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Advanced maternal age and pregnancy outcome: experience in a tertiary care center

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Summary

Purpose of investigation: The aim of this study is to compare pregnancy outcomes between women older than 35 years and a control group composed by younger patients. *Materials and Methods:* The study involves pregnant women admitted to the present Department from January 1, 2015 to December 31, 2015. Enrolled pregnants were divided into two groups: group 1 ("cases") included women over 35 years and group 2 ("controls") included women younger than 35 years. Clinical data were collected through the patients' obstetrical files. *Results:* Study population was composed of 2,030 patients, divided into two groups: group 1 including 844 women and group 2 including 1,186 women. The authors analysed clinical and obstetrical data regarding spontaneous miscarriage (SM), elective pregnancy termination (EPT), mode of delivery, incidence of obstetrics complications, and neonatal outcome. *Conclusions:* Women of advanced maternal age (AMA) have a greater risk to develop several obstetric complications. It is very important to follow them closely in order to detect early complications and obtain better pregnancy outcome.

Key words: Advanced maternal age; Fetal outcome; Maternal complications.

Introduction

Advanced maternal age (AMA) is defined as age greater or equal of 35 years at the time of delivery and it is considered to be a factor for pregnancy at risk [1]. Maternal age at childbirth increased in many high-income countries from 1970s; in fact the number of primigravidae older than 35 years in the United States increased nearly eight times from 1970 to 2006. In 2006, about one out of 12 first births were to women aged 35 years and over compared with one out of 100 in 1970 [2]. In Europe, instead, the mean age of women at childbirth increased from 29.3 in 2003 to 29.8 in 2009 [3]. Delay in childbearing in industrialized countries is caused by the need of acquiring a good education and an adequate economical status [4, 5]. An increase in maternal age can also be explained by the widespread use of assisted reproductive technologies (ART), caused by the natural decline of fertility in women over 35 years [6, 7]. Several studies have examined the association between AMA and obstetric complications such as chromosomal anomalies, preterm delivery (PTD), sudden fetal death, intrauterine growth restriction, gestational diabetes, or hypertension. An increased cesarean section (CS) rate and a growing risk for vertical transmission of congenital infectious diseases were also analyzed [8-13]; however, in literature contradictory results are reported. Such discordances could be explained by different population characteristics in terms of ethnic background, age, and healthy or risky pregnancies. The aim of this study is to compare pregnancy outcomes between women older than 35 years and a control group composed by younger patients, in terms of incidence of obstetric pathologies, CS rate and neonatal conditions at birth, valued by gestational age (GA), neonatal weight, and APGAR score.

Materials and Methods

The study was conducted at the Umberto I Hospital in Rome, a Public Tertiary centre affiliated to "Sapienza" University of Rome. It was a retrospective study involving all pregnant women admitted to the present Department from January 1, 2015 to December 31, 2015. Clinical data were collected through the patients' obstetrical files. Enrolled pregnancies were divided into two groups: group 1 ("cases") included women over 35 years and group 2 ("controls") included women younger than 35 years. Related demographic and obstetric characteristics were collected. The following parameters were evaluated for each group: incidence of spontaneous miscarriage (SM), elective pregnancy termination (EPT), GA at delivery, mode of birth - vaginal delivery (VD), operative delivery (OD) or CS, characteristics of pregnancy, incidence of fetal or obstetrical pathology, and neonatal outcome. Characteristics of pregnancy regarding the mode of conception; spontaneous conceive, intracytoplasmatic sperm injection (ICSI), in vitro fertilization with embryo transfer (IVF-ET), and heterol-

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ogous fertilizaton (HF) were also collected. The authors analysed obstetrical complications dividing them into two groups: the first included complication related to the fetus, as PTD, considered as GA at birth < 37 weeks and divided into very early PTD (GA at birth 24-28 weeks), early PTD (GA at birth 28-34 weeks), and late PTD (GA at birth 34-36+6/7 weeks), IUGR defined as neonatal weight at birth below the 10th percentile for GA, macrosomia defined as neonatal weight at birth over the 90th percentile for GA, polihydramnios and oligohydramnios defined respectively, as amniotic fluid index over the 90th percentile and under the 10th percentile for GA. The second group included complications related to the mother: diabetes, both gestational divided in two groups considering therapy and pregestational, pregnancy induced hypertension in terms of gestational hypertension, preeclampsia, eclampsia and chronic hypertension, obstetric cholestasis, placental abruption and placental adhesive disorders (PAD), including placenta previa, placenta accreta, placenta increta, and placenta percreta. Moreover, the authors evaluated the incidence of CS in patients who presented PAD. Neonatal outcome was evaluated in terms of neonatal weight and APGAR score at the first and the fifth minute after birth.

Variables measured in interval scales were described as the mean. Data points, collected for this study, were analyzed using Chi-square for comparisons between "cases" and "controls" control group data. P values smaller than 0.05 were considered statistically relevant.

Results

Study population was composed of 2,030 patients, divided into two groups: group 1 ("cases") including 844 women over 35 years of age (average maternal age 38.6 years, in the 35-52 years range) and group 2 ("controls") including 1,186 women younger than 35 years of age (average maternal age 29.2 years, in the 15-34 years range). The two groups were homogenous and statistically significant in term of age difference.

Two hundred-three women were admitted to the present Department for SM: 110 (54.2%) in group 1 and 93 in group 2 (45.8%). Average GA at the admission was 10.1 weeks (range 5-21 weeks): 9.9 weeks in group 1 (range 5-18.42 weeks), and 10.2 in group 2 (range 5-21.42 weeks) (n.s.) (Table 1).

Forty-eight women underwent EPT: 28 (58%) in group 1 and 20 (42%) in group 2; mean GA was 19.6 weeks: 20.1 in group 1 and 19.1 in group 2. Indications for EPT were chromosompathies in 24 patients: 20 in group 1 and four in group 2, fetal malformations in 21 cases: 15 in group 1 and six in group 2, and cytomegalovirus (CMV) infection in three cases: two in group 1 and one in group 2 (Table 2).

One thousand seven hundred seventy-nine deliveries and 1,815 newborns were reported in 2013: 706 deliveries and 727 newborns in group 1 and 1,073 deliveries and 1,088 newborns in group 2. The present analysis reported 1,749 singleton pregnancies: 688 in group 1 and 1,061 in group 2, spontaneous conception was reported in 1,452 patients: 473 in group 1 and 952 in group 2, while 324 underwent ART: 215 in group 1 and 109 in group 2 (Table 3).

Mean GA at birth was 38.5 weeks: 37.8 in group 1 and 38.5 in group 2, mean neonatal weight was 3,042,5 grams: 2993.3 in group 1 and 3082.3 in group 2, mean APGAR score was 8.1 after one minute: 8.0 in group 1 and 8.1 in group 2 and 9.3 after five minutes: 9.2 in group 1 and 9.7 in group 2. Seven hundred sixty-six VD were performed: 244 in group 1 and 522 in group 2, 71 patients performed OD: 20 in group 1 and 51 in group 2, and 978 patients underwent CS: 463 in group 1 and 515 in group 2 (Table 4).

Regarding obstetric complications related to the fetus, data analysis revealed PTD in 336 patients: 169 in group 1 and 167 in group 2, IUGR in 61 cases: 28 in group 1 and 33 in group 2, macrosomia in 25 patients: eight in group 1 and 17 in group 2, oligohydramnios in 92 patients: 49 in group 1 and 43 in group 2, and polihydramnios in 24 cases: 11 in group 1 and 13 in group 2 (Table 5).

Analysis of obstetrics complications revealed diabetes in 132 patients: 69 in group 1 and 63 in group 2, pregnancy Induced hypertension in 129 cases: 79 in group 1 and 50 in group 2, obstetric cholestasis in 34 patients: 24 in group 1 and 10 in group 2, placental abruption in 15 cases: 12 in group 1 and 3 in group 2, and PAD in 38 patients: 25 in group 1 and 13 in group 2. Among patients with PAD, 14 underwent a previous CS: ten in group 1 and four in group 2 (Table 6).

Discussion

AMA has numerous effects on maternal and neonatal outcomes; such outcomes could derive from organic modifications and greater susceptibility to develop metabolic diseases caused by natural aging. Van Katwijk and Peeters state that a loss of vessel compliance caused by aging is the main cause of the higher rate of pregnancy induced hypertension; moreover they report a higher incidence of gestational diabetes, that may be caused by a greater susceptibility to develop an insulin resistance in case of AMA [14]. A recent study edited by Wilding in 2014 hypothesizes that AMA should be considered as a genetic disease because of the effect of natural aging on the mitochondria of the oocytes [15]. The damage produced by aging on these cells may cause alterations in mitochondrial DNA and could correlate with a shorter lifespan of offspring [15]. In literature, many authors have examined the relationship between AMA and pregnancy outcome; however, those analyzed showed a large variability in the results, so that nowadays there is no universally recognized linear correlation between AMA and increased incidence of maternal and neonatal complications. The results of this study show that several diseases have an increased incidence in case of AMA, while others are not related to it. A significant increasing of SM in the cases group was reported. No relevant differences were found in terms of GA at SM and obstetrical history of previous SM between the two groups. The results of this study confirmed what is reported in literature about increased incidence of miscar-

Table 1. — *Patients admitted for SM.*

Characteristics	Group 1 (110 cases)	Group 2 (93 cases)	Total (203 cases)	*p* (<0.05)
Age	39.2	29.3	34.3	<0.05
Gestational age	9.9	10.2	10.1	n.s
Primigravidae	23	39	62	<0.05
Plurigravidae	87	54	141	<0.05
Previous SM	23	18	41	n.s
≥ 2 previous SM	13	4	17	n.s

Table 2. — *Patients admitted for EPT.*

Characteristics	Group 1 (28 cases)	Group 2 (20 cases)	Total (48 cases)	*p* (<0.05)
Age	38.4	29.7	34.7	<0.05
Gestational age	20.1	19.1	19.6	n.s.
Chromosomopathies	20	4	24	<0.05
-Trisomy 21	15	4	19	
- Trisomy 13/18	4	0	4	
- Monosomy X	1	0	1	
Fetal malformations	6	15	21	n.s.
CMV infection	2	1	3	n.s.

Table 3. — *Number of fetuses for pregnancy.*

Characteristics	Group 1 (706 cases)	Group 2 (1073 cases)	Total (1779 cases)	*p* (<0.05)
Singleton pregnancies	688	1061	1749	<0.05
Spontaneous conception	473	952	1425	<0.05
ART	215	109	324	<0.05
ICSI	75	65	140	
FIVET	109	44	153	
HF	31	0	31	
Twin pregnancies	14	10	24	n.s.
Spontaneous conception	3	7	10	<0.05
ART	11	3	14	<0.05
ICSI	2	1	3	
FIVET	6	2	8	
HF	3	0	3	
Multiple pregnancies	4	2	6	n.s.
Spontaneous conception	0	1	1	n.s.
ART	4	1	5	n.s.
ICSI	0	0	0	n.s.
FIVET	4	1	5	n.s.
HF	0	0	0	n.s.

Table 4. — *Characteristics of deliveries and newborns.*

Characteristics	Group 1 (727 babies)	Group 2 (1088 babies)	Total (1815 babies)	*p* (<0.05)
Gestational age	37.8	38.5	38.5	n.s
VD	244	522	766	<0.05
OD	20	51	71	<0.05
CS	463	515	978	<0.05
Weight	2993.3	3082.3	3042.5	n.s.
APGAR 1’	8.0	8.1	8.1	n.s.
APGAR 5’	9.2	9.7	9.3	n.s

Table 5. — *Obstetrics complications I- related to the fetus.*

Characteristics	Group 1 (727 babies)	Group 2 (1088 babies)	Total (1815 babies)	*p* (<0.05)
Preterm delivery	169	167	336	<0.05
Very early PTD	9	10	19	n.s.
Early PTD	55	42	97	n.s.
Late PTD	105	115	220	n.s.
IUGR	28	33	61	n.s.
Macrosomia	8	17	25	n.s.
Oligohydramnios	49	43	92	<0.05
Polihydramnios	11	13	24	n.s.
Total	434	440	874	<0.05

Table 6. — *Obstetrics complications II- related to the mother.*

Characteristics	Group 1 (706 cases)	Group 2 (1073 cases)	Total (1779 cases)	*p* (<0.05)
Diabetes	69	63	132	<0.05
GMD A1 white	35	44	79	<0.05
GMD A2 white	21	14	35	n.s.
Pregestational diabetes	13	5	18	n.s.
Pregnancy induced hypertension	79	50	129	<0.05
Gestational hypertension	31	31	62	<0.05
Preeclampsia	31	11	42	<0.05
Eclampsia	0	0	0	
Chronic hypertension	17	8	25	n.s.
Obstetrics cholestasis	24	10	34	<0.05
Placental abruption	12	3	15	<0.05
Placental adhesive disorders	25	13	38	<0.05
Placenta previa	16	9	25	n.s.
Placenta accreta	0	4	12	n.s.
Placenta increta	0	0	0	
Placenta percreta	1	0	1	n.s.
Previous CS	10	4	14	n.s.
Total	382	265	647	<0.05

riage in women older than 35 years [11, 12, 16, 17]. Regarding EPT, a significant increased incidence of chromosomal anomalies in the “cases” group were found. The incidence of malformations and TORCH infection does not show significant differences in the two groups. The increased risk of chromosomal anomalies in patient older than 35 years is well known in the literature [17, 18]. A study reported in 2013 by Amarin which compared 73 women, older than 35 years of age, with a control group composed of 471 young women, reported an increased risk of trisomy 21, but a non-increased risk of sexual chromo-

some-linked aneuploidies [19]. A recent article highlighted how not only maternal age, but also increased paternal age is linked to a rising number of chromosomal anomalies. Sharma *et al.* report a brief review highlighting an increased incidence of trisomy 21 in all studies examined, and a variable incidence of sexual aneuploidies and trisomy 13 and 18 [20]. The present data analysis about mode of conceive revealed a statistically significant increasing in use of ART in the case group in singleton and twin pregnancies. This difference was not significant in patients who obtained multiple pregnancies. Regarding fetal complications, a significant increased incidence of preterm delivery is reported by the present study, despite GA in which it occurs and oligohydramnios. No significant differences are reported between the two groups as regards IUGR, macrosomia and polihydramnios. Kenny *et al.* reported a higher rate of preterm delivery in AMA and not a statistically significant difference in term of fetal macromosomia and fetuses small for GA [11]. Regarding obstetric complications, the present authors reported an increased incidence in the elderly pregnant of diabetes both mellitus diabetes and no insulin-treated gestational diabetes, obstetrical cholestasis, placental abruption, and placental adhesive disorders. Moreover they noted an increased incidence of pregnancy induced hypertension and preeclampsia. No significant differences were reported in the incidence of chronic hypertension between the two groups. Jolly *et al.* reported an increased incidence of gestational diabetes, preterm delivery, and placenta previa in case of AMA, in line with the present results [21]. Other authors described an increased incidence of obstetric complications in case of AMA [12, 17, 19, 22, 23]. Several studies reported not an increased incidence of obstetrical complications in case of AMA [1, 13]; for instance, Wang *et al.* examined 6,619 pregnancy in a three-year study period and stated no significant difference between the two age groups regarding the incidence of preeclampsia, gestational diabetes, placental abruption, and pre-term delivery. Moreover they report an increased rate of chronic diseases such as hypertension or diabetes, and a higher rate of CS in case of AMA [24]. Finally, the present authors analyzed the mode of delivery and they noted a significant decreased rate of VD (both spontaneous delivery and OD) and a significant increasing CS rate in the case group. No significant differences were reported in terms of GA at birth, neonatal weight, and APGAR score at the first and fifth minute after birth. The literature confirms the present data in terms of increased rate of CS [1, 11, 12, 21, 22]. An article edited in 2005 studied pregnancy outcomes in 76 women of very AMA (more than 45 years) and found no significant differences in maternal and neonatal outcomes between the case group and a control group composed by young women. CS rate was the only parameter significantly increased in the older age group of this study [25]. A research article based on a ten-year study period reported an increased incidence of complication both in extremely young mothers and in case of AMA, stating that the ideal period to conceive and minimize adverse birth outcome is between 26 to 30 years of age [23].

Conclusions

There is no linear relationship between AMA and increased incidence of fetal pathologies and obstetrical complications. We could state that elder pregnant ladies have a greater risk to develop chromosomal abnormalities, to suffer before pregnancy by metabolic and systemic diseases, or to develop several obstetric complications. It is very important for clinicians to perform valid counselling reagarding genetic and obstetric complications that could occur in these types of patients, and to follow them closely in order to detect early complications, obtaining in this way a better pregnancy outcome for patients with AMA.

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