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ORIGINAL ARTICLE

Characterization of histopathological changes in pregnancy losses detected in a reference pathological anatomy service

Caracterização das alterações histopatológicas das perdas gestacionais detectadas em um serviço de anatomia patológica de referência

Paula Gouvêa Abrantes[1], Mariana Merçon da Silva Santos[1], Maria Christina Marques Nogueira Castañon[2], Fátima Fernandes Caldoncelli Leite[*3]

ABSTRACT

Introduction: Abortion is the most common obstetric complication, especially in the first trimester of pregnancy. Cytogenetic changes, most commonly trisomy, are described as its leading cause and correlate with advancing maternal age. Anatomical, immunological, and endocrine factors may also be associated with it. **Objectives:** Considering the importance of the information present in histopathological reports of pregnancy losses, the objective is to identify the main morphological alterations and their correlations with abortion recurrence and maternal age. **Methods:** Descriptive observational study in which 526 histopathological reports of pregnancy losses issued between 2016 and 2018 were analyzed in the Pathological Anatomy Service, located in Juiz de Fora - Minas Gerais, identifying the presence of villi and their characteristics, decidua, membranes, umbilical cord, ectopic pregnancy, fetal tissues and signs of chromosomal abnormalities. Furthermore, to observe the correlation of the alterations found by maternal age group. **Results:** The average age was 30.45, ranging from 15 to 55 years old. The main morphological alteration found was "signs of retention" in the chorionic villi, followed by "hydropic villi," "swollen villi," "hydatidiform mole," and "hydropic abortion." Most reports (229) were of 25-36-year-old women. **Conclusion:** The morphological study of pregnancy losses, combined with information such as maternal age and presence of comorbidities, is characterized as an important instrument for etiological elucidation and medical advice aimed at maternal well-being and safety for future pregnancies.

Keywords: Abortion; Histophatology; Maternal age.

[1] Faculdade de Medicina, Universidade Federal de Juiz de Fora, Minas Gerais, Brazil.

[2] Departamento de Morfologia (ICB), Universidade Federal de Juiz de Fora (UFJF), Minas Gerais, Brazil.

[3] Laboratório de Patologia, Hospital Universitário da Universidade Federal de Juiz de Fora (EBSERH), Minas Gerais, Brazil.

Responsible Editor:
Dr. Henrique Vitor Leite
Faculdade de Medicina da Universidade Federal de Minas Gerais.
Belo Horizonte/MG, Brazil.

Corresponding author:
Fátima Fernandes Caldoncelli Leite
Laboratório de Patologia, Hospital Universitário da Universidade Federal de Juiz de Fora (EBSERH), Minas Gerais, Brazil. E-mail: fatimacaldoncellileite@gmail.com

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RESUMO

Introdução: O aborto é a intercorrência obstétrica mais comum, principalmente no primeiro trimestre gestacional. Alterações citogenéticas, mais comumente as trissomias, são descritas como sua causa principal e correlacionam-se com o avanço da idade materna. Fatores anatômicos, imunológicos e endócrinos também podem estar associados. **Objetivo:** Considerando a importância das informações presentes nos laudos histopatológicos das perdas gestacionais, objetivou-se identificar as principais alterações morfológicas e suas correlações com recorrência do aborto e idade materna. **Métodos:** Estudo observacional descritivo no qual foram analisados 526 laudos histopatológicos de perdas gestacionais emitidos entre 2016 e 2018 em Serviço de Anatomia Patológica, localizado em Juiz de Fora, Minas Gerais, identificando a presença de vilosidades e suas características, decídua, membranas, cordão umbilical, gravidez ectópica, tecidos fetais e sinais de anormalidades cromossomiais. E, ainda, a correlação das alterações encontradas por faixa etária materna. **Resultados:** A idade média materna foi de 30.45, variando entre 15 e 55 anos. A principal alteração morfológica encontrada foi "sinais de retenção" nas vilosidades coriônicas, seguido por "vilosidades hidrópicas", "vilosidades edemaciadas", "mola hidatiforme" e "aborto hidrópico". A maioria dos laudos (229) era de mulheres de 26-35 anos. **Conclusão:** O estudo morfológico das perdas gestacionais, aliado às informações como idade materna e presença de comorbidades, caracterizou-se como um importante instrumento para elucidação etiológica e aconselhamento médico, visando ao bem-estar materno e segurança para as gestações futuras.

Palavras-chave: Aborto; Histopatologia; Idade materna.

Introduction

According to the World Health Organization (WHO), abortion is defined as the termination of pregnancy, whether spontaneous or induced, before 20 weeks of gestation or birth weight below 500 grams[1]. It corresponds to the most common complication of pregnancy, and it is estimated that spontaneous abortion occurs in 15%-20% of clinically diagnosed pregnancies[2-4], reaching 30% of pregnancies with a biochemical diagnosis[4]. About 25 to 50% of women of reproductive age will have at least one pregnancy loss[5].

It occurs mainly in the first trimester of pregnancy, usually between eight and 12 weeks, and half are due to chromosomal abnormalities[2,3]. Trisomy, followed by polyploidy and monosomy X, is the most common abnormality, with an increase in frequency with advancing maternal age[6]. About 99% of pregnancies with chromosomal abnormalities progress to miscarriage[3,6].

Anatomical disorders of the uterus, maternal infections, immune disorders, such as Antiphospholipid Antibody Syndrome, corpus luteum insufficiency, and other hormonal changes, may also be related to abortion[2]. However, in about 50% of cases, the cause remains unknown[5].

The hydatidiform mole (HM), an important etiology for pregnancy losses, is a premalignant form of the gestational trophoblastic disease, in which chromosomal changes play an essential role in its development and can be classified as complete (CHM, karyotype 46,XX or 46,XY) or partial (PHM, karyotype 69,XXX or 69,XXY)[7,8]. In Brazil, it is estimated that the hydatidiform mole occurs in 1:200-400 pregnancies, around 5 to 10 times more frequently than in Europe and North America[9].

Microscopically, moles can be identified through three classic findings: villous stroma edema, avascular villi, and nests of proliferating trophoblastic elements surrounding the villi[10,11]. The complete ones have two notable characteristics: 1) trophoblastic proliferation and 2) hydropic villi. Partial moles are reliably diagnosed when three or four main diagnostic criteria are demonstrated: 1) two villi populations; 2) prominent, irregular and dysmorphic villi (with trophoblastic inclusions); 3) villi grown and with cavities (≥3 to 4 mm), and 4) hyperplasia or atypia of the syncytiotrophoblast[12]. Recently, immunostaining for p57

can be used for diagnostic complementation since there is no expression of this protein in the complete moles[9].

A pregnancy that was retained inside the uterus after embryonic or fetal death, defined as a missed abortion, generates signs of retention such as a closed cervix and permanence of *in situ* products of conception. Usually asymptomatic, it may course with colic and bleeding[11].

Fetal hydrops is another relatively rare clinical entity characterized by abnormal accumulation of extravascular fluid and in cavities, which may cause anasarca.[13]It can be classified into two groups: Fetal Immune Hydrops (IHF) — evident in Rh isoimmunization, ABO incompatibility, and other blood complications — and Non-Immune Fetal Hydrops (NIFH) — correlated with several diseases, such as metabolic, cardiac, chromosomal, infectious, lymphatic, intestinal and pulmonary alterations, corresponding to 90% of cases[14,15].

Pregnancies external to the endometrial cavity, usually in the fallopian tube, characterize an ectopic pregnancy, occurring approximately in 11 out of 1,000 pregnancies[16]. Its incidence can be explained by the higher prevalence of sexually transmitted diseases, diagnostic tools with greater sensitivity, tubal role in fertility, delayed pregnancy and use of assisted reproduction technology, as well as increased use of the intrauterine device (IUD) and tubal sterilization[17].

The absence of identifiable embryonic elements indicates an anembryonic abortion, corresponding to approximately half of the pregnancy losses in the first trimester. Therefore, the rest are embryonic abortions and can be divided into those with chromosomal abnormalities (aneuploid abortions) and those with a normal chromosomal complement (euploid abortions)[1].

Chorioamnionitis, the inflammation of amniotic membranes, is associated with the infection of the amniotic fluid by microorganisms that ascend the birth canal to the uterine cavity. Morphologically characterized by an acute inflammatory infiltrate of neutrophils[18]. The contribution of infections to sporadic abortion is believed to be low, but the use of molecular evidence for viral or bacterial DNA in tissues from abortion suggests that infections have been underestimated[19].

Some authors claim that umbilical cord abnormalities are a significant cause of spontaneous miscarriage. Umbilical cord inflammation, called funisitis, represents a fetal response to amniotic fluid infection[18].

According to the Royal College of Obstetricians and Gynaecologists (RCOG), 3 or more successive pregnancy losses characterize recurrent abortion[20]. In turn, the World Health Organization defines recurrent abortion as 2 or more losses, not necessarily consecutive[21]. With advancing age and the number of consecutive losses, the success rate of a viable subsequent pregnancy decreases[1].

In addition, the use of alcohol, illicit drugs, active or passive smoking, previous miscarriage, a new pregnancy in the first 3 months after previous delivery, the use of Intrauterine Device (IUD), high-dose radiation, celiac disease, maternal Body Mass Index (BMI) below 18.5 or greater than 25 kg/m² and the use of certain medications such as non-steroidal anti-inflammatory drugs can be cited as risk factors for abortion[2].

In addition to severe physical morbidity and high mortality, pregnancy losses are also related to social and psychological repercussions on pregnant women and their families[2,4].

The presence of genetic abnormalities, intrauterine infection, structural alterations, gestational trophoblastic disease, or underlying maternal conditions associated with pregnancy loss influence the prognosis of a future pregnancy, and adequate psychological support and medical guidance are essential[2]. Thus, a morphological investigation of the products of conception can help in etiological elucidation, clinical counseling, and necessary care[22].

This study aimed to identify the morphological alterations present in histopathological reports of pregnancy losses between 2016 and 2018 and their correlations with maternal age and recurrence.

Methods

This work is a descriptive observational study carried out in a Pathological Anatomy Service, which receives materials of spontaneous pregnancy losses from two major obstetrics services in the city of Juiz de Fora, Minas Gerais, with analysis of histopathological reports of pregnancy losses from January 2016 to December 2018.

Of the 1,642 reports, 526 were included, which described the findings in detail or already had a diagnosis, e.g., "ectopic pregnancy." The reports were registered, stored, and analyzed according to the following characteristics: (1) Maternal age; (2) Year of material analysis; (3) Villi: (a) signs of retention; (b) mole; (b.1) partial mole; (b.2) complete mole; (c) hydropic; (d) hydropic abortion; (e) swollen; (f) signs of chromosomal changes; (4) Decidua: when present there are signs of inflammation; (5) Amniotic membranes: when present there are signs of inflammation; (6) Umbilical cord: when present there are signs of inflammation; (7) Anembryonic pregnancy and (8) Ectopic pregnancy. The other reports were excluded from the study as they only contained “ovular remains”, which did not allow us to fit them into any of the villus changes listed above.

The data was collected and stored manually and then, using descriptive statistics, the variables were tabulated and analyzed using Microsoft Excel 2016.

This study was approved by the Research Ethics Committee of the Santa Casa de Misericórdia de Juiz de Fora under CAAE 31342920.7.0000.5139 and decision number 4.080.156. The Informed Consent Form (TCLE) was waived as this research only analyzes secondary data.

Results

The average was 30.45 years regarding maternal age, ranging from 15 to 55 years old. The age group with the highest number of reports was 26-30 years, followed by 31-35 years and 36 to 40 years (Table 1).

Out of the 526 reports, 523 presented villi, with "signs of retention" being the most prevalent alteration (66.35%). Hydropic and swollen villi were identified in

10.52% and 9.37% of the reports, respectively. Sixteen reports corresponding to hydropic abortion (3.06%) and 35 suggestive of chromosomal alteration (6.69%) were identified. Thirty reports consistent with the diagnosis of hydatidiform mole (5.74%) were identified (Tables 2 and 3). Of these reports, 50.0% (15) were compatible with partial hydatidiform mole and 30.0% (9) with complete mole, while the remaining cannot be differentiated only with the histopathological study. The age group with the most hydatidiform mole reports was 31-35 years (8 cases), followed by 20-25 years (7 cases) (Tables 3, 4, and 5).

Ectopic pregnancy was observed in 7 reports, corresponding to 1.33% of the analyzed total. In turn, anembryonic pregnancy was identified 4 times (0.76%) (Table 6).

Regarding the amniotic membranes, they were observed in 51 reports and showed signs of inflammation in 7 of these (13.73%). The umbilical cord was present in 17 reports and with signs of inflammation in only 2 (11.76%). The decidua was identified in 305 reports and showed signs of inflammation in 10.82% of these (33) (Tables 7 and 8).

Five women presented two reports in different periods, characterizing recurrent abortion. The alterations found and age group they belong to are: (1) 20-25 years: the first report showing signs of retention and the second showing characteristics of the complete hydatidiform mole; (2) 31-35 years: both reports with signs of retention and the second indicating partial hydatidiform mole; (3) 36-40 years: both reports indicated villi with signs of retention, and in one of them inflammation in the decidua was identified; (4) 36-40 years: the two reports also presented villi with signs of retention and inflammation in the decidua in one of them; (5) over 40 years: the first report indicated the presence of hydropic villi and signs of inflammation in the decidua, while the second showed the presence of calcifications in villi.

Table 1. Total reports by age group.

Age group	Total	Average Age	Minimum Age	Maximum Age	Standard Deviation
>20 years	57	1.,40	20	15	1.29
20-25 years	94	23.19	25	21	1.48
26-30 years	115	28.13	30	26	1.48
31-35 years	114	33.26	35	31	1.34
36-40 years	101	37.65	40	36	1.30
>40 years	45	43.47	55	41	2.87
Overall Total	526	30.45	55	15	7.42

Table 2. Prevalence of villi alterations.

Age group	Retention	Mole	Signs of Chromosomal Alteration	Hydro-pics	Hydro-pic Abortion	Swollen	Total
<20 years	7.65%	0.76%	0.76%	0.96%	0.38%	0.57%	11.09%
>40 years	5.74%	0.38%	0.38%	0.57%	0.19%	0.57%	7.84%
20-25 years	12.05%	1.34%	1.34%	2.68%	0.76%	1.15%	19.31%
26-30 years	13.96%	0.76%	1.15%	1.91%	0.19%	2.10%	20.08%
31-35 years	13.58%	1.53%	1.91%	2.87%	0.96%	3.63%	24.47%
36-40 years	13.38%	0.96%	1.15%	1.53%	0.57%	1.34%	18.93%
Total	66.35%	5.74%	6.69%	10.52%	3.06%	9.37%	101.72%

Note: The villi can be classified in more than one alteration, so the sum exceeds 100%.

Table 3. The number of reports by alterations in villi.

Age group	Retention	Mole	Signs of Chromosomal Alteration	Hydro-pics	Hydro-pic Abortion	Swollen
>20 years	40	4	4	5	2	3
>40 years	30	2	2	3	1	3
20-25 years	63	7	7	14	4	6
26-30 years	73	4	6	10	1	11
31-35 years	71	8	10	15	5	19
36-40 years	70	5	6	8	3	7
Overall total	347	30	35	55	16	49

Table 4. Number of hydatidiform mole reports by age group.

Age group	Mole	Partial	Complete
>20 years	4	2	2
>40 years	2		1
20-25 years	7	3	2
26-30 years	4	3	1
31-35 years	8	5	2
36-40 years	5	2	1
Overall total	30	15	9

Note: Not all hydatidiform mole can be classified as partial or complete with the histopathological report alone.

Table 5. Mole prevalence and its variations by age group.

Age group	Mole	Partial	Complete
>20 years	13.33%	6.67%	6.67%
20-25 years	6.67%	0.00%	3.33%
26-30 years	23.33%	10.00%	6.67%
31-35 years	13.33%	10,00%	3.33%
36-40 years	26.67%	16,67%	6.67%
>40 years	16.67%	6,67%	3.33%
Total	100.00%	50,00%	30.00%

Note: Not all hydatidiform mole can be classified as partial or complete with the histopathological report alone.

Table 6. Prevalence of ectopic pregnancy and anembryonic pregnancy.

Age group	Ectopic pregnancy	Anembryonic pregnancy
<20 years		
>40 years		
20- 25 years	2	
26-30 years	1	1
31-35 years	2	1
36-40 years	2	2
Overall total	7	4
In relation to the total number of reports	1,33%	0,76%

Table 7. The number of reports with the presence of membranes, umbilical cord, decidua, and respective inflammations by age group.

Age group	Membra-nes	Inflammation of membranes	Umbilical cord	Inflammation of the cord	Deci-dua	Inflammation of the decidua
>20 years	7		3		29	1
>40 years	5	2	1		33	5
20-25 years	13		8	2	54	4
26-30 years	7	1	2		70	11
31-35 years	11	3	2		60	6
36-40 years	8	1	1		59	6
Overall total	51	7	17	2	305	33

Table 8. Prevalence of membranes, umbilical cord, decidua and their inflammations by age group.

Age group	Membra-nes	Inflammation of membranes	Umbilical cord	Inflammation of the cord	Deci-dua	Inflammation of the decidua
<20 years	13.73%		17.65%		9.51%	0.33%
>40 years	9.80%	3.92%	5.88%		10.82%	1.64%
20-25 years	25.49%		47.06%	11.76%	17.70%	1.31%
26-30 years	13.73%	1.96%	11.76%		22.95%	3.61%
31-35 years	21.57%	5.88%	11.76%		19.67%	1.97%
36-40 years	15.69%	1.96%	5.88%		19.34%	1.97%
Overall total	100.00%	13.73%	100.00%	11.76%	100.00%	10.82%
In relation to the total number of reports	9.70%	1,33%	3,23%	0,38%	57.98%	6.27%

Discussion

Rolnik et al. (2010)[3] performed karyotype analyses in 428 abortion products of patients with an average age of 33-year-old, ranging from 13 to 46 years old. These authors found that chromosomal abnormalities were present in 55.4% of the cases, corroborating other studies that indicate that this relation is from 45 to 70%. In our study, we identified a similar average maternal age (30.45), ranging from 15 to 55 years old.

According to the study by Andersen et al. (2000)[23], there is an increasing risk of pregnancy loss with advancing maternal age, especially in women over 30 years of age, regardless of the reproductive history. At the age of 42, for example, more than half of pregnancies ended up in miscarriage, ectopic pregnancy, or stillbirth.

Khalil et al. (2013)[24] demonstrated that advancing maternal age correlates with adverse outcomes in pregnancy, such as abortion, preeclampsia, and gestational diabetes mellitus. Compared to women under 35 years of age, the risk of abortion for those aged 35 to 39 was 1.3 times higher, and for those aged 40 years or older, the risk became 2.5 times higher.

In our study, the age group 26-30 years (115 cases) presented the highest number of cases, followed by: 31-35 years (114 cases), 36-40 years (101 cases), 20-25 years (94 cases), under 20 years (58 cases) and above 40 years (45 cases).

The retrospective study by Soares e Cançado (2018)[2] also showed that pregnancy losses were more frequent with increasing maternal age. In addition, the anatomopathological analysis identified that 95% of the losses occurred during the first trimester. In addition, 2.5% of the women had a previous history of fetal malformation, while 82.5% reported it to be the first pregnancy loss.

In the study by Mulisya et al. (2018)[7], the prevalence of hydatidiform mole was 6.1%, all of which were complete, diagnosed by histopathological examination, and confirmed by an immunohistochemical study for monoclonal antibody p57. The cases were correlated with advanced maternal age (35 years or more), a history of previous abortions, and gestational age above the first trimester at the time of evacuation.

The two main risk factors for the emergence of the complete hydatidiform mole are extreme maternal age and previous molar pregnancy. The risk of complete mole, when compared to women aged 21-35 years, is 1.9 times higher for those under 21 and over 35 years of age. For those over 40 years of age, the risk is 7.5 times higher. As for previous molar pregnancy, the risk of recurrence is about 1% or 10 to 20 times the risk to the general population[25].

The upper and lower extremes of maternal age imply a higher risk of gestational trophoblastic disease. This association is more significant for complete mole. Similarly, advancing paternal age was also associated with an increased risk[8].

In addition, the history of failure in a previous pregnancy also increases the risk of gestational trophoblastic disease: a history of previous miscarriage, for example, at least doubles the risk of molar pregnancy. In addition, a history of previous trophoblastic disease increases the risk of molar pregnancy in a subsequent pregnancy by at least ten times[8].

Although the literature reports several factors associated with possible causes of hydatidiform mole, the most important of which are extremes of age and previous abortions, it can occur in patients of reproductive age between 20 and 35 years old and even during their first pregnancy. Patients with molar pregnancies are initially asymptomatic and bleeding is the main sign.

Combined oral contraceptives have also been associated with an increased risk of trophoblastic disease. In turn, Vitamin A deficiency and low carotene intake were associated only with an increased risk of complete mole. While higher educational attainment, smoking, irregular menstrual cycles, and previous obstetric histories in which only male babies are among the live births are related to the partial mole[8].

We identified 30 cases corresponding to hydatidiform mole, representing 5.74% of the analyzed reports, most of which were incomplete. The highest number of reports indicative of this gestational trophoblastic disease, in decreasing order, by age group was: 31-35 years, 20-25 years, 36-40 years and under 20 years, 26-30 years, and over 40 years.

Ectopic pregnancy represented 1.33% of the reports in our study, and the literature ranges from 0.64% to 2.07%. Ectopic pregnancy remains the leading cause of early maternal death associated with pregnancy. The direct cause of death is related to severe hemorrhage from a tubal rupture[17].

The presence of an inflammatory process in amniotic membranes and the umbilical cord may be related to infectious etiology as a possible cause of abortion[18]. Our study found acute inflammatory changes in 13.73% and 11.76% in membranes and the umbilical cord, respectively.

Analysis of the morphological data revealed that the most prevalent change was "signs of retention", followed by "hydropic villi", "edematous villi", "hydatidiform mole" and "hydropic abortion".

This study observed that five women presented two reports in different periods, i.e., 0.95% of the reports analyzed represent recurrent abortion. Moreover, two of them had the diagnosis of hydatidiform mole in the second report, representing 6.66% of all identified hydatidiform mole.

The limitations of the study arise from collecting data mainly from medical orders. The clinical information they provided is often limited due to the lack of adequate completion of test requests. The materials received in our laboratory come from hospitals where we do not have access to the medical records, making detailed data collection impossible.

Conclusion

With this data, the importance of histopathological analysis of the materials obtained from abortion for the etiological diagnosis, mainly of hydatidiform mole, is emphasized due to its association with the development of trophoblastic neoplasms and its consequences for the following pregnancies.

Authors' contributions

We describe contributions to the papers using the taxonomy (CRediT) provided above: Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing: FFCL; MCMNC; PGA; MMSS. *Project administration, Supervision & Writing – original draft:* FFCL; MCMNC.

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