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Perinatal outcome in women over 40 years old over a three-year period at the Clínica Universidad de Navarra

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ABSTRACT / A current social trend is for women to delay their pregnancies. Late pregnancies are commonly associated with increased perinatal pathology. We carried out a retrospective observational study to analyse the maternal and fetal morbi-mortality in pregnant women over 40 years old. Clinical data were retrieved from the medical records of all pregnant women who had their pregnancy controlled at the Clínica Universidad de Navarra (CUN) between January 2011 and December 2013. A random group of women younger than 40 years of age was used as a control group. During the study period, the CUN oversaw 1035 pregnancies, of which 102 (10.1%) concerned women over 40. Whilst the over-40 group was statistically similar to the control group with respect to most variables analysed, women over 40 had statistically higher prevalence of gestational diabetes, number of pregnancies after Assisted Reproduction Techniques (ARTs), number of previous abortions, and prevalence of high-risk results from aneuploidy screening.

Key words: perinatal outcomes, older women, pregnancy.

Introduction

The social trend is for more and more women to undertake higher level educational studies and to work away from the home. In addition, more and more women are receiving infertility treatment. Typically, the age of first pregnancy is delayed, often until a woman is in her forties. For these reasons, the number of older women in the obstetric population is increasing as these women seek special care and handling during their pregnancy and perinatal period. For years, advanced maternal age has been considered an obstetric risk factor, associated with greater risk of malformations or other pathologies during pregnancy or childbirth. The retrospective observational study reported here investigates the perinatal risks faced by the older woman in her pregnancy.

Most published studies have observed that morbi-mortality is higher in elder pregnant women; there is, however, no evidence of an increased fetal morbidity or mortality. Relative to pregnancies in younger women, those in women over 40 are reported to have higher rates of parity, preterm labour, caesarean section, instrumental labour, preeclampsia, gestational diabetes, low birth weight, low apgar score at minute 1, anomalies in fetal presentation, and need of induction of labour.^{1, 2, 3, 4}

Tebeu PM et al. highlighted a higher rate of caesarean section and fetal mortality in pregnant women over 40 years old.⁵

According to Ojule JD, there were significantly higher rates of caesarean section, preterm labour and incidence of macrosomy in women over 40 years old. However, they did not observe significant differences in terms of other fetal or maternal pathology.⁶

Another study described higher rates of fetal mortality, preterm labour, macrosomy, prolonged gestation (over 42 weeks), and caesarean section in women over 40 years old, regardless of the previous births. This study found that there were lower rates of pathology in women of higher economic status.⁷

In the Carolan M. study, the cut-off point defining advanced maternal age was 45 years; they concluded there were higher rates of abortion, perinatal death, prematurity, low birth weight, gestational hypertension, gestational diabetes, preeclampsia and caesarean section in women over 45 years old. However, they observed a tendency of favourable perinatal results especially when women were previously healthy.⁸

Nolasco-Blé AK et al. described high rates of caesarean section, gestational diabetes and gestational hypertension in women over 40 years old.⁹

Giri A et al. used 35 years of age as the cut-off for advanced maternal age; they reported statistically significant differences in gestational hypertension and caesarean section, but they did not observe differences in haemorrhage, gestational diabetes, premature rupture of membranes, preterm labour or low birth weight.¹⁰

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Some studies, however, have found no significant differences in perinatal outcomes in older women as compared with younger ones,^{11, 12, 13} and this lack of inconclusiveness is the reason behind the current retrospective observational study, which aims to study the prevalence of pregnant women over 40 years old and also, to analyse the perinatal results in terms of fetal or maternal morbidity and mortality comparing the results with a control group of women under 40 years old.

Materials and methods

From January 2011 to December 2013, 1035 pregnant women controlled their pregnancy at the Department of Gynaecology and Obstetrics, Clínica Universidad de Navarra. For this study the inclusion criteria were: women over 40 who had controlled their pregnancy and had given birth at this hospital, so that, we had access to their complete pre and perinatal data. Exclusion were: women who had not given birth at the time of the study's data revision and women who had not finished their pregnancy at the hospital.

As control group we selected the same number of women below 40. Cross-match was done by choosing the woman below 40 who chronologically started to control her pregnancy at Clínica Universidad de Navarra immediately before the corresponding woman over 40 included in the study.

A standardized protocol sheet including all variables to be analysed was developed (Appendix 1) in

an Excel file (Microsoft Office Excel, Microsoft Corporation, Washington, USA). Our standardized protocol sheet contained different variables of relevance to our hypothesis. Some variables concerned demographic data, such as, age, parity, previous abortions, nulliparity or the use of Assisted Reproduction Techniques; other variables concerned maternal morbidity, such as, first trimester trisomy screening test, gestational hypothyroidism, gestational diabetes and gestational hypertension. In addition, we obtained data for fetal morbidity, such as, intrauterine growth retardation, macrosomy, prematurity, low weight or fetal anomalies. We also included data for obstetric morbidity, such as, first trimester abortion, threatened abortion, threatened preterm labour, premature rupture of membranes, third trimester haemorrhage, oligoamnios, caesarean section, fetal anomalies, uterine atony, perineal tear, cardiotocographic alterations, induction or umbilical cord alterations.

Data from the Excel file was exported to an SPSS data base (SPSS 22.0, SPSS Inc, Chicago, USA). Quantitative data were presented as mean (standard deviation) or median (interquartile range). We used one-way ANOVA or U Mann Whitney test, assuming a normal distribution. Qualitative data were expressed as number and percentage; the chi-squared test was used to compare qualitative variables. For interpretation of all the statistical tests, we considered $p < 0.05$ as statistically significant.

Appendix 1 / Protocol standardized sheet.		
Age	Parity	Previous abortions
Nulliparity	ARTs	First trimester trisomy screening test
Gestational hypothyroidism	Gestational Diabetes	Gestational Hypertension
Intrauterine growth retardation	Macrosomy	Prematurity
Low weight	Fetal anomalies	First trimester abortion
Threatened abortion	Threatened preterm labour	Premature rupture of membranes
Third trimester haemorrhage	3rd trimester haemorrhage	Oligoamnios
Caesarean section	Fetal anomalies	Uterine atony
Perineal tear	Cardiotocographic alterations	Reason for caesarean section
Induction	Umbilical cord alterations	Apgar minute 1
Apgar minute 5	Arterial pH	Venous pH

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Results

During the study period, there were 90 women (10.1%) over 40 years of age. There were three first-trimester abortions in each group, and so it should be noted that the percentages were calculated for 87 women in each group because we did not have data for the maternal, gestational or neonate morbidity in these 6 pregnancies.

Demographical data are shown in Table 1. We observed significant differences in terms of parity, nulliparity and percentage of pregnancies after ARTs, these variables being higher in the study group.

There was no significant difference in incidence of Down Syndrome, although there were more cases in the over-40 group (Table 4): there were three neonates with Down Syndrome in the study group and none in the control group.

Regarding obstetric morbidity (Table 5), there were no statistically significant differences in first trimester abortions, threatened abortion, threatened preterm labour, premature rupture of membranes, oligoamnios or third trimester haemorrhage.

There were no significant differences between both groups in the incidence of caesarean section,

Table 1 / Demographic data.

Group	Age (median)	Parity* (median)	Previous abortions** (median)	Nulliparity (%)‡	ARTs (%) ^o
≥40 years	41 (IQR 2)	3 (IQR 3)	0.50 (IQR 1)	17.8% (16)	13.3% (12)
<40 years	33 (IQR 5)	2 (IQR 2)	0 (IQR 1)	43.3% (39)	4.4% (4)

* p=0.001 / ** p=0.003 / ‡ p= 0.001 / ^o = 0.032

Regarding maternal morbidity (Table 2), we observed a statistically significant increase in having a high-risk result in aneuploidy screening in the study group. There was also a statistically significant difference in the incidence of gestational diabetes, which was more frequent in the over-40 group. However, we did not observe significant differences in gestational hypothyroidism and in gestational hypertension.

presentation anomalies, uterine atony, perineal tear, cardiotocographic alterations, cordon alterations or use of labour induction (Table 6).

There were no cases of maternal mortality, but there was one fetal death due to Down Syndrome. One neonate, who was transferred to the paediatrics intensive care area, had a minute-1 Apgar score of zero and was in cardiorespiratory stop after an emergency caesarean section undertaken in response to

Table 2 / Maternal morbidity.

Group	First trimester trisomy screening test (%)*	Gestational hypothyroidism (%)**	Gestational Diabetes (%)£	Gestational Hypertension (%)‡
≥40 years	17.3% (9)	6.9% (6)	19.5% (17)	5.7% (5)
<40 years	1.4% (1)	9.2% (8)	4.6% (4)	2.3% (2)

* p=0.002 / ** p=0.391 / £ p= 0.002 / ‡ p= 0.222

Concerning fetal morbidity (Table 3), we did not find statistically significant differences for intrauterine growth retardation, macrosomy, prematurity and low weight neonates. In relation to fetal anomalies we did not find significant differences despite the significant differences in the screening trisomy test of the first trimester.

changes in the cardiotocographic test that indicated a risk of loss of fetal wellbeing.

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Table 3 / Fetal morbidity.

Group	Intrauterine growth retardation (%) [*]	Macrosomy (%) ^{**}	Prematurity (%) [£]	Low weight (%) [¥]	Fetal anomalies (%) [∅]
≥40 years	5.7% (5)	4.6% (4)	4.6% (4)	7.5% (6)	10% (9)
<40 years	8% (7)	2.3% (2)	9.2% (8)	8.3% (7)	8.1% (7)

* p=0.383 / ** p=0.341 / £ p= 0.185 / ¥ p= 0.537 / ∅ p=0.378

Table 4 / Down Syndrome.

Down syndrome	Group ≥40	Group <40
Yes	3 (3.57%)	0 (0%)
No	81 (96.4%)	86 (100%)

p=0.10

Table 5 / Obstetric morbidity.

Group	First trimester abortion (%) [*]	Threatened abortion (%) ^{**}	Threatened preterm labour (%) [£]	Premature rupture of membranes (%) [¥]	Third trimester haemorrhage (%) [∅]	Oligoamnios (%) ^{&}
≥40 years	3.3% (3)	3.4% (3)	4.6% (4)	3.4% (3)	4.6% (4)	9.2% (8)
<40 years	3.3% (3)	1.1% (1)	8% (7)	2.3% (2)	1.1% (1)	6.9% (6)

* p=0.659 / ** p=0.310 / £ p= 0.268 / ¥ p= 0.500 / ∅ p=0.184 / & p=0.391

Table 6 / Obstetric morbidity .

Group	Caesarean section (%) [*]	Fetal anomalies (%) ^{**}	Uterine atony (%) [£]	Perineal tear (%) [¥]	Cardiotocographic alterations (%) [∅]	Induction (%) ^{&}	Umbilical cord alterations (%) ^{¶¶}
≥40 years	37.9% (33)	6.8% (6)	3.4% (3)	20.7% (18)	6.9% (6)	25.3% (22)	11.5% (10)
<40 years	27.6% (24)	2.3% (2)	5.7% (5)	18.4% (16)	2.3% (2)	20% (16)	11.5% (10)

* p=0.290 / ** p=0.278 / £ p= 0.360 / ¥ p= 0.807 / ∅ p=0.139 / & p=0.265 / ¶¶ p=0.594

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Discussion

In terms of prevalence, the percentage of pregnant women over 40 years old was higher (10.1%) than in other series of similar population size (1.4%-1.8%)^{2, 4, 6}. It may be relevant that our study was done in a private centre. A higher incidence of nulliparity than expected was found (17.8% versus 10.7%)⁴. The incidence of caesarean section in our study was 37.9%; in literature, caesarean section rates range from 18 to 71%^{2, 3, 4, 5, 6, 9, 10}. Some studies suggest that caesarean sections are more frequent in women over 40 years old, but we did not observe significant differences between our study group and the control group^{5, 6, 7}.

According to the literature, in women over 40, there is a higher rate of morbidity in the first pregnancy relative to the second. Our study did not find statistically significant differences on comparing gravidity as an independent variable (data not shown).

There was a lower incidence of macrosomy (4.6%) and prematurity (4.6%) than expected (10.2% and 10.8%, respectively) for the over-40 group⁶. Whilst, other investigators have reported significant differences in macrosomy and prematurity rates related to age, such differences were not observed in our study^{6, 7, 8}.

One published studies found significantly higher rates of prolonged gestation (over 42 weeks) in elder women⁷; there were no cases of prolonged gestation in our study and control groups. The same study also revealed low rates of maternal and fetal pathology in relation to high economic status⁷.

The expected non-age-related incidence of gestational diabetes was around 16% and of gestational hypertension was around 8 - 27%. We found similar rates (19.5% and 5.7%, respectively)^{2, 9, 10}. Incidence of gestational diabetes has been reported to be higher in older women, as we observed in our study^{1, 8, 9}, although other reports did not observe significant differences in incidence of gestational diabetes with age¹⁰.

We found no difference in incidence of gestational hypertension between the study and control groups. Some studies have reported higher rates in women over 40^{9, 10}.

In our study group, the incidence of fetal anomalies in women over 40 was higher (10%) than expected (2.9%) on the basis of published data⁹. Some studies had no cases of congenital malformation in either group⁶; however, in our study there were 9 (10%) neonates in the study group and 7 (8.1%) neonates in the

control group with fetal anomalies: three neonates in each group had Down syndrome.

We did not find significant differences in low birth weight between the study group and the control group. While some published studies report higher rates of low birth weight with women over 40 years old^{1, 8}, other studies report no significant differences^{6, 10}.

In agreement with other studies¹⁰, we found no significant differences in rates of premature rupture of membranes between the study and the control group.

When comparing studies it should be remembered that studies define the "older" group cut-off age in different ways: over 35, over 40 or over 45 years old^{8, 10}. Another complication in making comparisons is that studies are based in different geographical areas and it should not be assumed that all the women are Caucasoid^{2, 3, 5, 6, 10, 11}.

Interpretation of our results should take into account the limitations of our study. It was an observational retrospective study with a limited number of patients at a private hospital. Bias in our sample, particularly economic status, was not evaluated and our results may not be representative for the general population. Note that many women in our study decided not to do the aneuploidy screening test of the first trimester, and that could lead to an information bias. Use of assisted reproduction techniques was based on what women reported. Finally, ideally a study of this type should take into account women's previous health, BMI, cardiovascular disease, etc., which could affect pathology results.

In summary, the prevalence of pregnancy in women over 40 was higher than expected on the basis of the medical literature. In terms of maternal morbidity and mortality, we found that older women had a higher rate of gestational diabetes, and so we recommend strict glycaemic control of these patients. The use of ARTs was more common in older women. We also found a significant difference in results of the first semester trisomy test; however this was not related with a higher rate of fetal anomalies and no other significant differences in fetal morbidity and mortality were found. The perinatal outcomes in women over 40 years old at the Clínica Universidad de Navarra were, as a whole, no less satisfactory than those in younger women.

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