# Maternal complications and neonatal events associated with multiple pregnancies resulting from assisted reproduction techniques*

COMPLICAÇÕES MATERNAS E OCORRÊNCIAS NEONATAIS ASSOCIADAS ÀS GESTAÇÕES MÚLTIPLAS RESULTANTES DE TÉCNICAS DE REPRODUÇÃO ASSISTIDA

COMPLICACIONES MATERNAS E EVENTOS NEONATALES ASOCIADOS CON GESTACIONES MÚLTIPLES RESULTANTES DE TÉCNICAS DE REPRODUCCIÓN ASISTIDA

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**ABSTRACT**

Multiple pregnancy is the most frequent and serious iatrogenic complication of the assisted reproduction techniques. The purpose of this study was to know the maternal complications and neonatal events associated to multiple pregnancies, resulting from assisted reproduction in a reference center in the field of assisted reproduction. This was an observational, cross-section, descriptive and retrospective study performed at Hospital e Maternidade Santa Joana, a reference center in the area of human reproduction in the city of São Paulo, Brazil. The studied population consisted of 131 medical records of pregnant women admitted with clinical pathologies and in labor, resulting from multiple pregnancies resulting from assisted reproduction techniques. The predominant maternal complications were: premature labor (65.5%) and premature amniorrhexis (42%), The most frequent neonatal occurrences were respiratory diseases (65.1%), jaundice (38.4%), metabolic disorders (13%) and neurological diseases (9%).

**KEY WORDS**

Infertility.
Obstetrical nursing.
Reproductive techniques.

**RESUMO**

A gestação múltipla é a mais freqüente e a mais séria complicação iatrogênica das técnicas de reprodução assistida. O objetivo do estudo foi conhecer as complicações maternas e as ocorrências neonatais associadas às gestações múltiplas resultantes de reprodução assistida em um centro de referência na área de reprodução assistida. Trata-se de uma pesquisa observacional, transversal, descritiva e retrospectiva que foi realizada no Hospital e Maternidade Santa Joana, centro de referência na área de reprodução humana localizado no município de São Paulo, Brasil. A população estudada foi constituída por 131 prontuários de gestantes internadas com patologias clínicas e trabalho de parto, advindas de gestações múltiplas resultantes de técnicas de reprodução assistida. As complicações maternas predominantes foram: o trabalho de parto prematuro (65,5%), a amniorrexe prematura (42%). As ocorrências neonatais mais freqüentes foram as doenças respiratórias (65,1%), a icterícia (38,4%), os distúrbios metabólicos (13%) e as doenças neurológicas (9%).

**DESCRITORES**

Infertilidade.
Enfermagem obstétrica.
Técnicas reprodutivas.

**RESUMEN**

La gestación múltiple es la más frecuente y corresponde a la más seria complicación iatrogénica de las técnicas de reproducción asistida. El objetivo del estudio fue conocer las complicaciones maternas y los eventos neonatales asociados a las gestaciones múltiples resultantes de la reproducción asistida en un centro de referencia en el área de reproducción asistida. Se trata de una investigación observacional, transversal, descriptiva y retrospectiva que fue realizada en el Hospital y Maternidad Santa Joana, centro de referencia en el área de reproducción humana, localizado en el municipio de São Paulo, Brasil. La población estudiada fue constituida por 131 registros de gestantes internadas con patologías clínicas y trabajo de parto, provenientes de gestaciones múltiplas resultantes de técnicas de reproducción asistida. Las complicaciones maternas predominantes fueron: el trabajo de parto prematuro (65,5%) y la ruptura prematura del saco amniótico (42%). Los eventos neonatales más frecuentes fueron las enfermedades respiratorias (65,1%), la ictericia (38,4%), los disturbios metabólicos (13%) y las enfermedades neurológicas (9%).

**DESCRIPTORES**

Infertilidad.
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## INTRODUCTION

Infertility is clinically defined as the inability to conceive after one year of regular sexual relations without the use of any contraceptive method[1-4]. The World Health Organization (WHO) considers a two-year period as more adequate to establish the infertility diagnosis, since several couples achieve conception without any type of treatment after one year of unprotected intercourse.

Nearly 10% of couples fail to conceive in the period of one year with regular, unprotected sexual relations[5]. In past years, the percentage of infertile couples reached about 30% of those of fertile age and led to increased demands by couples at infertility clinics.

In the United States, there are over 400 institutions specializing in assisted reproduction techniques. Yearly, more than 100,000 *in vitro* procedures are performed, with 30,000 of them yielding normal children. This result represents less than 1% of all births registered in the United States yearly. Because of the lack of records worldwide, the exact number of *in vitro* fertilizations is unknown, but it has been estimated at around 1,300,000 to 1,500,000 cases[6].

The annual number of assisted reproduction procedures in Latin America rose from 11.7% in 2003 to 16.9% in 2004, with 24,588 total procedures, 64.4% of which were done in Brazil and Argentina[7].

Assisted reproduction technology consists of treating infertility, in which the reproductive cells (eggs and spermatozoids) are manipulated in laboratory and introduced in the female reproductive system artificially. These techniques include *in vitro* fertilization (IVF), intracytoplasmatic spermatozoid injection (ICSI) and other associated techniques that aid in the implantation of laboratory-produced embryos.

The techniques involve the use of hormones for ovarian stimulation and development of two or more follicles, improving the chance of impregnation. These hormones are usually defined by the client's age, the regularity of the menstrual cycle and the basal level of the follicle stimulating hormone (FSH). The objective is to achieve a reasonable amount of mature follicles in both quantity and quality to reproduce the embryos[8]. Other techniques, such as intra-uterine insemination (IUI), do not involve laboratory manipulation and allow fecundation to occur at its proper place, the oviducts.

Multiple pregnancy is the most frequent and serious iatrogenic complication in the assisted reproduction techniques. The relation of multiple pregnancies with prematurity is universally recognized, leading to increased mortality and morbidity for both mother and fetus. Indeed, complications are so common that some authors classify multiple pregnancies as a type of pathology[9].

In 2002, the gemelarity rate was 31.1 per 1000 live births, 63% higher than in 1980, and triplets were 1.9 per 1000 live births, 401% higher than the average in 1980[6].

The risk for multiple pregnancy increases with the use of ovarian stimulation medications used in assisted reproduction, such as clomiphene citrate (8%) increasing to 20% with the use of gonadotropins[10-11].

Assisted reproduction techniques are associated with obstetric and neonatal risks as well, such as: maternal age, previous sterility and an unfavorable obstetrical past [12]. Such risk factors can be aggravated according to the number of fetuses, increasing significantly with the gestation of three or more fetuses. In cases of preterm delivery, preeclampsia or early detachment of the placenta, the neonatal morbidity rate is higher in the short and long terms[13-14].

The incidence of multiple pregnancies can be differentiated according to the assisted reproduction technique employed, since its occurrence is related to the number of gametes or embryos transferred to the patients' uterus or oviducts. The transference of more than one embryo increases the risk of multiple implantations[13]. According to Brazilian law, a maximum of four embryos can be transferred, and once implanted, it is prohibited to use procedures aiming at embrionary reduction, as described in Regulation 1358/92 of the Federal Council of Medicine, passed in 1992[13].

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The interest for this subject arose from the necessity of a rigorous therapeutic control and the high complexity of nursing care for women impregnated with multiple fetuses, as well as the maternal and neonatal complications, factors that are significant for a successful gestation.

The objective of the research was to study the maternal complications and the neonatal occurrences that are a consequence of multiple gestations resulting from assisted reproduction in a reference center in the assisted reproduction field.

## METHOD

This is an observational, descriptive, cross-sectional and retrospective study, developed at Hospital e Maternidade Santa Joana, a reference center in the human reproduction field in the city of São Paulo, Brazil.

The population consisted of 131 medical records of women with multiple pregnancies resulting from assisted reproduction techniques, hospitalized with clinical pathologies and labor, in the years 2004 and 2005. For the record to be included in the study, it had to identify the assisted

reproduction technique used. Spontaneous multiple pregnancies or records without the identification of the assisted reproduction technique were excluded.

The study variables were selected according to the obstetric risk profile described in literature. The following maternal variables were studied: age, marital situation, assisted reproduction technique, parity, number of previous abortions, number of fetuses, gestational age at the time of delivery, current obstetric pathologic diagnosis, necessity of immediate postpartum care in an intensive care unit and breastfeeding.

The neonatal variables we re: weight at birth, neonatal occurrences and the length of the hospital stay in the high-risk nursery.

The category *no information available* was included in some study variables, as long as their significant dimension was low, i.e., lower than 10%.

Data collection was performed after the project was approved by the Ethicis Committee of Hospital e Maternidade Santa Joana and Universidade Federal de São Paulo. Data was collected from the archive of medical records, after the selection of those indicating multiple fetuses in the two years of study (CEP 1731/05).

The study variable data were registered in a Microsoft Office Excel 2000™ spreadsheet.

## RESULTS

A human reproduction reference center was created at Hospital e Maternidade Santa Joana in 2002, with adequate structure, equipment and human resources for the specialty. The result of the care provided to infertile couples at the center is 12.3 babies per month on average.

There were 22,065 births in the period selected for the research, of which 370 multiple pregnancies were identified (1.67%), 65 of which were spontaneous (17.5). Since 174 medical records showed no indication of whether multiple pregnancy was spontaneous or induced, they were excluded from the study (47%). Another 131 multiple pregnancy records were included in the study since they mentioned assisted reproduction techniques (35.4%).

The qualitative variables are presented in absolute (N) and relative (%) frequencies. Average and median values were used as summary measurements for the quantitative variables, and standard deviation, minimum and maximum values were used to indicate variability.

Age varied from 22.9 to 49 years, averaging at 33.9 years. The 33-38 year old age range was predominant (Table 1). It is known that the woman's age exerts a marked influence on the spontaneous fertility rate, and it is also expected that it influences the results in all forms of infertility treatment[14].

**Table 1 -** Distribution of the studied population, according to sociodemographic and obstetric variables. City of São Paulo, 2004-2005

| Variables | | N | % |
|---|---|---|---|
| Age (in years) | ≤ 30 years old | 32 | 24.4 |
| | 30 ┤ 33 | 28 | 21.4 |
| | 33 ┤ 38 | 38 | 29.0 |
| | > 38 | 33 | 25.2 |
| Marital status | single | 3 | 2.3 |
| | married | 125 | 95.4 |
| | consensual union | 3 | 2.3 |
| Number of pregnancies | 0 | 1 | 0.8 |
| | 1 | 92 | 70.2 |
| | 2 | 27 | 20.6 |
| | 3 | 6 | 4.6 |
| | 4 | 4 | 3.1 |
| | 5 | 1 | 0.8 |
| Number of deliveries | 0 | 118 | 90.1 |
| | 1 | 9 | 6.9 |
| | 2 | 3 | 2.3 |
| | 3 | 1 | 0.8 |
| Number of abortions | 0 | 100 | 76.3 |
| | 1 | 26 | 19.8 |
| | 2 | 3 | 2.3 |
| | 3 | 2 | 1.5 |
| Number of fetuses | 2 | 99 | 75.6 |
| | 3 | 30 | 22.9 |
| | 4 | 2 | 1.5 |
| Gestational age at delivery (weeks) | < 20 | 2 | 1.5 |
| | 20 ┤ 30 | 18 | 13.7 |
| | 30 ┤ 34 | 24 | 18.3 |
| | 34 ┤ 36 | 41 | 31.3 |
| | > 36 | 33 | 25.2 |
| | No information | 13 | 9.9 |
| Puerperium | ICU | 4 | 3.1 |
| | Hospitalization | 114 | 87.0 |
| | No information | 13 | 9.9 |
| Breastfeeding | No | 37 | 28.2 |
| | Yes | 89 | 67.9 |
| | No information | 5 | 3.8 |

Regarding marital status, a total of 125 married women were found, with three others being single and another three living in consensual union. Nearly 70.2% of the women were primigest, which contributes to the consensus that women are delaying their pregnancies until their fourth or fifth decades in order to prioritize their careers, seek financial stability and a stable partner[15].

The resolution of the delivery according to gestational age happened between the 30th and the 36th week (49.6%), and all cases registered a cesarean section procedure.

Most of the studied population spent the immediate puerperium period at the hospital, excluding four puerpera that

were referred to the intensive care unit. Approximately 67.9% of the women started breastfeeding during hospitalization.

*In vitro* fertilization was the most common assisted reproduction technique (67.2%), and its indications were: poor quality of the sperm, problems in fertilization and azoospermy (obstructive), followed by ovarian stimulation (28.2%), intra-uterine insemination (3.1%) and intracytoplasmatic injection of spermatozoids (1.5%).

In the present study, 90.9% of the women presented with complications during the gestational period, during labor or in the immediate puerperium. In 65.6% of the patients, early labor contributed towards a high prematurity rate, followed by premature amniorrhexis in 42% of the pregnancies. Urinary infection was present in 15.3% of the pregnancies (Table 2).

**Table 2 -** Distribution of the maternal complications in the population studied. City of São Paulo, 2004-2005

| Maternal Complications | N | % |
|---|---|---|
| Early labor | 86 | 65.6 |
| Premature amniorrhexis | 35 | 26.7 |
| Urinary infection | 20 | 15.3 |
| Preeclampsia | 16 | 12.2 |
| Iron-deficiency anemia | 16 | 12.2 |
| Olygoamnion | 11 | 8.4 |
| Hypothyroidism | 10 | 7.6 |
| Placenta previa | 6 | 4.6 |
| Isthmus-cervical insufficiency | 6 | 4.6 |
| Chronic hypertension | 6 | 2.3 |
| Diabetes Mellitus | 2 | 1.5 |
| Restriction of intra-uterine growth | 2 | 1.5 |

Early labor is especially noted among the maternal complications emerging from the study, especially due to its implications for neonatal occurrences.

Out of 131 multiple gestations resulting from assisted reproduction techniques included in this study, there were 272 live births, 18 (13.7%) fetal deaths and 11 stillborns (8.3%). Following birth, 13 newborns were sent to the regular nursery (4.7%), while the other 259 were sent to the high-risk nursery.

**Table 3 –** Weight at birth in grams. City of São Paulo, 2004-2005

| Weight | N | Average | Median | Standard deviation | Minimum | Maximum |
|---|---|---|---|---|---|---|
| 1st newborn | 116 | 1982.5 | 2137.5 | 678.8 | 150.0 | 3130.0 |
| 2nd newborn | 116 | 1951.4 | 2137.5 | 678.3 | 0.0 | 3055.0 |
| 3rd newborn | 29 | 1397.1 | 1360.0 | 706.8 | 20.0 | 2645.0 |
| 4th newborn | 1 | 340.0 | 340.0 | - | 340.0 | 340.0 |
| All newborns | 272 | 1890.5 | 2025.0 | 716.1 | 0.0 | 3130.0 |

The average weight (Table 4) was 1,982.5g for the first newborn, 1,951.4 g for the second and 1,397.0g for the third. The Apgar values for all newborns in the first minute were: 7.5 for the first, 7.2 for the second and 7.0 for the third. In the fifth minute, the values rose to 8.7, 8.4 and 8.0, respectively.

**Table 4 –** Neonatal occurrences according to the assisted reproduction technique used. City of São Paulo - 2004-2005

| | | Method | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | IVF | | ICSI | | IUI | | Ovarian stimulation | |
| | | N | % | N | % | N | % | N | % |
| Congenital anomalies | No | 167 | 94.9 | 3 | 75.0 | 7 | 100.0 | 68 | 95.8 |
| | Yes | 9 | 5.1 | 1 | 25.0 | - | - | 3 | 4.2 |
| Birth traumas | No | 174 | 98.9 | 4 | 100.0 | 7 | 100.0 | 70 | 98.6 |
| | Yes | 2 | 1.1 | - | - | - | - | 1 | 1.4 |
| Jaundice | No | 109 | 61.6 | 2 | 50.0 | 6 | 85.7 | 45 | 63.4 |
| | Yes | 68 | 38.4 | 2 | 50.0 | 1 | 14.3 | 26 | 36.6 |
| Metabolic disorders | No | 154 | 87.0 | 4 | 100.0 | 7 | 100.0 | 65 | 91.5 |
| | Yes | 23 | 13.0 | - | - | - | - | 6 | 8.5 |
| Respiratory diseases | No | 46 | 25.7 | 2 | 50.0 | 4 | 57.1 | 39 | 54.9 |
| | Yes | 133 | 74.3 | 2 | 50.0 | 3 | 42.9 | 32 | 45.1 |
| Hematologic diseases | No | 152 | 85.9 | 4 | 100.0 | 7 | 100.0 | 67 | 94.4 |
| | Yes | 25 | 14.1 | - | - | - | - | 4 | 5.6 |
| Otologic diseases | No | 162 | 91.0 | 3 | 75.0 | 7 | 100.0 | 68 | 95.8 |
| | Yes | 16 | 9.0 | 1 | 25.0 | | | 3 | 4.2 |
| Cardiocirculatory diseases | No | 160 | 90.4 | 3 | 75.0 | 7 | 100.0 | 67 | 94.4 |
| | Yes | 17 | 9.6 | 1 | 25.0 | - | - | 4 | 5.6 |
| Neurologic diseases | No | 161 | 91.0 | 4 | 100.0 | 7 | 100.0 | 64 | 90.1 |
| | Yes | 16 | 9.0 | - | - | - | - | 7 | 9.9 |
| Infectious diseases | No | 156 | 88.1 | 3 | 75.0 | 7 | 100.0 | 68 | 95.8 |
| | Yes | 21 | 11.9 | 1 | 25.0 | - | - | 3 | 4.2 |
| Gastrointestinal diseases | No | 176 | 99.4 | 4 | 100.0 | 7 | 100.0 | 71 | 100.0 |
| | Yes | 1 | 0.6 | - | - | - | - | - | - |
| Renal diseases | No | 175 | 98.9 | 4 | 100.0 | 7 | 100.0 | 71 | 100.0 |
| | Yes | 2 | 1.1 | - | - | - | - | - | - |
| Parenteral nutrition | No | 123 | 69.5 | 3 | 75.0 | 5 | 71.4 | 63 | 88.7 |
| | Yes | 54 | 30.5 | 1 | 25.0 | 2 | 28.6 | 8 | 11.3 |
| Intra-uterine fetal death | No | 193 | 95.5 | 2 | 50.0 | 7 | 77.8 | 72 | 93.5 |
| | Yes | 9 | 4.5 | 2 | 50.0 | 2 | 22.2 | 5 | 6.5 |

Considering the neonatal occurrences in the total amount of live births, we observed that respiratory diseases were present in 65.1% of the cases, most often in the third newborn, followed by neonatal jaundice in 37.5% and the use of parenteral nutrition in 25.1%. Congenital anomalies, usually mentioned in literature, accounted for 5% of the total neonatal occurrences, including hydrocephaly and coxofemoral instability.

**Table 5 –** Average stay of the newborns in the high-risk nursery, in days. City of São Paulo, 2004-2005

| Days in the high-risk nursery | N | Average | Median | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|---|---|
| 1st newborn | 116 | 18.2 | 4.5 | 30.2 | 3.0 | 140.0 |
| 2nd newborn | 115 | 15.3 | 6.0 | 20.1 | 3.0 | 95.0 |
| 3rd newborn | 28 | 28.4 | 18.5 | 29.5 | 3.0 | 98.0 |

The average stay of newborns in the high-risk nursery varied from three to 140 days for the first newborn; three to 95 days for the second and three to 98 days for the third.

Early neonatal death occurred in seven cases (2.7%) and late neonatal death occurred in three (1.5%).

## DISCUSSION

Limitations of the results in this study stem from the low establishment of causal relations and prognostics, a characteristic of cross-section outlines. However, the results present implications for nursing practice because they expose maternal complications and neonatal occurrences associated with these pregnancies in a specialized center, thus making the need for improving knowledge evident, as well as qualifying obstetric nursing care in the field of assisted reproduction in order to treat these complications in non-specialized centers.

For *Red Latinoamericana de Reproducción Assistida*[7], the age of the infertile woman is one of the most important variables, because female fertility starts to decrease at age 30, decreasing more markedly at age 35 and practically disappears at age 45. This is present in the findings of this study, with the predominance of women aged 33 or older.

Female age also influences the results of all forms of infertility treatment[16]. Women postpone pregnancy towards the fourth or fifth decade of their life in order to prioritize their career, seeking financial stability and a stable partner[9,17]. Marital stability was observed in this study, since 95.4% of the women were married.

Regarding maternal complications presented by 90.9% of the studied population, it is known that multiple pregnancies bring maternal risks that are at least twice as high, including iron-deficiency anemia, hydramnions, hypertension, premature delivery, uterine atony and hemorrhage, preeclampsia and cesarean delivery[18]. The results show that preeclampsia and iron-deficiency anemia were observed in 12.2% of the cases, and olygoamnion in 8.4%.

A 10-year study performed at the Department of Gynecology and Obstetrics of the Los Andes Clinic in Chile, started in 1995 with multiple pregnancy patients as a result of assisted reproduction techniques, reported that the most frequent pathologies were threatened abortions, early labor, premature amniorrhexis, intra-uterine growth restriction (IUGR) and anemia. There were 30% of patients with triple pregnancies and 75% of patients with quadruple gestations who required parenteral tocolysis at some point during their gestation. IUGR was detected in 25% of the cases in at least one of the twins[19].

In the study of spontaneous trigemelary pregnancies and their maternal and perinatal complications, authors note early labor as the main reason for hospitalization and describe uterine hyperdistention as a triggering factor for premature contractions, and anemia and urinary infections as contributing factors[18].

Long maternal hospitalizations are frequent due to the aforementioned complications, and the demand for specialized nursing care is fundamental for the optimal outcome of said patients. Gemelary pregnancies promote frequent cervical changes, and the early detection of uterine contractions, which allows for the intervention in early labor threats with hospitalization, rest, hydration, tocolytic therapy and pulmonary maturation induction[17].

Early labor is worth noting among the maternal complications found in this study. This information is especially important due to its secondary implications, such as prematurity and other associated neonatal occurrences, which are described next.

In the four assisted reproduction techniques analyzed, we found high rates (74.3%) of respiratory diseases present in *in vitro* fertilization (IFV) cases. The most common pathologies were wet lung syndrome and acute respiratory distress. A similar result was obtained by another author who studied the result of neonatal characteristics among twins of both genders when compared with single pregnancies, observing respiratory diseases in 84% of the gemelary fetuses and in 78.0% of the single fetuses born after 24 weeks[18].

Metabolic disorders were also significant in IVF and ovarian stimulation fetuses, representing 13% and 8.5%, respectively. The disorders found most often were hyponatremia and hyperkalemia.

Hematologic diseases were observed in 25 IVF fetuses, and neurologic disorders in 16 fetuses. Of these, anemia was the highest category for this complication (hematologic disease), and intraventricular hemorrhage was very representative in the neurological complication index.

Infectious diseases were observed in 21 IVF fetuses. Early or late sepsis and fungal infections contributed to this number.

Assisted reproduction techniques seem to influence the neonatal results by generating multiple fetuses, although

we cannot conclude whether the type of technique used influences that result. Early labor was the main maternal complication, having prematurity and low weight at birth as its consequences.

Respiratory diseases were the most frequent complications observed in all neonatal complications, followed by jaundice, metabolic disorders, infectious and neurologic diseases.

The model of immediate care for newborns from pregnancies due to assisted reproduction techniques is interventionist, but, in view of the conditions of the newborn, this is an attempt to provide first care within the maternal visual field and facilitate early contact, which is important for promoting bonding between mother and child[20].

In this research, it was verified that, in spite of neonatal occurrences due to multiple pregnancies, most babies (96.1%) were discharged from the hospital. However, the objective of the research was not to quantify or qualify the amount of secondary complications regarding the existing prematurity.

## CONCLUSION

The predominant maternal complications were: early labor (65.5%) and premature amniorrhexis (42%). The most frequent neonatal occurrences were respiratory diseases (65.1%), jaundice (38.4%), metabolic disorders (13%) and neurologic diseases (9.0%).

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