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# Do induced twin pregnancies influence the obstetric and neonatal results of multiple births born before 32 weeks? Comparison to spontaneous gestation

*Gestações gemelares induzidas modificam o resultado obstétrico e perinatal de partos antes da 32<sup>a</sup> semana? Comparação com gestações espontâneas*

## Original Article

### Keywords

Twins  
Induced reproduction  
Pregnancy outcome

### Palavras-chave

Gêmeos  
Reprodução assistida  
Resultado da gravidez

### Abstract

**PURPOSE:** To compare obstetric outcomes of induced preterm twin births (under 32 weeks gestation) with those spontaneously conceived. **METHODS:** Prospective study of twin pregnancies (25 induced and 157 spontaneously conceived) developed over a period of 16 years in a tertiary obstetric center. Demographic factors, obstetric complications, gestational age at delivery, mode of delivery, birth weight and immediate newborn outcome were compared. **RESULTS:** The analysis of obstetrical complications concerning urinary or other infections, hypertensive disorders of pregnancy, gestational diabetes, fetal malformations, intrauterine fetal death, intrauterine growth restriction and intrauterine discordant growth reveal no significant statistical differences between the two groups. First trimester bleeding was higher in the induced group (24 versus 8.3%,  $p=0.029$ ). The cesarean delivery rate was 52.2% in spontaneous gestations and 64% in induced gestations. Gestational age at delivery, birth weight, Apgar scores at first and fifth minutes, admissions to Neonatal Intensive Care Unit and puerperal complications show no statistically significant differences between the two groups. These results were independent of chorionicity and induction method. **CONCLUSION:** The mode of conception did not influence obstetric and neonatal outcomes. Although induced pregnancies have higher risk of first trimester bleeding, significant differences were not observed regarding other obstetric and puerperal complications and neonatal results.

### Resumo

**OBJETIVO:** Comparar os resultados obstétricos de gestações gemelares induzidas com as concebidas espontaneamente, em partos ocorridos antes da 32<sup>a</sup> semana de idade gestacional. **MÉTODOS:** Estudo prospectivo de gestações gemelares (25 induzidas e 157 concebidas espontaneamente) desenvolvido durante um período de 16 anos num centro terciário de Obstetrícia. Foram comparados fatores demográficos, complicações obstétricas, idade gestacional no parto, tipo de parto, peso ao nascer e o outcome imediato do recém-nascido. **RESULTADOS:** A análise das seguintes complicações obstétricas: infeções urinárias ou outras, distúrbios hipertensivos da gravidez, diabetes gestacional, malformações fetais, morte fetal intrauterina, restrição de crescimento intrauterino e crescimento intrauterino discordante não revelou diferenças estatísticas significativas entre os dois grupos. No grupo das gestações induzidas, observou-se maior taxa de metrorragias do 1<sup>o</sup> trimestre (24 versus 8,3%,  $p=0,029$ ). A taxa de cesariana foi de 52,2% nas gestações espontâneas e 64% nas gestações induzidas. Idade gestacional no parto, peso ao nascer, índice de Apgar no primeiro e quinto minutos, internamento em unidade de cuidados intensivos neonatal e complicações puerperais não apresentam diferenças estatisticamente significantes entre os dois grupos. Esses resultados foram independentes do tipo de placentação e método de indução. **CONCLUSÃO:** O modo de concepção não influenciou os resultados obstétricos e neonatais. Embora as gestações induzidas tenham maior risco de metrorragias do primeiro trimestre, não foram observadas diferenças significativas em relação a outras complicações obstétricas, complicações puerperais e em relação aos resultados neonatais.

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## Introduction

Advances in neonatal intensive care have led to an increased survival of preterm infants at extremes of gestational age (GA) with its associated morbidities<sup>1,2</sup>. During the last two decades, there has been an increase in the incidence of preterm births worldwide with a range of 7–13%<sup>3,4</sup>. One of the reasons seems to be the widespread use of assisted reproduction techniques (ART) leading to pregnancies with multiple gestations<sup>5</sup>. Data show that around 22% of all deliveries after ART occur in pregnancies with more than one fetus — 20.7% of twins and 1% of triplets<sup>6,7</sup>.

It is well known that maternal and obstetrical complications are more frequent in twin pregnancies than in singleton pregnancies. However, studies comparing perinatal outcomes in multiples conceived following ART *versus* spontaneous conception (SC) have reported conflicting results in terms of mortality and morbidity<sup>8,9</sup>. Some reasons that have contributed to these results might be: inclusion of term and preterm infants in the cohort, studies with small sample size and failure to control perinatal characteristics<sup>10</sup>.

Some studies report comparable perinatal outcomes<sup>11-14</sup> but others report a higher risk of adverse perinatal outcome such as: gestational diabetes (GD), hypertension, intrauterine growth discordance, preterm birth and cesarean sections rates, low birth weight and higher Neonatal Intensive Care Unit (NICU) admissions<sup>15-17</sup>; other recent studies, a retrospective<sup>18</sup> and a prospective one, showed that rates of very preterm birth, extremely low birth weight, admission to a NICU and perinatal mortality were significantly higher in the ART group<sup>17</sup>.

There are others studies that find a better perinatal outcome after ART<sup>18</sup>. There have been published two reports comparing outcomes of very low birth weight infants ( $\leq 1,500$  g) conceived following ART *versus* SC and both have reported no difference in mortality and neonatal morbidities<sup>17</sup>. In both studies, outcomes were compared amongst singletons and multiples, and increased neonatal morbidity was attributed to plurality<sup>3</sup>.

The aim of the present study was to compare obstetric outcomes among multiple births less than 32 weeks of GA of all induced twin pregnancies (ovulation induction – OI and ART) with those spontaneously conceived. We hypothesized that preterm multiple births less than 32 weeks of GA born following the use of ART will have increased rate of adverse outcome.

## Methods

Data from files of all twin pregnancies who deliver in our tertiary obstetric center over the period of 16 years

(between January 1996 and December 2011) were prospectively collected and analyzed for this study. A cohort study was conducted.

No intervention was done besides the normal twin surveillance protocol in those with surveillance in our center. This study was included in an investigation project approved by the Ethics Committee of the Hospital and University Center of Coimbra.

Triplets or high-order and monoamniotic multiple gestations were excluded from the analysis. All twin pregnancies (dichorionic and monochorionic) spontaneously conceived, those obtained following an induction method/technique – OI or assisted reproduction techniques (*in vitro* fertilization – IVF/intracytoplasmic sperm injection – ICSI) and all twin pregnancies that delivered before 32 weeks were included.

In a first analysis, two groups were formed: one of all spontaneously conceived twin pregnancies and other one of all induced twin pregnancies. In both groups, the following parameters were analyzed and compared: maternal age (categorized in the following classes <18, 18–25, 26–35, 36–40 and >40 years), parity, personal or family history of twins, personal disease history and habits (current or previous use of smoke, drugs or alcohol).

Obstetric complications included were: first trimester bleeding; urinary, genital or other infections; anemia; fetal malformations; hypertensive diseases of the pregnancy (gestational hypertension, pre-eclampsia, eclampsia and HELLP syndrome; GD; preterm premature rupture of membranes – PPRM, considered the occurrence of premature rupture of membranes after 24 and before 32 weeks of gestation; intrauterine growth restriction – IUGR, defined as fetal measure of abdominal perimeter <10<sup>th</sup> centile; discordant growth restriction, defined as 20% difference between fetal birth weight and fetal death).

About birth, mode of delivery (categorized in vaginal, cesarean during delivery, elective cesarean and cesarean to the second twin), birth weight of both twins, Apgar score at first and fifth minutes of both twins and admission of the neonates in the NICU were analyzed.

The occurrence of puerperal complications was also analyzed, namely: anemia, hemorrhage, hypertension complications and endometritis.

The GA was calculated from the data of embryo transfer for the induced pregnancies obtained from ART and from the last menstrual period on the spontaneously conceived group, both confirmed and corrected by the time of the first trimester ultrasound. Chorionicity was also determined in the first trimester scan (by lambda and T signs).

In a second step, we analyzed the influence of chorionicity and of the type of induced technique (OI, IVF or ICSI) in the mentioned conditions.

A global characterization of the sample (25 induced twin pregnancies and 157 spontaneously conceived) was performed considering the listed parameters. Categorical variables were characterized by absolute frequencies and relative frequencies, and continuous variables were characterized using the mean, standard deviation, quartiles, minimum and maximum.

As for categorical variables, differences in proportions between the two groups were evaluated using the  $\chi^2$  test or Fisher's exact test. As for the continuous variables, the *t*-test was used to compare means between the two groups and the Mann-Whitney test was used to compare the distribution of values of continuous variables, where the assumptions for the use of the *t*-test are not satisfied. The normal distribution of values for continuous variables and the equality of their variances were tested using the Kolmogorov-Smirnov and Levene tests, respectively. To analyze the stratification of risks according to age and chorionicity, the Breslow-Day test was used.

The significance level used in this analysis was 5%. Resorted to the software *Statistical Package for the Social Sciences* (SPSS)<sup>®</sup>, version 19.0.0.2.

## Results

During the study period — January 1996 to December 2011 —, there were 878 deliveries of twin pregnancies in our center. Regarding the type of conception, 698 were spontaneous (79.5%) and 180 were induced pregnancies (20.5%).

Over the studied period, we found a significant growing tendency for induced twin pregnancies ( $p=0.001$ ), that represent 20.3% of twin deliveries in our center. This tendency is no longer observed if we regard to the mode of conception individually over the years, as they remain stable — OI (that accounts for 31.5% of these pregnancies), IVF (that accounts for 41% of these pregnancies) or ICSI (that accounts for 27.5%).

There were 182 (20.8%) births under 32 weeks of GA. From these, regarding the type of conception: 157 (86.3%) were spontaneous and 25 (13.7%) were induced pregnancies.

Maternal characteristics in both groups were analyzed (Table 1). As expected, women in the induced group had higher rates of infertility (25 *versus* 2%;  $p<0.001$ ) and all of them were nulliparous (100 *versus* 50%;  $p<0.001$ ).

There were no significant differences regarding their personal medical history (hypertensive, endocrine, renal or other systemic diseases) or habits (smoking, alcohol, drugs).

The analysis of obstetrical complications (Table 2) concerning anemia, infections, hypertensive disorders of pregnancy, GD, fetal malformations, PPRM, intrauterine fetal death, intrauterine discordant growth, and IUGR revealed no major significant differences between the two groups.

**Table 1.** Maternal characteristics of both groups (spontaneous and induced pregnancies)

Maternal characteristics of both groups	Spontaneous pregnancy		Induced pregnancy		p-value
	n	%	n	%	
<b>Age (years)</b>					
>35	133	84.7	20	80	n.s.
<35	24	15.3	5	20	
<b>Twins' personal history</b>	44	29.3	0	0	0.002
<b>Personal medical history</b>					
Renal	3	1.9	0	0	n.s.
Hypertensive	5	3.2	0	0	n.s.
Endocrine	5	3.2	0	0	n.s.
Systemic	6	3.8	2	8	n.s.
Psychiatric	4	2.6	0	0	n.s.
STD	1	0.6	0	0	n.s.
Smoking/alcohol	1	0.6	0	0	n.s.
<b>Personal infertility history</b>	2	1.3	25	100	<0.001
<b>Nulliparity</b>	78	50	25	100	<0.001

n.s.: not significant; STD: sexually transmitted diseases.

**Table 2.** Obstetrical results and fetus data of both groups (spontaneous and induced pregnancies)

Complications	Spontaneous pregnancy		Induced pregnancy		p-value
	n	%	n	%	
First trimester bleeding	13	8.3	6	24	0.02
Urinary infections	16	10.2	3	12	n.s.
Hypertension induced by pregnancy	3	1.9	0	0	n.s.
Preeclampsia	5	3.2	1	4	n.s.
Gestational diabetes	4	2.5	1	4	n.s.
PPROM	61	39.4	7	28	n.s.
Fetal malformations	5	3.2	2	8	n.s.
IUFD	12	7.6	2	8	n.s.
TTTS	14	8.9	1	4	n.s.
IUGR	21	13.4	4	16	n.s.
Growth discordance – 20%	10	6.4	2	8	n.s.
Cesarian rate	82	52.2	16	64	n.s.
Puerperium complications	34	21.8	6	24	n.s.
NICU admission – F1 and/or F2	94.4%		100%		n.s.
Birth weight – Fetus 1	1,322±471g		1,205±405g		n.s.
Birth weight – Fetus 2	1,331±466g		1,144±412g		n.s.
Apgar Fetus 1 – 1 <sup>st</sup> minute	7.3±2.1		7.7±1.5		n.s.
Apgar Fetus 1 – 5 <sup>th</sup> minute	9.2±1.3		9.2±1.4		n.s.
Apgar Fetus 2 – 1 <sup>st</sup> minute	6.8±2.3		7.0±1.8		n.s.
Apgar Fetus 2 – 5 <sup>th</sup> minute	9.0±1.4		9.1±1.0		n.s.

n.s.: not significant; PPRM: preterm premature rupture of membranes; IUFD: intrauterine fetal death; TTTS: twin to twin transfusion syndrome; IUGR: intrauterine growth restriction; NICU: Neonatal Intensive Care Unit.

First trimester bleeding was higher in the induced group (8.3 *versus* 24%,  $p=0.02$ ; OR=3.49; 95%CI 1.18–11.3).

Regarding delivery, the induced group had higher cesareans rates (64 *versus* 52.2%;  $p=0.6$ ), however without significant differences. Birth weight, Apgar scores at first and fifth minutes, and admissions to NICU were not statistically different in both groups. In terms of puerperal complications, the results were similar, with no significant differences between the two groups (24% in the induced *versus* 21.8% in the spontaneous) (Table 2).

When stratifying the risk of obstetric complications by chorionicity, all the results were independent of chorionicity ( $p=0.8$ ).

In the analyses of the influence of the methods of pregnancy induction in pregnancy complications, we found that the results were also independent of the induced method (OI or ART – IVF or ICSI).

## Discussion

Since the birth of the first IVF conceived infant in 1978, diverse ART techniques have developed rapidly and were implemented in clinical practice. The increasing use of assisted reproduction techniques has led to an increase in the incidence of multiple pregnancies.

ART have become a widespread option for the treatment of human infertility and data show that around 22% of all deliveries after ART occur in pregnancies with more than one fetus<sup>6</sup>. It is known that, since 1980, there has been a worldwide increase in multiple births. This seems to be due to an increase in the age of reproduction, the use of OI and the use of IVF<sup>19</sup>.

Studies have shown that singleton pregnancies that are the product of IVF are at an increased risk of preterm delivery, low birth weight, induction of labor, cesarean delivery and pregnancy-induced hypertension compared with SC singleton pregnancies<sup>20,21</sup>. However, studies that have compared IVF with SC twin pregnancies have yielded conflicting results. Some have not shown any evidence of increased risk in these pregnancies as compared with ones in the general population excluding a few specific parameters such as lower birth weights and discordance, emergency and elective cesarean sections. Other studies showed great differences in pregnancies conceived with IVF assistance<sup>22</sup>.

However, whether it is the technology (hormonal stimulation, gamete manipulation, cryopreservation and *in vitro* culture) or the underlying infertility that plays a greater role in causing poor outcomes has not yet been clearly elucidated<sup>23</sup>. Raatikainen et al.<sup>24</sup> pointed out that maternal factors relating to subfertility and not only treatment are associated with adverse pregnancy outcome. These results show that maternal factors associated with

infertility rather than the ART procedures themselves may contribute to the poor consequences<sup>25</sup>. An Australian study found that the increased risk of birth defects associated with IVF was no longer significant after adjustment for parental factors<sup>24</sup>.

For example, the mechanism by which ART may increase the risk of preterm birth is not clear. However, several mechanisms have been suggested: increased levels of relaxin (observed in stimulated pregnancies), the infertility treatment or the cause of infertility and the anxiety related to these pregnancies<sup>3</sup>.

Twin pregnancies are associated with increased perinatal morbidity and mortality as well as a higher rate of cesarean deliveries. The obstetric complications include preterm labor, anemia, pregnancy induced hypertension, postpartum hemorrhage, prematurity and low birth weight. So, it has been suggested that the higher rates of prematurity, low birth weight and perinatal complications in newborns resulting from ART may result from the higher prevalence of multiple pregnancy in this population<sup>26,27</sup>.

The objective of this study was to compare the risk of obstetric complications among multiple births under 32 weeks of GA following ART *versus* SC. In our study, all twin pregnancies were included, and then we analyzed the impact or influence of the chorionicity in the results. We also included all types of induced pregnancies, OI and ART, and then we evaluated their influence in the global results.

In our study, we showed, as expected, that in the group of induced pregnancies there were higher rates of infertility and nulliparity. First trimester bleeding was also significantly higher in the induced group.

Concerning to obstetrical complications, birth weight, Apgar scores at first and fifth minutes, admissions to NICU, fetal malformation, perinatal mortality and puerperal complications, there were no differences in both groups. Regarding delivery, the induced group had higher rates of caesareans, as described in other studies<sup>21,28</sup>.

We found that all the results were independent of chorionicity and the induced method chosen.

So, in our study, the mode of conception did not influence neonatal morbidities and mortality in preterm multiples born at under 32 weeks of GA. Our findings are consistent with several studies published, for example, a retrospective study comparing obstetric and perinatal outcomes of twin pregnancies conceived following IVF/ICSI treatment with SC showed that assisted conception do not have significant disadvantage over naturally conceived twin pregnancies<sup>29</sup>; Schimmel et al.<sup>20</sup> and Messerschmidt et al.<sup>30</sup> compared the outcomes of singleton and multiple very low birth weight infants, conceived by IVF *versus* SC. After accounting for confounding variables (maternal age, parity, multiple type, GA, sex and small for

gestational age), there was no difference in the incidence of morbidity and mortality in the IVF group. Our study also corroborate another one, conducted by Shah et al.<sup>3</sup>, who compared the composite outcomes (death or severe neonatal morbidities) among multiple births under 32 weeks of GA following ART *versus* SC, found no differences between the two groups. However, one of the limitations of these last studies was that they did not evaluate the influence of the chorionicity.

We believe that the information of this study has clinical implications, as it represents an important contribution to this subject, because we evaluated the influence of chorionicity and conception mode in the results. However, it has some limitations: we excluded from the study the singletons, so we were unable to comment the influence of plurality on the outcomes and we were unable to evaluate the long-term neurological development of these infants – both analyses are still in course.

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