CHARACTERIZATION OF WOMEN WITH RECURRENT PREGNANCY LOSS FOLLOWED UP IN HIGH-RISK PRENATAL CARE

CARACTERIZAÇÃO DE MULHERES COM PERDA GESTACIONAL RECORRENTE ACOMPANHADAS NO PRÉ-NATAL DE ALTO RISCO

CARACTERIZACIÓN DE MUJERES CON PÉRDIDAS GESTACIONALES RECURRENTES ATENDIDAS EN EL PRENATAL DE ALTO RIESGO

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ABSTRACT
Objective: To characterize the clinical and epidemiological profile of women with Recurrent Pregnancy Loss (PGR) in a high-risk prenatal service at a university hospital. **Methods:** Observational, retrospective study, with data from medical records of 72 patients with PGR treated in high-risk prenatal care at a university hospital in Paraíba, between 2015 and 2021. The results were analyzed using descriptive statistics. **Results:** The main characteristics of the patients were the average age of 31.5 years, housewife (40.2%), high school education (55.6%), income below the minimum wage (82.1%), mixed race (52.8%) and in a stable union (50%). The majority had three pregnancy losses (75%) and previous viable pregnancies (70.8%). Synechiae (2.8%), septate uterus (1.4%), thrombophilia (2.8%) and isthmocervical insufficiency (1.4%) were identified as causes of PGR. **Conclusions:** It was possible to highlight the health profile of women with PGR. The etiology of PGR in our sample was not defined. We suggest that more studies be carried out so that we can improve our understanding of the subject.
Descriptors: Habitual Abortion. Health Profile. Women's Health.

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RESUMO
Objetivo: Caracterizar o perfil clínico e epidemiológico de mulheres com Perda Gestacional Recorrente (PGR) em um serviço de pré-natal de alto risco de um hospital universitário. **Métodos:** Estudo observacional, retrospectivo, com dados de prontuários de 72 pacientes com PGR atendidas no pré-natal de alto risco em hospital universitário na Paraíba, entre 2015 e 2021. Os resultados foram analisados por estatística descritiva. **Resultados:** As principais características das pacientes foram a idade média de 31,5 anos, do lar (40,2%), ensino médio (55,6%), renda inferior a um salário-mínimo (82,1%), pardas (52,8%) e em união estável (50%). A maioria apresentava três perdas gestacionais (75%) e gestações viáveis anteriores (70,8%). Foram identificadas como causas de PGR sinéquias (2,8%), útero septado (1,4%), trombofilia (2,8%) e insuficiência istmocervical (1,4%). **Conclusões:** Foi possível evidenciar o perfil de saúde de mulheres com PGR. A etiologia da PGR em nossa amostra não foi definida. Sugerimos que mais estudos sejam realizados a fim de que possamos melhorar nossa compreensão sobre o assunto.
Descritores: Aborto Habitual. Perfil de Saúde. Saúde da Mulher.

RESUMEN
Objetivo: Caracterizar el perfil clínico y epidemiológico de mujeres con Pérdida Recurrente del Embarazo (PGR) en un servicio prenatal de alto riesgo de un hospital universitario. **Métodos:** Estudio observacional, retrospectivo, con datos de las historias clínicas de 72 pacientes con PGR atendidas en el control prenatal de alto riesgo en un hospital universitario de Paraíba, entre 2015 y 2021. Los resultados fueron analizados mediante estadística descriptiva. **Resultados:** Las principales características de los pacientes fueron edad promedio de 31,5 años, ama de casa (40,2%), educación secundaria (55,6%), ingresos inferiores al salario mínimo (82,1%), mestizo (52,8%) y residencia estable. unión (50%). La mayoría tuvo tres pérdidas gestacionales (75%) y embarazos viables previos (70,8%). Como causas de PGR se identificaron sinequias (2,8%), útero septado (1,4%), trombofilia (2,8%) e insuficiencia istmocervical (1,4%). **Conclusiones:** Se logró resaltar el perfil de salud de las mujeres con PGR. La etiología de la PGR en nuestra muestra no fue definida. Sugerimos que se realicen más estudios para que podamos mejorar nuestra comprensión del tema.
Descriptores: Aborto Habitual. Perfil de Salud. Salud de la mujer.

INTRODUCTION

Recurrent gestational loss (RPL) is associated with maternal morbidity and major psychological trauma, and is a public health problem.[1] Its prevalence is 3% when at least two losses are considered, and around 1% with more than three losses. Despite being widely studied, there is no consensus in the literature on its definition and propaedeutics.[2]

PGR is classically defined as three or more consecutive gestational losses before 20 weeks' gestation, but its concept varies according to the reference.[3]

The *American Society for Reproductive Medicine* (ASRM) in its 2012 guideline defines PGR as from two clinical gestational losses, i.e. documented by ultrasound or histopathological examination and recommends clinical evaluation after two consecutive losses in the first trimester, but defines a minimum limit of three losses for epidemiological studies.[4]

In 2022, the *European Society for Human Reproduction and Embryology* (ESHRE) presented divergent opinions among its members in its guideline and defined gestational loss as starting from two. In addition, it pointed out that there is no pathophysiological evidence to allow consensus on the discussion of consecutive losses *versus* non-consecutive losses.[5]

More recently, in 2023, the *Royal College of Obstetricians and Gynaecologists* (RCOG) maintained its position of three or more gestational losses in the first trimester, but encourages an individualized medical decision for investigation after two losses. In addition, it does not differentiate its recommendations between women with consecutive and non-consecutive losses, due to the fact that there seems to be no difference between the incidence of some etiologies of PGR between these groups.[6]

At the place where this research was carried out, the definition of recurrent pregnancy loss follows a more classic definition. The service's 2020 Obstetric Care Protocol includes the concept of habitual miscarriage, defining it as "three consecutive spontaneous miscarriages, classified as primary or secondary whether or not preceded by childbirth". In this situation, the guidance is to refer for investigation of the possible cause in the intergestational interval.[7]

PGR can be divided into primary - pregnancy in women who have never reached viability - and secondary - pregnancy in a woman who has had a previous living child. In secondary OPG, the prognosis for a successful pregnancy is better.[8]

The risk of pregnancy loss is 11-13% in the first pregnancy. After one spontaneous pregnancy loss, it increases to 14-21%, after two to 24-29% and after three to 31-33%.[3] On the other hand, a successful pregnancy can reduce the risk in subsequent pregnancies. Several factors influence this risk, such as the gestational age of the loss, the interval between pregnancies, maternal age and chromosomal alterations.[9]

The etiology of PGR is multiple and several factors have been identified for their direct impact on early embryonic development. 50% of cases have an unexplained etiology, and this is a very heterogeneous group, with loss caused by chance or by an unidentifiable cause. The most common causal factors are anatomical, genetic, immunological, thrombophilic, endocrine, infectious and environmental alterations.[2]

Women identified with PGR may have uterine anatomical abnormalities, which are classified as congenital or acquired. With regard to the first group, a septate uterus is the most common

alteration identified. Isthmocervical insufficiency can be congenital or acquired and is associated with PGR, especially in the second trimester.[8,9]

Intrauterine trauma resulting from curettage, manual vacuum aspiration and endometritis can result in synechiae and lead to fetal loss due to the endometrium's inability to support placental development.[10] Submucosal fibroids are related to PGR, but small subserosal and intramural fibroids, which do not distort the cavity, are not. [11]

Genetic abnormalities include specific gene diseases and chromosomal alterations. These alterations can be diagnosed through the couple's karyotype or through genetic analysis of the conceptus. The occurrence of genetic abnormalities is not exclusively inherited and can happen at random.[2]

Autoimmune and alloimmune mechanisms have been proposed as causes of PGR, but it is difficult to assess the role of immunological factors in reproductive failure, as the mechanisms that allow the mother to tolerate her semi-allogeneic conceptus are not fully elucidated.[12] From an autoimmune point of view, antiphospholipid syndrome (APS) is the only condition with a well-established association with PGR, which is one of the diagnostic criteria for the disease.[13]

With regard to maternal hereditary thrombophilias, there is a wide and contradictory literature on the association with first trimester losses. Studies point to an increased risk of developing PGR in the presence of factor V Leiden G1691A mutation, prothrombin G20210A mutation and protein S deficiency, when compared to women without thrombophilias.[14]

Polycystic ovary syndrome (PCOS), insulin resistance, inadequate glycemic control, hyperprolactinemia, untreated clinical and subclinical hypothyroidism are related to a higher risk of PGR.[2]

To date, there is no scientific evidence to support any pathogen as the cause of PGR.[11] Caffeine intake above 300mg a day, high doses of alcohol, smoking and obesity significantly increase the risk of miscarriage, but there is no concrete evidence of their relationship with PGR.[9,15]

Thus, considering the possible causes of PGR, the aim of this study was to characterize the clinical and epidemiological profile of women with PGR in a high-risk prenatal service at a university hospital in Paraíba. Studies like this can contribute to a better understanding of the epidemiological aspects involved and can be useful in improving care at the service, as well as in building public policies that cater for

women, who represent 70% of users of the Unified Health System (SUS).[16]

METHODS

This is an observational, retrospective and quantitative study carried out at the high-risk prenatal clinic of a university hospital in the Northeast. The service's High Risk Prenatal Care (HRPP) is a follow-up to the Women's Health Unit, which follows the principles of the Child-Friendly Hospital and Woman-Friendly Care and the guidelines of the Stork Network and currently the Maternal and Child Care Network (RAMI), which is an update of the Stork Network proposal, both with the aim of reducing Maternal and Child Mortality in the country. It is a referral hospital, but it is not the only one that performs high-risk prenatal care. On average, around 827 consultations are carried out at PNAR.

All the medical records of patients seen between January 2015 and December 2021 who were referred for high-risk prenatal care due to three or more pregnancy losses were evaluated. Women who had three or more gestational losses by the 24th week of pregnancy, whether sequential or not, were included in the study. Patients under 18 years of age and with induced abortions were excluded.

Sampling was non-probabilistic, for convenience, as PGR has a low prevalence and the number of women who come to the service each year for this reason is small. It was also decided to carry out a retrospective study by analyzing medical records, in order to include as many patients as possible.

Data was collected from medical records between February and August 2022 at the Medical Records and Statistics Service (SAME) of the referral hospital. The medical records analyzed were selected from the screening records of the hospital's High Risk Prenatal Clinic.

The variables were collected using the data collection instrument drawn up by the authors, and recorded in an Excel spreadsheet for later statistical analysis. Some information could not be collected due to lack of information in medical records. The following variables were analyzed in this study: socioeconomic (age; origin; usual occupation; level of schooling; color; marital status), obstetric history (number of miscarriages, number of previous viable pregnancies, outcome of last pregnancy), related to the uterus (anatomical changes, diagnostic examination and number of uterine evacuations), genetic evaluation and presence of comorbidities (polycystic ovary syndrome, thrombophilia, diabetes mellitus, hypothyroidism, hyperprolactinemia and other cause).

Secondly, from September to December 2022, the participants were contacted using the telephone number provided in their medical records. The women who answered the call were invited to take part in the study, with guidance on the objectives of the study, research methods, risks and benefits and a guarantee of their anonymity and data confidentiality, and that participation was voluntary, without any charge or remuneration. Patients who agreed to take part in the study and signed the online informed consent form were interviewed, and the same variables collected in the medical records were analyzed, plus per capita income.

Regarding ethical aspects, the project was sent to the Ethics Committee of the Medical Sciences Center (CCM) of the Federal University of Paraíba, and was approved under CAAE 50671821.9.0000.8069.

The data was analyzed by descriptive statistics using the *IBM SPSS Statistics 21* program. The qualitative variables were described as absolute and relative frequencies and the quantitative variables as mean with standard deviation or median with maximum and minimum. Normality was tested using the Kolmogorov-Smirnov test.

RESULTS

In this study, 76 medical records were selected that met the inclusion criteria, of which one was excluded due to divergent information. As for the interviews, 31 patients answered the phone and signed the online informed consent form. Of those interviewed, 3 were excluded from the study because they had induced abortions, totaling less than three spontaneous pregnancy losses. The final total of participants in the study was 72. 72 medical records were analyzed. Twenty-eight participants were interviewed by telephone, in addition to the analysis of the medical records.

Most of the participants were residents of João Pessoa-PB, corresponding to 75% of the total. The rest of the patients were from other cities in the state.

As for occupation, the participants were classified according to the division established by the IBGE (2002). The categories "household" and "agriculture" were added. The vast majority of the women in this study were included in the "household" category, followed by service occupations, corresponding to 40.2% and 23.6%, respectively. The other occupations were: 6.9% ill-defined, 6.9% administrative occupations, 5.6% personal hygiene service occupations, 5.6% technical, scientific, artistic and similar

occupations, 4.2% teacher, 1.4% manufacturing occupations, 1.4% artists, related and auxiliary occupations, 1.4% farmer. No occupation was recorded for 2.8%.

With regard to level of schooling, the majority fell into the high school category, with 55.6%, followed by 22.2% elementary school, 18% higher education and 1.4% with no schooling. It was not possible to differentiate between the categories of complete or incomplete education. There was no information in the medical records for 2.8% of the sample.

The group of interviewees (n=28) was also assessed in terms of per capita income. The vast majority, 82.1%, lived on less than 1 minimum wage per capita, 14.3% on between 1-2 minimum wages and 3.6% on between 2-3 minimum wages.

Of the seventy-two patients, 52.8% declared themselves brown, 19.4% black, 18% white, 4.2% yellow and 4.2% indigenous. With regard to marital status, 50% of the women were in a stable union, 30.5% were married, 16.7% were single and 1.4% were divorced. 1.4%, corresponding to one patient in absolute terms, had no information on these variables in their medical records.

Age was taken to mean the age at which the patient entered high-risk prenatal care at the referral hospital where the study was carried out during her last pregnancy. The average age of the patients was 31.5 years, with a standard deviation of 6.53. Age showed a normal distribution (Kolmogorov-Smirnov test; $p>0.05$).

As for the number of pregnancy losses, the majority of patients had three losses, corresponding to 75% of the total, as shown in Table 1. The median number of pregnancy losses was 3, with a minimum of 3 and a maximum of 14 and an interquartile range of 0.8.

Most of these women, 70.8%, had previously had successful pregnancies. The number of previous pregnancies is shown in Table 2.

With regard to the outcome of the last pregnancy in which they were being monitored, 70.8% had a viable pregnancy. The distribution of outcomes is shown in Table 3.

Table 1 - Frequency distribution of the number of pregnancy losses among women with recurrent pregnancy loss n=72, 2023.

Number of pregnancy losses	Absolute value	Value relative (%)
Three	54	75
Four	8	11
Five	4	5,6
Six	2	2,8
Seven	1	1,4
Nine	1	1,4
Eleven	1	1,4
Fourteen	1	1,4
Total	**72**	**100**

Source: prepared by the authors

Table 2 - Frequency distribution of the number of previous successful pregnancies of women with recurrent pregnancy loss n=72, 2023.

No. of previous successful pregnancies	Absolute value	Value relative (%)
Zero	21	29,2
One	23	31,9
Two	20	27,8
Three	3	4,2
More than three	5	6,9
Total	**72**	**100**

Source: prepared by the authors

Table 3 - Frequency distribution of the type of outcome of the last pregnancy of women with recurrent pregnancy loss, n=72, 2023.

Type of outcome of last pregnancy	Absolute value	Value relative (%)
Successful	51	70,8
New pregnancy loss	5	6,9
Intrauterine death	2	2,8
Neonatal death	2	2,8
In progress	2	2,8
Loss of follow-up in the service	9	12,5
Referral to another service for delivery	1	1,4
Total	**72**	**100**

Source: prepared by the authors

As for the presence of anatomical changes in the uterus, 6.9% had myoma, but it was not possible to classify the type or size. Synechiae were present in 2.8% and a septate uterus in 1.4%. 88.9% had no diagnosis of anatomical alteration.

Most of these data were obtained (90.2%) by obstetric ultrasound. The rest were assessed outside the gestational

period: 4.2% by transvaginal ultrasound and 5.6% by videohysteroscopy.

With regard to uterine evacuations (curettage or manual vacuum aspiration),

the majority of women had undergone at least one evacuation, according to Table 4.

Table 4 - Frequency distribution of the number of previous uterine evacuations in women with recurrent pregnancy loss n=72, 2023.

Number of uterine evacuations	Absolute value	Value relative (%)
Zero	20	27,8
One	17	23,6
Two	12	16,6
Three	20	27,8
Four	3	4,2
Total	**72**	**100**

Source: prepared by the authors

Karyotyping of the couple was carried out on only 1.4% of the sample for genetic investigation of pregnancy loss. The karyotype of only the mother was carried out on 1.4% of the sample. No alterations were identified in these tests. There was no data on the genetic analysis of the conceptus.

With regard to polycystic ovary syndrome, 11.1% of the participants had a diagnosis in their medical records or reported it during an interview. However,

it was not possible to identify the criteria used to define the condition in both situations. 2.8% were diagnosed with diabetes mellitus and 1.4% with hypothyroidism. With regard to investigation of the thrombophilic cause, 59.7% of all patients had not been investigated for thrombophilia. 25% had started an investigation but had not completed it. In 12.5% this diagnosis was ruled out and in 2.8% it was confirmed.

Table 5 - Distribution of the thrombophilic cause investigation *status of* women with recurrent pregnancy loss n=72, 2023.

Thrombophilic investigation *status*	Absolute value	Value relative (%)
Not investigated	20	27,8
Investigation not concluded	17	23,6
Discarded	12	16,6
Confirmed	20	27,8
Total	**72**	**100**

Source: prepared by the authors

Other possible causes of pregnancy loss identified in the medical records were: use of alcohol and illicit drugs during pregnancy (1.4%) and isthmocervical insufficiency (1.4%). There was no record of a patient with hyperprolactinemia.

Patients' weight and height were collected to assess obesity using BMI. However, it was not possible to standardize the sample, as most patients had no previous weight records and the gestational age at the first high-risk prenatal visit varied greatly, making it impossible to compare the weight recorded at that time.

DISCUSSION

There is no consensus in the literature on the definition of recurrent pregnancy loss, and it is a great challenge to study it. The major societies researching the subject have been updating their diagnostic criteria over the years.[4,5,6] This conceptual advance is important, because despite its low prevalence, pregnancy loss can be an emotionally traumatic experience, generating anguish and frustration in these women. In addition, these updates can help to identify preventable and treatable causes earlier, which can lead to a better prognosis.

In this study, we chose to include only women with three or more pregnancy losses, because the referral service where this study was carried out uses this cut-off point in its practice.[7] In addition, this limit seems to be safer for characterizing the profile of these women.[4] Consecutive and non-consecutive losses were taken into account and the exact gestational age of the losses was not identified, since it was not possible to differentiate between them using the medical records and even in the interviews the women had difficulty remembering this information.

Ideally, the service recommends that the investigation of patients with PGR should take place in the inter-gestational period.[7] However, the information obtained in this study mostly referred to the last prenatal follow-up, since most of

these women left the service and a minority had been investigated outside the gestational period.

In general, the patients were residents of João Pessoa (75%), which may be associated with greater ease of access compared to residents of the state's inland cities.

Most of the women were housewives (40.2%), had started or finished high school (55.6%), and had a per capita income of less than one minimum wage (82.1%) - the latter data was obtained only from the patients interviewed. These socio-economic characteristics may be associated with the difficulty in accessing complementary tests for the etiological evaluation of RMP and loss of connection with the service observed in this study.

Of the 72 patients, most declared themselves black (brown or black), accounting for 72.2%. In addition, with regard to marital status, 50% of the participants were in a stable union and 30.5% were married. These data are similar to those found in an epidemiological study carried out in Salvador, Bahia, in 2014, in which the vast majority of patients also declared themselves black and were married or in a stable union.[17]

The fact that most of the patients are in a stable union or married may be associated with greater emotional stability

in coping with the pregnancy loss and willingness to make new attempts[17] . In our study, we found that 70.8% of the patients had at least 5 pregnancy attempts when we add up the minimum number of pregnancy losses (three), previous viable pregnancies (table 3) and the last prenatal follow-up as a reference for the information obtained in this study.

The literature points to advancing age as an independent factor in pregnancy loss, with a significant increase after the age of 35[18]. The average age of the patients was 31.5 years (±6.5). As the age collected was the age at which the last prenatal care was taken, these women had previous pregnancy losses at an earlier age. We also found that 70.8% of these patients had previous viable pregnancies. In this sense, these associated factors may have influenced the fact that most of the patients also had viable pregnancies during their last prenatal care (70.8%), given that these aspects confer a better prognosis, as already described.[9]

With regard to congenital uterine anatomical alterations, a septate uterus is the main cause of PGR.[8] This malformation was identified in 1.4% of the participants and was the only congenital cause observed. As for acquired alterations, synechiae were identified in 2.8% of the patients, all of whom had a history of previous uterine evacuations. On the other

hand, when we consider all the patients who had uterine evacuations (72.2%), only 3.8% had synechiae. With regard to fibroids, the literature points to submucosal fibroids, which distort the uterine cavity, as a possible cause of pregnancy loss.[11] This association could not be assessed in this study, as it was not possible to collect precise location, size and relationship with the uterine cavity.

The literature shows that most pregnancy losses are due to genetic causes. However, these alterations can happen by chance, without inheritance from the parents. There is no consensus among the societies that study the subject as to the need or ideal time to carry out a karyotype of the couple or genetic analysis of the conceptus. [2,4,5,6,11] Only 2.8% of the patients underwent some kind of complementary genetic investigation. In addition to the lack of consensus on the use of these methods, this low percentage can be explained by the difficulty in carrying them out for logistical reasons and the increased costs of the investigation.

Of the possible metabolic causes for PGR, PCOS was the main one identified (11.1%), but it should be noted that it was not possible to identify the criteria used for the diagnosis. Only 2.8% of the women were diagnosed with DM prior to pregnancy and 1.4% with hypothyroidism. It is important to note that the association

with pregnancy loss is related to poorly controlled disease.[2] Isthmocervical insufficiency was identified by 1.4% as a cause of PGR, and this association is well documented in the literature when it occurs in the second trimester.[9] On the other hand, the use of alcohol and illicit drugs during pregnancy, identified in 1.4% of the women, has an unproven association with recurrent pregnancy loss, despite a well-established relationship with sporadic pregnancy losses.[9,15]

Less than half of the patients were investigated for thrombophilia, of which it was only possible to complete the investigation in just over ⅓. Possibly, this context is correlated with the low availability of resources, as previously discussed, to carry out tests with serological markers, as well as the loss of follow-up.

No other clinical manifestations related to PGR were identified. It is worth noting that most of the women had not previously been investigated with complementary exams in the intergestational period for causes of PGR, which may have had an impact on the identification of these alterations.

CONCLUSIONS

The clinical and epidemiological profile observed in our study was of women with an average age of 31.5 years,

from home, brown, in a stable union, with at least three pregnancy losses, previous viable pregnancies and a new successful pregnancy. The identifiable causes were septate uterus, synechiae, thrombophilia and isthmocervical insufficiency. Other causes identified were myoma, polycystic ovary syndrome, diabetes mellitus and hypothyroidism, but it was not possible to identify the relationship with the uterine cavity, diagnostic criteria and lack of glycemic control, respectively, which makes it impossible to evaluate these factors as a cause of PGR.

It was noted that most of the patients had no defined etiology for their OPG. It is possible to infer that although this is a subject with traumatic emotional impacts for women, we have not yet been able to provide more satisfactory answers as to the causes of OPG. More in-depth studies in this area could help to clarify matters further.

The main limitations of this study relate to the collection of data from medical records. Some information could not be obtained, such as gestational age at pregnancy loss, previous weight, diagnostic criteria for PCOS, anatomical characteristics of fibroids, control of diabetes mellitus and hypothyroidism.

PGR is still a controversial topic in the literature, but it has been updated over the years. We suggest that health services base their investigation protocols for PGR on up-to-date references based on scientific evidence and new local epidemiological studies.

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