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Perinatal outcomes of induction of labour for advanced maternal age

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Abstract
Background: The decision to delay childbearing until age 40 or older in developed countries has been a relatively common social trend since the second half of the 20th century. Advanced maternal age is associated with several adverse maternal and neonatal outcomes like stillbirth. Induction of labor at 39 weeks' gestation in older mothers is widely practiced as an intervention perceived to reduce the risk of late stillbirth.
Objective: The objective of this study was to compare neonatal outcomes of non medically indicated induction at term to those of expectant management in women over 40 years old.
Study design: This is a retrospective cohort study of all women delivering at ≥ 39 weeks' gestation in the city of Vigo from Jan 1, 2012 to Dec. 31, 2017. Data were derived from the Hospital Álvaro Cunqueiro birth cohort. We compared expectant management (women who delivered from Jan 1, 2012 to Dec 31, 2014) to non medically indicated induction of labor (women who delivered from Jan 1, 2015 to Dec 31, 2017). The primary outcome was the perinatal results.
Results: There was a total of 603 pregnant women in the expectant management group compared to 634 women in the induction group. The women in the expectant management group were more likely to require neonatal intensive care unit admission and need pediatric support.
Conclusion: Induction of labor at 39 weeks of gestation, compared to expectant management, results in significantly better neonatal outcomes.

Keywords: advanced maternal age, induction of labor, cesarean section, neonatal outcomes

Introduction
The birth rate for women aged 40 years or older has been rising steadily. Delaying childbearing is an ongoing and universal phenomenon. In Spain, in the last 10 years the number of births to women aged 40 and older has increased by 63.1%. While in 2008 4.2% of births were to women with maternal age ≥ 40 years, in 2019 this percentage increased to 9.7% [1].
Advanced maternal age has been historically defined as being≥35 years at the time of delivery and is widely associated with adverse obstetric outcomes. The risks of hypertensive disorders, gestational diabetes mellitus, placenta previa, placental abruption and stillbirth are higher among women 35 years of age or older than among younger women [2, 3, 4, 5, 6]. The incidence of stillbirth at 39-40 weeks of gestation equates to 2 in 1000 for women ≥ 40 years of age compared to 1 in 1000 for women < 35 years old. Women ≥ 40 years of age having a similar stillbirth risk at 39 weeks of gestation to younger women at 41 weeks of gestation.[4] Induction of labor in older mothers is widely practiced as an intervention perceived to reduce the risk of late stillbirth [5, 6, 7]
Non medically indicated induction of labor compared with spontaneous labor is associated with an increased risk of cesarean delivery especially in nulliparous women. However, spontaneous labor may not be an ideal comparison. Detail data regarding outcomes of non medically indicated induction of labor are still limited. As of Jan 1, 2015, the Gynecology and Obstetrics service of the Álvaro Cunqueiro Hospital offered induction of labor to women aged ≥ 40 from the 39th week of gestation onwards. The objective of this study is to compare neonatal outcomes of non medically indicated induction at term to those of expectant management in women over 40 years old.

Material and Methods
Study design
A retrospective cohort study including all women aged ≥40 and at ≥ 39 weeks` gestation that delivered in the city of Vigo from Jan 1, 2012 to Dec. 31, 2017. Data were derived from the Hospital Álvaro Cunqueiro birth cohort, an electronic database created from gestational, birth and neonatal data from hospitalizations in the Vigo delivery room.
Women aged ≥40 years with a singleton pregnancy were included in the database. Women with < 39 weeks' gestation and multiple gestations were excluded. In January 2015, the gynecology and obstetrics service of Vigo implemented the protocol for induction of labor due to advanced maternal age, because of this, patients were divided according to the management of labor at term. We compared expectant management (women who delivered from Jan 1, 2012 to Dec 31, 2014) to non medically indicated induction of labor (women who delivered from Jan 1, 2015 to Dec 31, 2017).
The primary outcome was neonatal outcomes. Neonatal outcomes were stillbirth, birth weight, 5-minute Apgar score, arterial cord pH value, pediatric birth support, degrees of neonatal resuscitation and admission to a neonatal intensive care unit (NICU). To analyze the type of pediatric support at birth this outcome was divided into 3 groups: group 1 included those newborns who did not require pediatric assistance at birth; group 2 included newborns who required suctioning; group 3 included the 3 most advanced

degrees of resuscitation, suctioning and oxygen administration, use of ambu and intubation.

Statistical analyses

Data will be analyzed with SPSS 19.0 statistical software. Qualitative variables were reported with their absolute frequency and percentage while quantitative variables were reported as mean and standard deviation (SD) or median and interquartile range if they did not fit a normal distribution. Kolmogorov-Smirnov test was selected for normality test. Univariate analysis was performed to determine whether there are differences between the two study groups. For the relationship with qualitative variables the Chi-square test was used while for the comparison of quantitative variables the parametric T-student test or the non-parametric Mann-Whitney test was applied. A value of $p < 0.05$ was considered statistically significant. Ethics committee approval for this study was obtained from the Ethics and Clinical Research Committee of Galicia with approval number 2020/617.

Results

From Jan 1, 2012 to Dec. 31, 2017, there were 1,776 women aged ≥40 years who delivered at Álvaro Cunqueiro Hospital. Excluded were women who had multiple gestations and women delivering at < 39 weeks' gestation. There was a total of 603 pregnant women in the expectant management group compared to 634 women in the induction group.

Neonatal outcomes are shown in Table 1. Not statistically significant differences were found for Apgar value at 5 minutes and umbilical artery pH value. There were 2 cases of stillbirth in the expectant management group and no intrauterine fetal deaths were registered in the induction group. These differences were not statistically significant (p=0,147).

The expectant management group needed more advanced pediatric support at birth compared to the type of neonatal resuscitation required in the labor induction group. (Table 2). Rate of admission to the NICU was lower in the labor induction group (p=0,000).

Table 1: Neonatal outcomes

Variable	Expectant management group (N = 603)	Induction of labor group (N = 634)	P value
Sex no. (%)			
Male	285 (47, 3)	324 (51, 1)	
Female	318 (52, 7)	310 (48, 9)	
Birth weight (g)			0,001
Mean	3371,61g	3270, 23g	
Range	2050g-4630g	2215g- 4600g	
Apgar score at 5 min			0,317
Mean	9,85	9,91	
Range	0-10	6-10	
Umbilical-cord-arterial pH			0,083
Mean	7,20	7,23	
Range	0-7, 41	6,95-7, 46	
Stillbirth no. (%)	2 (0, 3)	0 (0)	0,147
Required intervention no. (%)	357 (59, 3)	184 (29)	0,000
NICU adminission no. (%)	143 (23, 7)	65 (10, 3)	0,000

Table 2: Groups based on the degree of neonatal resuscitation

	Group 1*	Group 2**	Group 3***
2012-2014	245(40,7%)	279 (46, 3%)	78 (13%)
2015-2017	450 (71%)	135 (21,3%)	49 (7,7%)

Group 1: No pediatric assistance at birth
Group 2: suctioning
Group 3: suctioning and oxygen administration, use of ambu and intubation

Discussion

This study analyzes expectant management versus induction of labor at 39 weeks of gestation in women 40 years of age or older at the time of delivery. In older women, active labor management results in better perinatal outcomes compared to the expectant management group.

We found statistically significant differences for the variables weight of the newborn, need for neonatal resuscitation and degree of resuscitation and admission to the NICU, in the same way, when the variables sex of the newborn, Apgar value at 5 minutes and the pH value of the umbilical artery are compared, no differences were found between groups, but neither were worse results in the group of induction due to advanced maternal age.

In the neonatal resuscitation variable, the differences between groups were statistically significant, that is, of the 603 births in the pre-protocol group, 59.3% of them required pediatric support at birth compared to 29% of the 634 deliveries collected in the group post-protocol, which represents a decrease of 30.3%. The risk of needing neonatal resuscitation in the expectant management group is 2.04 times higher than in the labor induction group from week 39 (95% CI, 1.78-2.35).

To analyze the type of pediatric support received at each delivery, neonatal resuscitation grades were divided into grade 0 (no resuscitation required), grade I (aspiration), grade II (aspiration and oxygen administration), grade III (use of ambu for administration of oxygen therapy) and grade IV (intubation). Statistically significant differences were also found between these groups, with a 30.3% increase in the percentage of deliveries in which pediatric care was not required and a 6.3% decrease in the need for more complex respiratory support measures in the active management group (p = 0.000).

In the same way, we found a decrease in the need to transfer the newborn to the Neonatal Intensive Care Unit (NICU) of 13.4%, going from 23.7% in the expectant management group to 10.3% in the group of active management. The risk of admission to the NICU in the pre-protocol group is 3.31

times higher in the group where labor induction was not applied.

Published evidence in this regard is diverse. Kawakita *et al* [7] found no differences in the composition of severe neonatal outcomes, but they did find that in their study, non-medically indicated induction of labor at week 40 of gestation was associated with a decrease in the odds of admission to the NICU compared to expectant management [7]. Another analysis reported a statistically significant trend of increased frequency of perinatal adverse outcome (death, ventilatory support, Apgar 3 or less at 5 minutes, hypoxic ischemic encephalopathy, seizures, sepsis, meconium aspiration syndrome, birth trauma, intracranial or subgaleal) as gestational age increased among those with expectant management: 5.1% at 39 weeks, 5.9% at 40 weeks, and 8.2% at 41 to 42 weeks of gestation [8]. On the other hand, one of the studies with the highest statistical power, which is the one carried out by study group 35/39, did not find significant differences in terms of neonatal variables between the groups assigned to the strategy of expectant management and labor induction management between week 39 and 39 + 6 [9]. When the results of labor induction at week 39 are analyzed without differentiating by maternal age, the results are more consistent towards better neonatal outcomes in the labor induction group. In a meta-analysis of six cohort studies that included a total of 66,000 women who underwent elective induction of labor at 39 weeks' gestation and compared with more than 584,000 women undergoing expectant treatment beyond that age gestational, elective induction was associated with a significantly lower risk of adverse perinatal outcomes (respiratory morbidity, intensive care unit admission, perinatal mortality) [10].

Assessing maternal age as an independent risk factor for worse neonatal outcomes, many studies do not find a significant relationship between Apgar scores at 5 minutes <7, advanced maternal age, and parity [11, 12, 13, 14]

If it was observed that the need for intensive care was significantly higher in women of advanced maternal age [3, 14, 15].

Long-term outcome data regarding outcomes for infants born after elective induction vs expectant management are limited. In an observational study comparing third-grade math or reading scores of children born after induction at 39 or 40 weeks with those of children born after expectant management beyond that gestational age, the results were similar between the two groups. However, since the inductions were for both medical and elective indications, the authors report that these results may be biased [17].

Research Implications

There is a continuous risk for baby with rising maternal age with numerous studies reporting multiple adverse fetal and maternal outcomes associated with advances maternal age. Induction of labor at 39 weeks of gestation would reduce these adverse outcomes. However, at present there are insufficient data available on the effect such a policy would have on cesarean rates and perinatal outcomes specifically in older women. Our study analyses the effect of labor induction compared with expectant management in women over 40 years old. Our results provide data on neonatal morbidity.

Strengths and Limitations

Our study has several limitations. The definition of advanced maternal age in the literature varies, with publications using different criteria. The definition used in our study aligns to the hospital`s policy of ≥ 40 years. The major limitation of our study is its retrospective nature. The retrospective dataset was subject to incomplete data entry and variation in practice. Despite our limitations, there are few studies in the literature that evaluate obstetric and perinatal outcomes according to active or expectant management in pregnant women of advanced maternal age and consider parity within their data.

Conclusion

In conclusion, induction of labor at 39 weeks of gestation compared to expectant management in women of advanced maternal age results in significantly better neonatal outcomes. Hence, it is important that advanced maternal age pregnant women be informed of the risks involved in delaying childbearing until the fourth decade of life. Further studies on this topic are necessary to develop new policies for clinical care in this group of pregnant women.

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