

## Prematurity in pregnancies resulting from in vitro fertilization

*Prematuridad en embarazos resultantes de fertilización in vitro*

*Prematuridade em gestações resultantes de fertilização in vitro*

### Abstract

A quantitative, descriptive, retrospective and documentary study is presented to assess the rate of premature births in pregnancies resulting from in vitro fertilization, using the Cryolife program for data collection, which is the program used by the clinic present in the research, for storage of patients' electronic medical records. The study was carried out in a human reproduction clinic in northern Paraná, where we established criteria to identify the index and possible causes of premature births in women with a prevalence of age from 34 to 38 years old who became pregnant through in vitro fertilization among the years 2015 and 2019, using the fresh embryo transfer technique or embryo thaw. It was obtained that in this period 156 babies were born, 59.61% were male, 64.1% were single gestation, 23% were born less than 37 weeks old and 33.3% were born weighing less than 2500 g. And relating to single and twin pregnancies, it was found that 50% of premature babies and 71.15% of babies born with low weight were twins. It is concluded that the rate of premature births in IVF is high, however there was a predominance of single pregnancies during the human reproduction process in the 4 years evaluated.

**Descriptors:** Infertility; Reproductive Technology; High-Risk Pregnancy.

### Resumén

Se presenta un estudio cuantitativo, descriptivo, retrospectivo y documental para evaluar la tasa de partos prematuros en embarazos resultantes de la fecundación in vitro, utilizando el programa Cryolife para la recolección de datos, que es el programa utilizado por la clínica presente en la investigación, para almacenamiento de registros médicos electrónicos de los pacientes. El estudio se llevó a cabo en una clínica de reproducción humana en el norte de Paraná, donde se establecieron criterios para identificar el índice y posibles causas de partos prematuros en mujeres con una prevalencia de edad de 34 a 38 años que quedaron embarazadas por fecundación in vitro entre los años 2015 y 2019, utilizando la técnica de transferencia de embriones frescos o descongelación de embriones. Se obtuvo que en este período nacieron 156 bebés, el 59,61% eran varones, el 64,1% gestación única, el 23% nacieron con menos de 37 semanas y el 33,3% nacieron con un peso inferior a 2500 g. Y en relación con los embarazos individuales y gemelares, se encontró que el 50% de los bebés prematuros y el 71,15% de los bebés nacidos con bajo peso eran gemelos. Se concluye que la tasa de partos prematuros en FIV es realmente alta, sin embargo hubo un predominio de embarazos únicos durante el proceso de reproducción humana en los 4 años evaluados.

**Descritores:** Esterilidad; Tecnología Reproductiva; Embarazo de Alto Riesgo.

### Resumo

Apresenta-se um estudo quantitativo, descritivo, retrospectivo e documental para avaliação do índice de partos prematuros em gestações resultantes de fertilização *in vitro*, mediante a utilização do programa *Cryolife* para coleta de dados, sendo este o programa utilizado pela clínica presente na pesquisa, para armazenamento dos prontuários eletrônicos das pacientes. O estudo foi realizado em uma clínica de reprodução humana do norte do Paraná, onde estabelecemos critérios para identificar o índice e possíveis causas dos partos prematuros em mulheres com a prevalência de idade de 34 a 38 anos que engravidaram por meio da fertilização *in vitro* entre os anos de 2015 e 2019, utilizando a técnica de transferência de embrião a fresco ou descongelamento de embrião. Obteve-se que neste período nasceram 156 bebês, 59,61% eram do sexo masculino, 64,1% eram de gestação única, 23% nasceram de menos de 37 semanas e 33,3% nasceram com peso inferior 2500 g. E relacionando com gestações únicas e gemelares, obteve-se que 50% dos prematuros e 71,15% dos bebês que nasceram com baixo peso eram gêmeos. Conclui-se que o índice de partos prematuro na fertilização *in vitro* é realmente elevado, contudo houve a predominância de gestações únicas durante do processo de reprodução humana nos 4 anos avaliados.

**Descritores:** Infertilidade; Tecnologia Reprodutiva; Gravidez de Alto Risco.

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## Introduction

The ability to generate a descendant for humans is much more than just the continuation of the species and can be considered an important desire for adult individuals. Most couples dream of having a child, but not all of them are able to achieve a natural pregnancy, and couples who are unable to spontaneously generate this child, due to infertility, need treatments to resolve this situation.

Infertility is characterized by the impossibility of a couple who has regular sexual intercourse, without using any contraceptive method for a period greater than or equal to one year, to maintain a pregnancy<sup>1</sup>.

Also, the World Health Organization (WHO) says that infertility affects 50 to 80 million people worldwide and, in Brazil, about 8 million people can be infertile. And, even with such high numbers, the subject is still a gap in the field of current research, because little is discussed about it<sup>2</sup>.

Infertility must be considered as a Public Health problem, since being healthy is not just the absence of disease, but a complete physical, mental, social, and spiritual well-being. Emotional changes, such as anxiety, depression, anger, discord, and personal devaluation, are associated with infertility processes, which leads to an impairment of the individual's health conditions and is causally related to the impairment of harmony in the couple's relationship, once which may be associated with decreased libido, sexual intercourse and erectile dysfunction<sup>1,3</sup>.

The Unified Health System (SUS), facing the demands related to the situation of infertility, still faces barriers and many challenges for coping and greater resolution of cases, because in vitro fertilization (IVF) or artificial insemination, treatment recommended in some cases specific, is not yet widely disseminated and accessible to all. The solution found by these couples is the search for treatment linked to the private network, which places a financial burden on the family due to the high costs of these procedures<sup>1,3</sup>.

The causes of infertility are diverse and can be considered multifactorial. In females, difficulties can occur for different reasons, such as changes in the fallopian tubes, ovulatory dysfunctions, endometriosis. In males, they are related to the alteration of seminal parameters or to the obstruction of the ejaculatory ducts. Although different aspects make it difficult to maintain pregnancy, one of the most important factors in fertility and treatments for assisted reproduction is the woman's age<sup>4</sup>. Defects in the late stages of antral follicular development are believed to exist in women over the age of 40, as they present changes in the process of follicular formation, growth, and maturation, characterized by the ovulation of a follicle that has a smaller diameter, impairing the chances of successful fertilization<sup>5,6</sup>.

The Brazilian Society for Human Reproduction (SBRH) conceptualizes assisted reproduction as the "set of techniques in which a multidisciplinary team has a close participation in monitoring follicular development, detecting and inducing ovular posture, facilitating it and holding gametes, as well as in the luteal phase optimization"<sup>7</sup>.

However, associated with reproduction techniques and which highlights the need for the present study is prematurity (birth with gestational age less than 37 weeks and / or birth weight below 2,500 gr). The early birth of children is one of the most important determinants of infant mortality in children under one year of age in Brazil, which, according to IBGE, presents the index of 12.4 (2018) and 12.8 (2017) each thousand live births<sup>9</sup>.

The participation of health professionals with technical capacity and skill is essential for a favorable outcome of the fertilization technique. The nurse, as an active member of the team, performs all the monitoring, mainly in family counseling.

The approach is carried out through an intensive interview that takes place in the initial phase of treatment, including anamnesis and physical evaluation concomitantly with the guidelines to address the couple's possible doubts.

Infertility rates are constantly growing, about 2 million new couples annually seek access to treat this problem during their reproductive life<sup>7</sup>. This, associated with the scarcity of information on the subject and the high rates of prematurity related to human reproduction techniques, justifies the present research, both for population empowerment about the weaknesses, potentialities of the method, as well as for guidance and updating of health professionals.

In view of the above, the objective of this study is to evaluate the rates of prematurity in women who have undergone in vitro fertilization with embryo transferred fresh or after thawing embryo.

## Methodology

Quantitative, descriptive, retrospective and documentary study, since the data were collected in a single time interval, in which the percentage of premature births in women who underwent in vitro fertilization was analyzed.

The present study was carried out in a human reproduction clinic in northern Paraná, founded in 2000, which has a medical team formed by a urologist specialized in male infertility, a geneticist, a gynecologist specialized in fetal medicine, nurses, and biomedical doctors responsible for the fertilization.

Data collection was performed using a closed instrument. The basis for collection was electronic medical records of women who underwent the in vitro fertilization procedure.

The inclusion criteria were age over 18, and women who became pregnant between 2014 and 2019. The data were included in the Criolyfe program and were analyzed between the months of March and April 2020.

The results were organized and tabulated in an electronic spreadsheet prepared by the researchers in the Microsoft Excel 2016 software. And analyzed using descriptive statistics by absolute and relative frequency.

The present study respected all ethical precepts, with referral to the Standing Committee on Ethics in



Research with Human Beings, under No. CAAE 28985120.5.0000.5539 and Opinion No. 3,850,628 and authorization from the site, with signature of the term of risk and confidentiality. With respect to confidentiality, the names of the participants, as well as any information about their identity will not be revealed.

## Results and Discussion

A total of 128 women were obtained, with a prevalence of age from 34 to 38 years, representing 53.9%. As a result of the treatment, 156 babies were born, of which 59.61% were male, 64.1% came from a single pregnancy, as shown in Table 1.

**Table 1.** Characterization of the profile of women who underwent IVF treatment and of babies born. Maringá, PR, Brazil, 2015-2019

Variables	Absolute Frequency (AF)	Relative Frequency (RF)%
<b>Age</b>		
24-26	2	1,56
27-29	16	12,5
30-32	24	18,75
33-35	37	28,90
36-38	32	25
39-41	14	10,93
42-44	2	1,56
>=45	1	0,78
<b>Babies sex</b>		
Feminine	63	40,38
Male	93	59,61
<b>Gestation</b>		
Only	100	64,10
Twin	28	35,9

A human reproduction laboratory at HC / UFG, in Goiânia / Goiás, carried out, in 2016, a survey revealing information on 278 cycles of women who underwent IVF, ICSI and IIU techniques as a treatment for infertility, and obtained as conclusion that the woman's age is a risk factor for infertility from the age of 40, due to changes in the process of follicular formation, growth and maturation<sup>5</sup>. However, in the present study there is a prevalence of women aged up to 35 years, which reduces the possible changes in antral follicles and complications in pregnancy or birth of the baby.

Contradicting the data found in the present study, an analysis of 439 IVF procedures, performed at the Human Reproduction Center of Hospital Israelita Albert Einstein from January 1995 to December 2003, observed that the IVF success rate varied between 25% and 30% and the rate of multiple pregnancies in that period was 31.1%<sup>10</sup>, while the rate of multiple pregnancies in natural conception is approximately 1%; associated with these data, there are the highest incidences of prematurity<sup>10,11</sup>.

Multiple pregnancies are associated with the transfer of two or more embryos to the maternal uterus, a method used to increase the success of fertilization, leading to a higher rate of twin pregnancies and their serious maternal and perinatal repercussions. Thus, there is a need for the choice of the number of embryos to be transferred

to be made responsibly, always evaluating the woman's age and the quality of these embryos<sup>11</sup>. In addition, in Brazil, Resolution of the Federal Council of Medicine No. 1,358 / 92 states that the number of embryos to be transplanted cannot exceed four to increase the existing risks of multiparity<sup>12</sup>.

Nos dados obtidos em relação ao índice de prematurity in pregnancies resulting from IVF shown in Table 2, it is evident that in 2015 40 babies were born. Of these, 25% were born less than 37 weeks old, 40% were born weighing less than 2500 g. However, in 2016, 33 babies were born; of these, 12% were born less than 37 weeks old, 21% were born weighing less than 2500 g.

The year 2017 was equivalent to the birth of 42 babies. Of these, 23% were born at less than 37 weeks, 30% weighing less than 2500 g. It is noted that premature births and low weight remained basically at the index that in the previous year, with an increase of little relevance. However, in 2018, 37 babies were born; of these, 32.4% were born at less than 37 weeks, 43.2% weighing less than 2500 g. We observed that this was the year with the highest rate of prematurity and low weight, even though it was among the years with the fewest births. In 2019 there were only four births, and a limiting factor this year is the return with neonatal and clinical information by mothers, which has not yet happened.



**Table 2.** Characterization of the prematurity index in pregnancies resulting from in vitro fertilization. Maringá, PR, Brazil, 2015-2019

IVF prematurity index	Absolute Frequency (AF)	Relative Frequency (RF)%
<b>2015</b>		
<37 weeks	10	25
<2500 g	16	40
<b>2016</b>		
<37 weeks	4	12,12
<2500 g	7	21,21
<b>2017</b>		
<37 weeks	10	23,80
<2500 g	13	30,95
<b>2018</b>		
<37 weeks	12	32,43
<2500 g	16	43,24
<b>2019</b>		
<37 weeks	0	0
<2500 g	0	0
<b>2015-2019</b>		
<37 weeks	36	23,07
<2500 g	52	33,33

From the data presented, it is evident that the rate of prematurity in fertilization, from 2015 to 2019, was 23%. In addition to prematurity, 33.3% of babies were born with low weight. Considering the research by the Oswaldo Cruz Foundation "Born in Brazil: National Survey on Childbirth and Birth", 2014, which points Brazil as the 10th country in the world prematurity ranking, reaching the proportion of 11.3% of births premature births in natural pregnancies in our country, we can consider 23% a high rate of prematurity in IVF, more than double, compared with the rate of premature births in Brazil<sup>13</sup>.

Infants conceived by IVF are significantly more likely than other newborns to experience neonatal complications, involving genetic issues and the effects of multiple pregnancies, especially in higher degrees of multiples (equal to or greater than four). In the 18-year comparative study, which includes all newborns conceived in assisted reproductive therapies and admitted between 1998 and 2015 to the neonatal intensive care unit at the military hospital in Tunis, the risk of premature birth was statistically higher in pregnancies resulting from IVF, both in twin

pregnancies and in single pregnancies, presenting a risk index of premature delivery three times higher than the other newborns<sup>14</sup>.

A study carried out with 123 premature newborns, in a hospital in the southern region of Brazil, observed the occurrence of at least one health problem in 96.7% of premature infants, conditions ranging from vomiting due to gastric reflux, to severe pneumonia<sup>15</sup>. With this, it shows the extreme importance of guiding couples who undergo IVF on the risks of premature birth, so that they prepare themselves emotionally. And the health professionals who provide care to these couples need to be aware of the risks, to provide efficient assistance and care and to avoid the premature delivery of this child as much as possible.

The high rate of newborns with low weight in IVF occurs due to premature births, as the last trimester of pregnancy is equivalent to fetal weight gain. Thus, a premature birth is related to low birth weight, as seen in Table 3, which reveals that, between the years 2015 to 2019, of the 36 premature births, 50% were twins; and of the 52 babies born with low weight, 71.15% were twins.

**Table 3.** Characterization of the prematurity index in twin pregnancies. Maringá, PR, Brazil, 2015-2019

Twin pregnancy vs. prematurity	Absolute Frequency (AF)	Relative Frequency (RF)%
<b>2015-2019</b>		



Twins born below 37 weeks	18	50
Total babies born less than 37 weeks	36	100
<b>2015-2019</b>		
Twins who were born weighing less than 2,500 kg	37	71,15
Total babies born weighing less than 2,500 kg	52	100

The prematurity index in twin pregnancies, in a Maternal and Child Center in the North, was evaluated in the years 2015 and 2016. The survey showed that 67.35% of women had their birth before 37 weeks of gestation, however, it was also found that 31.25% of women who went into labor between 34 and 35 weeks had comorbidities related to smoking, and about 59% of these were nulliparous. In addition, the study states that prematurity can be attributed to twin pregnancies, but also to maternal, fetal, and placental complications during pregnancy, which can become an indication for childbirth<sup>16</sup>. The data presented corroborate with the present study, in which not all multiple pregnancies obtained premature outcomes, thus, it is important to emphasize the need for an efficient prenatal monitoring, which assesses gestational risks according to personal and family history.

A bibliographic survey carried out from 2004 to 2018, related to the main complications found in twin pregnancies, revealed that 60.35% (59,026 newborns) of twins were born with low weight and, of these, 0.7% were born with less than 500 g<sup>17</sup>. Low birth weight below 2500 g can be found in term births and single pregnancies, however,

the rates are still surprisingly higher in multiple pregnancies, which provides the need for a different look at the health of these children, to specially to avoid neonatal complications, such as pneumonia related to impaired lung maturation.

Based on these data, we can consider that in IVF, in addition to the high rate of prematurity, the high rate of babies born with low weight stands out. And, in this case, the number of twin pregnancies can be considered the main cause of these births, since most babies born weighing less than 2500 g are twins.

### Final Considerations

Based on this research, it is possible to conclude that the age with the highest prevalence of demand for performing human reproduction techniques is 33 to 35 years old, which shows the wait for the progressive reduction of the woman's physiological fertility. In the association between IVF and prematurity and multiple pregnancies, a relationship was found only with early births and low birth weight, especially in 2018.

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