Genetic Disorders that can cause a Miscarriage

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Abstract. Objective: Analyse the chromosomal and genetic anomalies that can cause a spontaneous abortion and their effects on the fetus. **Methodology:** Review of basic concepts to improve understanding of the subject in question and carrying out electronic searches on scientific platforms and journals. **Results:** Around 50% to 70% of spontaneous miscarriages occur because of chromosomal and genetic anomalies, especially those that result in excess genetic material, such as trisomy. **Conclusion:** Factors such as parental age and history of many miscarriages contribute to chromosomal and genetic anomalies, including trisomy, where excess genetic material ends up influencing spontaneous abortion, but there is still much to be researched and discovered.

Keywords. Genetics, miscarriage, chromosomes

1. Introduction

A spontaneous abortin or involuntary interruption of pregnancy is defined as the death of the fetus or embryo before it has the ability to survive outside the mother`s uterus, and can occur up to 12 to 20 weeks of gestation.

In Brazil, the rate of spontaneous abortion or pregnancy loss is between 10% and 15%, however this value is highly underestimated, since in many cases of early spontaneous abortion, the mother is not even aware of her pregnancy, interpreting what happened only such as a delay in your menstruation, followed by a large flow of blood, which is very unlikely to be reported to the doctor, seen normally.

A miscarriage can occur for several reasons, many zygotes, blastocysts and morulas espontaneously abort, with the implantation of the blastocysts in the uterus being a critical moment of development that can fail, usually caused by inadequate production of progesterone and estrogen.

Another reasons for miscarriage would be the malformation in the anatomy of the mother`s uterus, which could be a bicornuate, unicornuate, didelphic, septade or retroverted uterus. However one of the main reasons for a miscarriage is chromosomal and genetic anomaly.

2. Chromosomal Abmormalities

Chromosomes are found in the nucleus of cells and contain the genetic material of a living being. Each healthy diploid cell has 23 pairs of chromosomes, totaling 46 chromosomes, including the sex chromosomes. The chromosomal anomalies generally occur during cell division, in the process of meiosis, the cell division responsible for the formation of gametes. Nondisjunction is when there is an incorrect distribution in the gametes, caused by erros during the separation of chromosomes.

2.1 Aneuploidies

One of the types of chromosomal anomalies is classified as numerical chromosomal anomalies, also called aneuploidies, where there are changes in the usual number of chromosomes. These anomalies can be Polyploidies when there is an increase in the total number os chromosomes. There are also Haploidies or Monoploidies, where there is a decrease in the total number of chromosomes.

2.2 Structural Chromosomal Anomaly

Another types of anomalies are structural chromosomal anomalies, where changes occur in the structures of chromosomes, with the following names, according to the affected chromosomal structure.

- **Deletion:** When part of the chromosome is lost.
- **Duplication:** When there is a part of the chromosome is duplicated.
- **Inversion:** When a segment of a chromosome is inverted.
- **Translocation:** When parts of a chromosome are rearranged, which can be Reciprocal or Robertsonian.

- **Chromosomal Iso:** When a chromosome has two short arms or two long arms, because of an abnormal division of the centromere

3. Methodology

The research was carried out by reviewing basic concepts to better understand the subject in question and carrying out eletronic searches on platforms such as Google Scholar, Scielo and PubMed, as well as reading the subject in the journal Nature.

To form a consistent basis for the research, the following criteria were selected: searching for articles published between 2015 and 2023 to ensure more up-to-date information. Other criteria were the titles and abstracts with a greater focus on the interaction between spontaneous abortion and chromosomal and genetic abnormalities, also with English and Portuguese language requirement.

4. Results

The research reported a series of data, showing the relationships between chromosomal and genetic anomalies and spontaneous abortions. In this way, the data was organized chronologically according to the publication dates of the articles, so that the evolution of research and the acquisition of new data over time can also be observed.

4.1 Definition of Miscarriage

The first article written by Ibrahim A. Abdelazim presents the definition of a spontaneous abortion and its main causes, including the chromosomal abnormalities listed below.

Approximately 50-60% of early spontaneous miscarriages associated with aneuploidy, especially autosomal trisomy. In couples with RM, increases with advancing maternal age.

4.2 Trisomy

The following article, written by Alessandra Bernadete Trovó de Marqui, presents more specific information regarding chromosomal abnormalities and spontaneous abortion, mainly the numerical anomalies listed below:

The main results of the couples with recurrent miscarriage were: the frequency of chromosomal abnormalities which varied from 1.23% to 12% and there was a predominance alteration of the chromosomal structures (reciprocal translocations, followed by Robertsonian). In products of conception, the results observed were: the frequency of chromosomal abnormality was above 50% in approximately 70% of the studies; there was a predominance alteration of the numerical chromosomal (trisomy - chromosomes 16, 18, 21 and 22, followed by polyploidy and monosomy X).

Below we have descriptions of some of the chromosomal anomalies mentioned above.

- **Trisomy 16**

The cases in which babies are born are considered very rare, considering that trisomy 16 is a frequent cause of miscarriages during the first trimester.

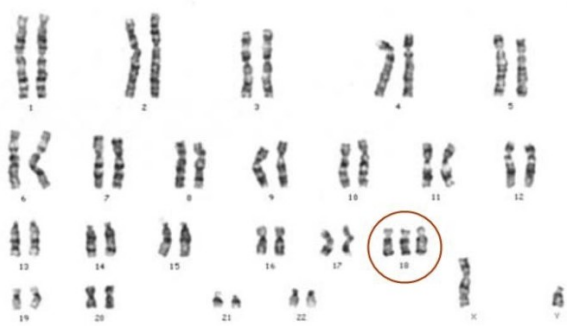

Fig. 1 – Edwards Sindrome, Trisomy – 18

Trisomy 18 is the second most common trisomy and often results in miscarriages. The baby presents abnormalities such as intrauterine growth restriction, typical craniofacial characteristics, overlapping fingers, congenital heart defects, externally turned feet and a protruding heel.

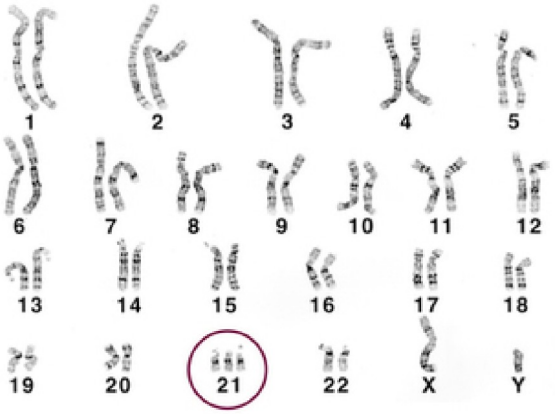

Fig. 2 – Downs Sindrome, Trisomy – 21

Trisomy 21 is a very common and frequent syndrome that ends in a spontaneous abortion most of the time. In cases where the baby is born, he presents delays in his cognitive and intellectual development and physical characteristics such as: rounded face, small ears, small and flat nose, eyes with an ascending line, muscular flaccidity, single palm crease and short, thick neck. Another characteristic is the high risk of developing heart and gastrointestinal tract malformations, hearing and vision problems, thyroid changes and diabetes.

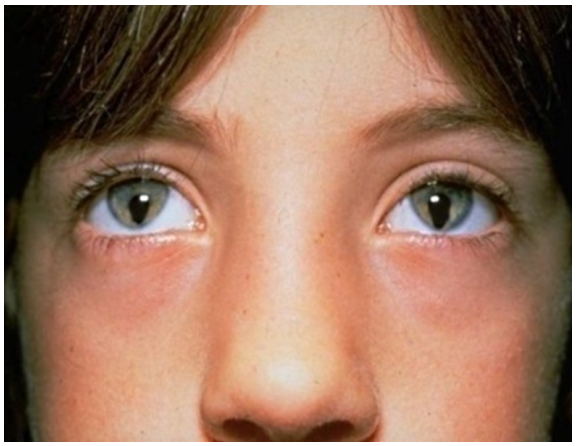

Fig. 3 – Schmid-fraccaro Sindrome, Trisomy – 22

Also known as cat's eye syndrome, trisomy 22 is considered a rare syndrome, characterized by changes in the appearance of the eyes, with defects in the epidermis, anus and ears, but can also present cardiac and renal malformations.

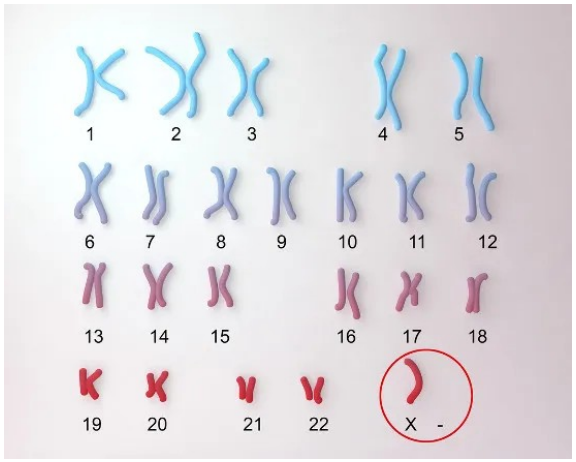

Fig. 4 – Turner Sindrome, Monosomy – X

Turner syndrome is characterized by monosomy of the X chromosome, with the absence of a second sex chromosome in women. The physical characteristics caused by the syndrome include short stature, cardiac malformations and widely separated nipples. We also have the presence of infertility, late puberty, sometimes the absence of menstruation and learning difficulties.

- **Recurrent miscarriages**

Another important fact is that these chromosomal anomalies become more frequent in couples with a history of a greater number of miscarriages, as we can see:

Another study showed that chromosomal abnormalities were found in 5% of couples with a history of two miscarriages, in 10.3% with three miscarriages, and in 14.3% with four or more miscarriages.

4.3 Genetic Variations

In the article written by Silvia Buonaiuto, published in Nature magazine in 2022, with the observation that chromosomal anomalies are the cause of 50% to 70% of pregnancy losses, there are also cases of spontaneous abortions in healthy women, having embryos chromosomally healthy. In this way, genetic alterations in the STAG2 and TLE4 genes were investigated, as they have a greater risk of early spontaneous abortion.

The analyzes showed that the STAG2 gene, responsible for encoding the subunit of the cohesion complex, was lethal in mice when inactivated. The TLE4 gene physically interacts with a region of chromosome 9, related to spontaneous abortions, especially if this interaction suffers from an anomaly, resulting in trisomy of chromosome 9, considered a frequent cause of miscarriage.

4.4 2023

The latest article written by Pedro Melo, Ph.D has more up-to-date and specific information regarding chromosomal abnormalities and spontaneous miscarriages as we can see below:

Chromosomal abnormalities are diagnosed in over 50% of first-trimester miscarriages, becoming less prevalent in second- and third-trimester losses. On karyotyping, most chromosomal abnormalities are numerical (termed aneuploidy, usually because of chromosomal nondisjunction during meiosis), including autosomal trisomies (30%– 60%), triploidy (11%–13%), monosomy X (10%–15%), and tetraploidy (9%), whereas only a minority result from structural chromosome rearrangements (2%–6%) and mosaicism (8%).

The article also makes an important observation, showing that there is a shortage of research into specific genetic variations that can also stimulate spontaneous abortion:

Although chromosomal imbalances are a well-documented cause of miscarriage, there is a paucity of data on specific parental and fetal gene mutations that may increase the risk of pregnancy loss. In 2017, a systematic review of 428 case-control studies identified an association between unexplained recurrent miscarriage and 21 variants in parental genes involved in immune response, coagulation, metabolism, and angiogenesis, although the evidence was mostly of low certainty

Another fact covered in the article is the impact of parental age on the emergence of chromosomal abnormalities.

Female age is by far the strongest risk factor for miscarriage, with the probability of pregnancy loss being highest at the extremes of women's reproductive lives (i.e., <20 years and R40 years).

The effect of paternal age on the risk of miscarriage appears to increase with time, and male partners

aged R40 years exhibit on average 69% higher odds of miscarriage compared with those aged 20–29 years.

5. Conclusion

Due to the facts mentioned, spontaneous abortion can occur for a variety of reasons, but chromosomal and genetic anomalies have a relevant influence, showing that factors such as older parental age and a history of many recurrent spontaneous abortions contribute to genetic imbalance. and chromosomal. The chromosomal abnormalities that most contribute to spontaneous abortion are numerous, mainly trisomy, where there is an excess of genetic material in cells.

There are also cases where the couple and the fetus are chromosomally healthy, but changes in specific genes contributed to the spontaneous abortion. When related to spontaneous abortions, research has a greater focus on chromosomal changes, while genetic anomalies have a scarcity of research, showing that there is still much to be researched and discovered.

6. References

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