

# Early Miscarriage: Morphological Data Useful to Clinical and Nosographic Classification

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## ABSTRACT

The most frequent complication of the pregnancy is miscarriage. One in five pregnancies ends in miscarriage and the risk of recurrence increases with the increase of previous spontaneous abortions. In the present article an original checklist is shown to classify the causes of abortion based on morphological criteria that can be highlighted on abortive tissue. These histopathological elements are useful in distinguishing fetal from maternal causes of spontaneous abortions and those are used for a nosographic classification.

**Keywords:** causes of miscarriage; early miscarriage; nosographic classification; spontaneous abortion.

## 1. INTRODUCTION

Pregnancy is represented by complicated biological events that follow each other. When this subtle regulation does not happen, the probability of success of a pregnancy decreases. The most frequent complication of the pregnancy is miscarriage [Regan et al., 2000]. Miscarriage is the spontaneous fetal death before 25<sup>th</sup> week, that it's not caused by external interventions. The miscarriage is particularly defined; it's pre-embryonic miscarriage if it happens before 5<sup>th</sup> week of pregnancy, it's embryonic miscarriage if it happens between 6<sup>th</sup> and 9<sup>th</sup> week and it's fetal miscarriage if it happens between 10<sup>th</sup> and 25<sup>th</sup> week.

Miscarriages can be sporadic, repeated, recurring.

When the spontaneous abortion occurs only one time in all reproductive life of a woman, it's a sporadic miscarriage. If it occurs twice, the second abortion is defined as a repeated miscarriage and, finally, recurring miscarriage can be defined three or more events of fetal or embryonic intrauterine spontaneous death in the same woman.

The most susceptible period of miscarriage is represented by first trimester and in these cases it's early miscarriage.

A mathematical and statistic model has established that about 75% of fertilized eggs end in early miscarriage even before a clinical diagnosis [Roberts et al, 1975], while the remainder 25% of cases are diagnosed during a known pregnancy. Many studies report that about one in five pregnancies (15%-20%) ends in miscarriage including 80% of cases of early miscarriage [Maconochie et al., 2007, American College of Obstetricians, 2015]. In about

half cases of spontaneous abortion, the cause is unknown [Alijotas-Reig et al, 2013].

Many maternal diseases can induce intrauterine fetal death, including endocrine disorders, autoimmune diseases, uterine diseases, infections, nutritional factors and maternal age. Often maternal factors act by determining vascular defects of chorionic plate.

As regards fetal causes of miscarriage, we have identified some histological elements to outline a checklist useful in distinguishing fetal causes of miscarriage, in order to classify abortive events basing on their etiology. Our checklist is structured using ten morphological criteria highlighted on tissue histological examination of the miscarriage material. The examination of these ten histopathological pictures has made possible to distinguish four causes of early miscarriage: chromosomal fetal defects incompatible with life, chromosomal fetal defects potentially compatible with life, maternal vascular pathologies and generic maternal factors.

## 2. MATERIALS AND METHODS

The study has been conducted in the laboratory of surgical pathology, during the period between 1<sup>st</sup> December 2017 and 31<sup>st</sup> August 2018. All cases of specimens from uterine curettage in early demise have been microscopically analyzed through routine hematoxylin and eosin stained slides on formalin fixed and paraffin embedded tissue. 90 cases have been examined in this study. Critical report revision of histological picture has been made by an experienced pathologist in placental and perinatal pathology.

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### 3. CHECKLIST: MORPHOLOGIC DATA USEFUL FOR DETECTING CLINICAL CAUSES OF EARLY MISCARRIAGE

This is the list of microscopic characteristics detected from critical revision of uterine specimens from early miscarriage.

CHECKLIST
A. INDIRECT DATA OF EMBRYONIC'S FORMATIONS (presence of amniotic membrane and/or embryonic nucleated red cells)
B. EMPTY EGG
C1. OEDEMATOUS AND SWOLLEN STROMA <sup>1</sup>
C2. CISTERNS <sup>1</sup>
C3. CONTAINING SYNCITYOTROPHOBLAST <sup>1</sup>
C4. BIZARRE VILLOUS ASPECT <sup>1</sup>
C5. AVASCULAR VILLI <sup>1</sup>
C6. NECROTIC VILLI <sup>1</sup>
C7. TROPHOBLAST HYPERPLASIA <sup>1</sup>
D. NECROTIC AREA OF CHORIONIC PLATE

<sup>1</sup> abnormalities of chorionic villi

### 4. RESULTS

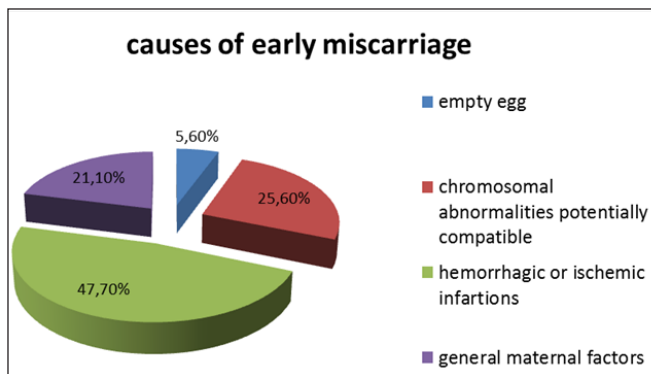
Indirect signs of embryonic presence are represented by evidence of amniotic membrane formation or nucleated red blood cells in vessels of chorionic villi. Empty egg is the final consequence of complex chromosomal abnormalities stopping the embryo formation. These chromosomal deficits are defined as incompatible with life.

In presence of sure embryonic formation, the detection of some abnormalities in chorionic villi results in a clinical picture suspicious for chromosomopathies potentially compatible with life, the most frequent being Down and Turner Syndromes.

At the other end, the presence of necrotic chorionic villi with ischemic area of chorionic plate are caused by vascular maternal factors. Instead, lack of morphological alterations in chorionic plate and villi together with the evidence of the presence of embryonic formation defines a miscarriage that can be attributed to generic maternal factor.

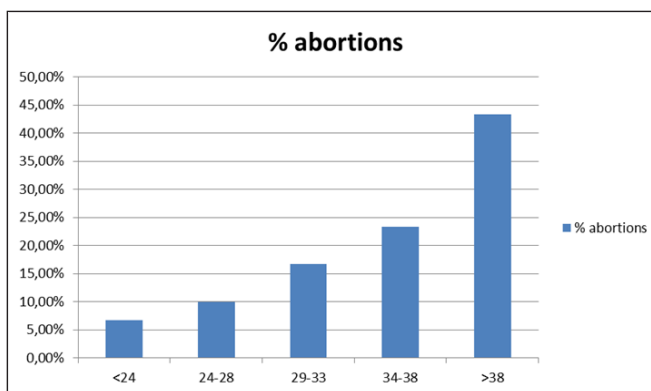
The histological slides concerning 90 cases of early miscarriage have been critically reviewed basing on the microscopic pictures reported in the checklist, with the aim of etiologically classifying the cases in the four recognized classes.

The data obtained report that 47.7% of early miscarriage are due to vascular maternal deficits, 5.6% to chromosomal deficits potentially compatible with life, 25.6% of early intrauterine death can be referred to chromosomal abnormalities incompatible with life and 21.1% of the cases lack morphological anomalies, so they can refer to systemic maternal causes (Graph 1).



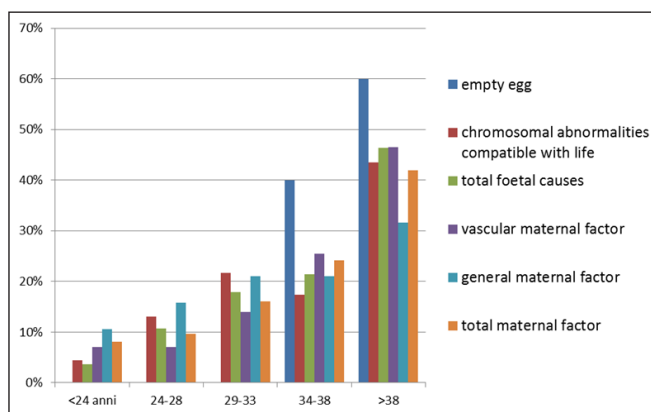
Graph 1: Results of cause of early miscarriage

Subsequently, every case of abortion has been correlated with maternal age and patients were divided in five groups: <24 years (6 cases), 24-28 years (9 cases), 29-33 years (15 cases), 34-38 years (21 cases), >38 years (39 cases) (Graph 2).



Graph 2: Distributions of early miscarriage events on the basis of patients' age

Finally, number of abortions have been correlated with the causes of abortions and maternal age (Graph 3).



Graph 3: correlations between causes of abortion and maternal age

### 5. DISCUSSION

The checklist includes the ten morphological indicators of spontaneous abortion. Most important morphological pictures are pathologic characteristics microscopically detecting.

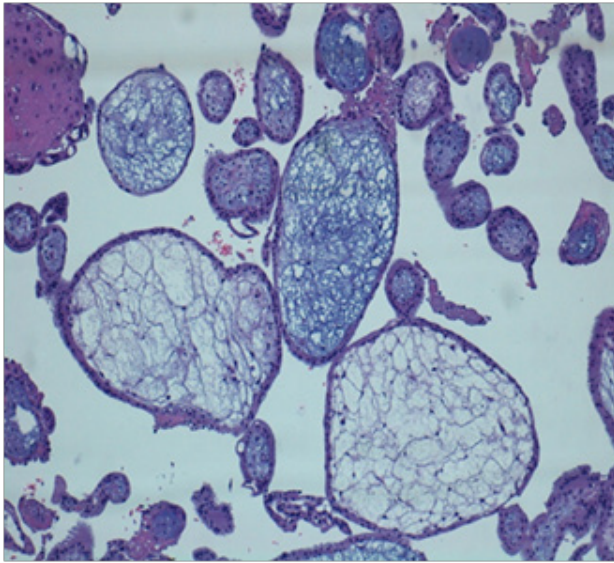


Fig. 1: Chorionic villi with edematous and swollen chorion. [10x]

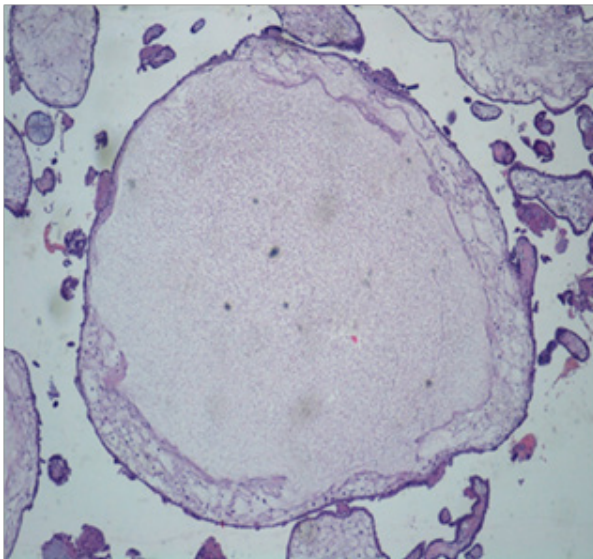


Fig. 2: Cisterns in chorionic villi. [20x]

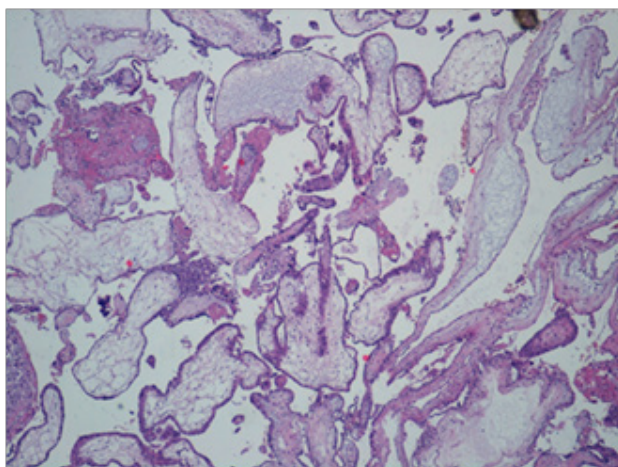


Fig. 3: Chorionic villi with a bizarre form containing syncytiotrophoblast inclusions.[10x]

Figures numbers 1, 2, 3 and 4 present six abnormalities of chorionic villi compatible with chromosomal defects. In case of chromosomopathy compatible with life, amniotic

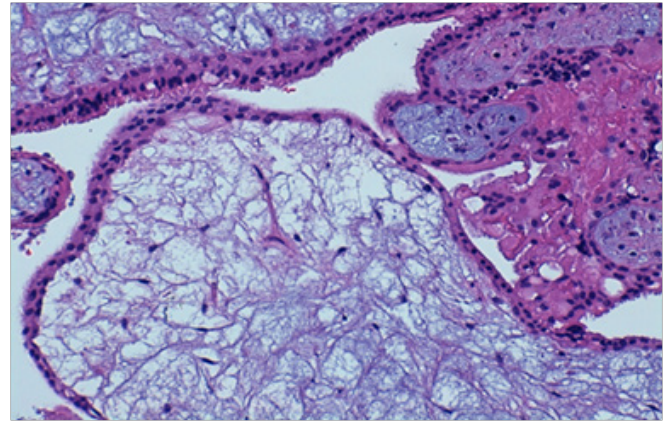


Fig. 4: Avascular villus and trophoblastic hyperplasia. [20x]

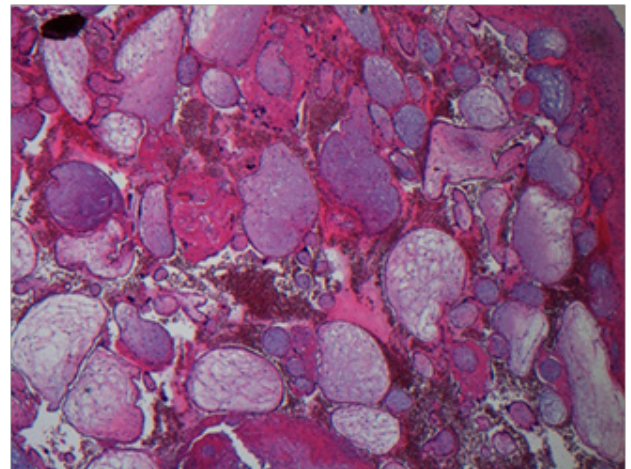


Fig. 5: Necrotic area of chorionic plate and necrotic villi. [10x]

membrane and nucleated red blood cells are detected in the specimen, together with morphological alterations of chorionic villi. In case of chromosomal defects incompatible with life, an empty egg can be supposed, in absence of indirect evidence of embryonic formation.

The figure number 5 presents a typical picture of infarction, that is the most frequent vascular maternal factor responsible of early miscarriage.

Finally, in case of none abnormality picture can be detected on histological specimen, the reason of early miscarriage can be due to general and systemic maternal factor. These cases would require better serological and clinical history.

Even chromosomal deficit has to be referred to fetal causes of early miscarriage, while vascular and systemic factors have to be considered maternal causes of intrauterine death. Fetal causes can be responsible of sporadic abortion and these may not recurs in the next pregnancy. Instead, maternal causes of early miscarriage can potentially recur in next pregnancy of the same woman. Primarily, results in this study point out that the number of abortions increases with advanced maternal age. Subsequently, the study shows that 72% of abortions are due to maternal factors, above all in patients age 34 and over.

Also, 100% of abortions caused by chromosomal deficits incompatible with life are detected in patients age 34 and over, the same age suffering of the most of early miscarriage events (60.9%) due to chromosomal abnormalities potentially compatible with life.

## 6. CONCLUSION

Early miscarriage represents a physically painful and psychologically damaging event for the mother and it is the most common complication of pregnancy.

In the present study, 90 cases of spontaneous abortions have been critically revisited from an expert pathologist. In the same period, 577 pregnancy have been reported to the same hospital, so it has been calculated that 15.6% is the percentage of pregnancy ended as early miscarriage. This percentage of spontaneous abortion of the present study agrees with epidemiologic international reports.

Early miscarriage is a very complex pathology. It isn't totally understood by gynecologists and pathologists because there is a partial knowledge of its etiology. In fact, the scientific literature reports 50% of early miscarriage have an unknown cause.

Also, public opinion of pathologic diagnosis of miscarriages calls it useless. In fact, the most of histopathological diagnosis consists only of a microscopic report of presence of chorionic materials, without a real interpretation of the microscopic picture. In order to make the histopathological diagnosis reliable, reproducible and easily understandable, the checklist reported in the present study can represent an instrument to objectify terminology. Also, a more complete diagnosis is possible by the use of the microscopic checklist, with a more clinical benefit. Then, the etiological classification shows

that 70% of abortions are caused by maternal factors, that would be predictable and preventable.

In particular, incorrect style of life, like as a poor or unbalanced diet and the use of toxic fetal substances adversely affect placental blood flow in all women of childbearing potential. In fact, in the present study, 50% of spontaneous early abortions are due to maternal vascular deficits.

The most important target of our microscopic and diagnostic checklist is the prevention of early miscarriage. In this view, if this proposal diagnostic method is combined with a more careful health policy for women of childbearing potential, the percentage of early miscarriage would be drastically reduced, with a great benefit as for patients and for health cost.

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