It has been shown that the incidence of placental abruption increases by 23% with increasing maternal age from 35 to 49 years, especially in twin pregnancies. Joseph et al. (5) reported odds ratio (OR) for placental abruption in different ages, which are (1.39, 95% CI 1.12 to 1.73), (1.64, 95% CI 1.24 to 2.16), and (1.82, 95% CI 0.99 to 3.34) for maternal age of 30 - 34, 35 - 39, and ≥ 40 years, respectively compared with maternal age between 20 to 24 years.

The higher parity and progressive vascular and endothelial dysfunction are two etiologies of placenta previa. It was found by Salihu et al. (19) that the proportion of cases of placenta previa attributable to women aged from 35 to 39 years increased from 18.5% from 1988 to 1991 to 33.4% from 1998 to 2002, and those due to women ≥ 40 years increased from 3.5 to 7.7% in same period. However we found no correlation between the maternal age and the placenta previa.

It is postulated that age-related changes in the uterine vasculature, poorer placental perfusion, or trans-placental flux of nutrients result in decreased birth weight and increased the LBW neonates. Our study suffered from some limitations, because it was hospital based, and biased in selection of cases. Also measuring the blood pressure was done in supine position, however, for assessing eclampsia, sitting position would have been more appropriate.

This study showed that delayed childbearing is associated with an increased risk for complications of pregnancy and neonatal outcomes. Thus pregnancy later than 35 years of age should be avoided and if happened should be accompanied by a strict screening program in order to prevent complications. Best outcomes achieved relate to appropriate maternal health and pregnancy care.

Authors' Contributions

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References

1. Astolfi P, Zonta LA. Delayed maternity and risk at delivery. *Paediatr Perinat Epidemiol.* 2002;**16**(1):67–72.
2. Tough SC, Newburn-Cook C, Johnston DW, Svenson LW, Rose S, Belik J. Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. *Pediatrics.* 2002;**109**(3):399–403.
3. Berkowitz GS, Skovron ML, Lapinski RH, Berkowitz RL. Delayed childbearing and the outcome of pregnancy. *N Engl J Med.* 1990;**322**(10):659–64.
4. Benzies KM. Advanced maternal age: are decisions about the timing of child-bearing a failure to understand the risks? *CMAJ.* 2008;**178**(2):183–4.
5. Joseph KS, Allen AC, Dodds L, Turner LA, Scott H, Liston R. The perinatal effects of delayed childbearing. *Obstet Gynecol.* 2005;**105**(6):1410–8.
6. de La Rochebrochard E, de Mouzon J, Thepot F, Thonneau P, French National IA. Fathers over 40 and increased failure to conceive: the lessons of in vitro fertilization in France. *Fertil Steril.* 2006;**85**(5):1420–4.
7. Huang L, Sauve R, Birkett N, Fergusson D, van Walraven C. Maternal age and risk of stillbirth: a systematic review. *CMAJ.* 2008;**178**(2):165–72.
8. Hung TH. Advanced maternal age and adverse perinatal outcome: a call for investigations on Asian women. *Taiwan J Obstet Gynecol.* 2008;**47**(3):257–8.
9. Ziadeh S, Yahaya A. Pregnancy outcome at age 40 and older. *Arch Gynecol Obstet.* 2001;**265**(1):30–3.
10. Jahromi BN, Husseini Z. Pregnancy outcome at maternal age 40 and older. *Taiwan J Obstet Gynecol.* 2008;**47**(3):318–21.
11. Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy.* 2001;**20**(1):IX–XIV.
12. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* 1998;**15**(7):539–53.
13. Gareen IF, Morgenstern H, Greenland S, Gifford DS. Explaining the association of maternal age with Cesarean delivery for nulliparous and parous women. *J Clin Epidemiol.* 2003;**56**(11):1100–10.
14. Jacobsson B, Ladfors L, Milsom I. Advanced maternal age and adverse perinatal outcome. *Obstet Gynecol.* 2004;**104**(4):727–33.
15. Usta IM, Nassar AH. Advanced maternal age. Part I: obstetric complications. *Am J Perinatol.* 2008;**25**(8):521–34.
16. Delbaere I, Verstraelen H, Goetgeluk S, Martens G, De Backer G, Temmerman M. Pregnancy outcome in primiparae of advanced maternal age. *Eur J Obstet Gynecol Reprod Biol.* 2007;**135**(1):41–6.
17. Cnattingius S, Berendes HW, Forman MR. Do delayed childbearers face increased risks of adverse pregnancy outcomes after the first birth? *Obstet Gynecol.* 1993;**81**(4):512–6.

18. Gilbert WM, Nesbitt TS, Danielsen B. Childbearing beyond age 40: pregnancy outcome in 24,032 cases. *Obstet Gynecol.* 1999;**93**(1):9–14.

19. Salihu HM, Shumpert MN, Slay M, Kirby RS, Alexander GR. Childbearing beyond maternal age 50 and fetal outcomes in the United States. *Obstet Gynecol.* 2003;**102**(5 Pt 1):1006–14.