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Reproductive outcome in pregnant women with recurrent pregnancy loss

Êxito reprodutivo em mulheres com perdas gestacionais de repetição

Original Article

Kewords
Pregnancy outcome
Abortion, habitual
Prenatal care
Overweight

Palavras-chave
Resultado da gravidez
Aborto habitual
Cuidado pré-natal
Sobrepeso

Abstract

PURPOSE: To estimate the future pregnancy success rate in women with a history of recurrent pregnancy loss. **METHODS:** A retrospective cohort study including 103 women seen at a clinic for recurrent pregnancy loss (loss group) between January 2006 and December 2010 and a control group including 204 pregnant women seen at a low-risk prenatal care unit between May 2007 and April 2008. Both groups were seen in the university teaching hospital the Maternidade Climério de Oliveira, Salvador, Bahia, Brazil. Reproductive success rate was defined as an alive-birth, independent of gestational age at birth and survival after the neonatal period. Continuous variables Means and standard deviations (SD) were compared using Student's t-test and nominal variables proportions by Pearson χ^2 test. **RESULTS:** Out of 90 who conceived, 83 (91.2%) had reproductive success rate. There were more full-term pregnancies in the control than in the loss group (174/187; 92.1 versus 51/90; 56.7%; p<0.01). The prenatal visits number was satisfactory for 76 (85.4%) women in the loss group and 125 (61.3%) in the control (p<0.01). In this, the beginning of prenatal care was earlier (13.3; 4.2 versus 19.6; 6.9 weeks). During pregnancy, the loss group women increased the weight more than those in the control group (58.1 versus 46.6%; p=0.04). Although cervix cerclage was performed in 32/90 women in the loss group, the pregnancy duration mean was smaller (34.8 weeks; SD=5.6 versus 39.3 weeks; SD=1.6; p<0.01) than in the control group. Due to gestational complications, cesarean delivery predominated in the loss group (55/83; 64.7 versus 73/183; 39.5%; p<0.01). **CONCLUSION:** A very good reproductive success rate can be attributed to greater availability of healthcare services to receive pregnant women, through prenatal visits (scheduled or not), cervical cerclage performed on time, and available hospital care for the mother and newborn.

Resumo

OBJETIVO: Avaliar o êxito reprodutivo na gestação subsequente de mulheres com perdas gestacionais de repetição. **MÉTODOS:** Estudo de coorte retrospectivo incluindo 103 mulheres com perdas gestacionais de repetição (grupo de perdas) atendidas entre janeiro 2006 e dezembro 2010 e 204 gestantes de baixo risco (grupo controle) de maio 2007 a abril 2008 na Maternidade Climério de Oliveira, Salvador, Bahia. Êxito reprodutivo foi definido para o recém-nascido, independentemente da idade gestacional ao nascimento, que sobreviveu após o período neonatal. As médias e desvio padrão (DP) das variáveis contínuas foram comparadas utilizando o teste *t* de Student. As frequências das variáveis nominais foram comparadas utilizando-se o teste de χ^2 de Pearson. **RESULTADOS:** Das 90 que engravidaram, 83 (91,2%) tiveram êxito reprodutivo. Gestações a termo no grupo controle foram mais frequentes que no de perdas (174/187; 92,1 *versus* 51/90; 56,7%; p<0,01). O número de consultas no pré-natal foi satisfatório para 76 (85,4%) mulheres no grupo de perdas e para 125 (61,3%) no grupo controle (p<0,01). Nestas, o início do pré-natal foi mais precoce (13,3; 4,2 versus 19,6; 6,9 semanas). O grupo de perdas teve ganho de peso acima do esperado mais frequentemente que as gestantes de baixo risco (58,1 *versus* 46,6%; p=0,04). Apesar de a cerclagem do colo uterino ter sido realizada em 32/90 mulheres com perdas, a duração média da gestação nestas foi menor (34,8

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Received
07/10/2015

Accepted with modifications
08/18/2015

DOI: 10.1590/S0100-720320150005445

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Conflicts of interests: none.

semanas; DP=5,6 versus 39,3 semanas; DP=1,6; p<0,01). O tipo de parto predominante nas gestantes com perdas foi a cesariana (55/83; 64,7 *versus* 73/185; 39,5%; p<0,01) devido principalmente a complicações obstétricas. **CONCLUSÃO:** O êxito gestacional foi considerado satisfatório e é atribuído à realização de cerclagem do colo uterino em tempo hábil, ampla disponibilidade da equipe para o atendimento às gestantes, que se traduziu por retornos mais frequentes agendados, e por livre demanda, além de um pronto suporte hospitalar para mãe e feto.

Introduction

Reproductive success outcome in pregnancy is the goal and motivation of women with a history of recurrent pregnancy loss, and is shared with the family, obstetricians, and all healthcare professionals. Recurrent pregnancy loss (RPL) has a controversial definition. The American Society for Reproductive Medicine[1] defines it as the loss of two or more pregnancies confirmed by ultrasound or histopathological examination. They suggest a clinical evaluation should proceed following two first-trimester pregnancy losses, and, ideally, the threshold of three or more losses should be used for epidemiological studies. The European Society of Human Reproduction and Embryology and the Royal College of Obstetricians and Gynecologists, on the other hand, define recurrent miscarriage as three or more consecutive pregnancy losses[2,3]. As the diagnosis of RPL is based on self-reported losses which occurred in the past, it may not be accurate, although there is an element which is not considered in the definitions above, but is very important for the patients — the biochemical loss[4]. Women in the general population do not have their βhCG routinely measured and, consequently, their biochemical loss rate is underestimated. In contrast, women with RPL often have closer biochemical monitoring, which is less likely to be missed. A study[5] shows that 3,165 women undergoing IVF have significantly higher reported biochemical pregnancy losses compared with 954 women with RPL (18.4 versus 7.9%; p<0.001). If the biochemical losses were to be considered true miscarriages, this would promote an increase in the rate in general population as high as 60%. These women may suffer three biochemical pregnancy losses due to chance alone. From this, the authors[5] estimated that the incidence of RPL occurring by chance varies significantly with age, ranging from 0.13 to 13.3% for ages 20 to 24 and 40 to 44, respectively. The proportion of women with unexplained RPL (approximately one of three) may have environmental risk factors or endogenous pathologies not detected by current routine investigations.

The inclusion criterion of patients with RPL is very important in the comparison and interpretation of results, because failed pregnancies can occur at several gestational ages[6], although they predominate in the first-trimester, after late miscarriages, and very preterm[6,7]. One study[8] including 325 women with unexplained RPL, of which 226 conceived, the success rate was 75%, with successful outcome being regarded as survival beyond 24 weeks. Another study[9] showed a 25% rate of miscarriages in women less than 30 years, increasing to 52% in a group of women older than 40 years. After investigation, the women with unexplained recurrent first trimester miscarriage had an excellent pregnancy outcome without pharmacological intervention when they were offered supportive care in the setting of a dedicated miscarriage clinic. They also concluded that increasing maternal age and number of previous miscarriages both had a negative effect on pregnancy outcome. To the contrary, a history of a live birth did not influence the outcome of the next pregnancy. In a tertiary academic centre, 51 couples with a structural chromosome rearrangement were followed prospectively, and after evaluation and treatment of concomitant factors there were 58 monitored pregnancies, with a live birth rate of 71%[10].

In a population of women with RPL, losses are likely to occur again at gestational ages similar to those previously documented[7]. These observations suggest the possibility of specific, but yet undiscovered, causes of loss that influence the viability of pregnancy at precise gestational ages. The chromosomal abnormalities are present in more than 90% of preembrionic-aborted tissues, compared with only 6 to 12% of losses after 20 weeks gestation. The women with mid-trimester pregnancy loss represent a heterogeneous group with widely varying presentations and origins. Fetal loss may have more than one cause, and the presence of dual or even triple pathologies increases the risk of a further late-term miscarriage or preterm delivery[11]. Mid-trimester pregnancy loss can be attributed to Antiphospholipid Syndrome and anatomic cervical incompetence. These authors[11] analyzed 351 mid-trimester pregnancy loss women in a clinic in the UK, which showed 51% patients with unexplained causes and 33% with Antiphospholipid Syndrome. These mid-trimester pregnancy loss cases are important because medical intervention can give them the possibility to progress beyond the early preterm period.

Cervical incompetence has been noticed as an important cause for mid-trimester pregnancy loss, in which surgical cure through the uterine cerclage has been a medical practice for several decades[12,13]. In maintaining the fetus in the uterus, the results of uterine cerclage have been debated for years[14,15], and its indication changed after the routine use of transvaginal ultrasound for cervical evaluation[16,17]. A study[17] of 138 pregnant women treated with elective cerclage showed 54.3% of term deliveries and 9.0% preterm less than 25 weeks. The recovery

of the cervical pessary[18,19], the treatment with 17 alfa-hydroxyprogesterone caproate[20,21], in addition to the advanced technology available to the neonatologists, have all contributed to a reduction in the rate of early preterm birth. This has had a favorable impact on the survival and future well-being of newborns.

For women with unexplained recurrent miscarriage, with or without thrombophilia, the efficacy and safety of anticoagulant agents has been debated[22,23], and is very different from the proved efficacy in those with antiphospholipid syndrome[24]. There is still a contingent of women with RPL in whom a thorough clinical and laboratory investigation reveals a normal health. For these women, supportive care in early pregnancy and prenatal consultations in the setting of a miscarriage clinic confer a significant beneficial effect on pregnancy outcome.

The objective of this study was to estimate the percentage of babies who survived beyond the neonatal period in a recurrent pregnancy-loss clinic and to identify associated factors with favorable results.

Methods

A retrospective cohort study consisting of interviews and medical-record reviews of 103 women who were seen at a Recurrent Pregnancy Loss Clinic (loss group) between 2006 and 2010. The control group consisted of 204 pregnant women seen at a low-risk prenatal care unit between May 2007 to April 2008, both in a university teaching hospital (Maternidade Climério de Oliveira, Salvador, Bahia, Brazil).Those who did not live in Salvador were excluded from this study. From 310 patients on the database, 30 patients (9.1%) had no phone number available. From those with phone number, 3 attempts to contact them were made: 92 (28.3%) had changed their phone number, 85 (25.9%) did not answer. From the103 who were included, 90 had their gestation period followed in the clinic and 13 did not conceive. Of the pregnant women, 46 arrived pregnant and, as the others, were submitted to investigations to exclude known associations of recurrent pregnancy loss, such as anatomic and hormonal abnormalities, screening for antiphospholipid antibodies. They were treated if necessary. Other conditions were identified in 7 patients: bicornuate uteri 1 woman; systemic lupus erythematosus (SLE) (2 womans); and chronic high blood pressure (4 womans). These patients were also included in this study. A nutrition specialist followed overweighted women during their entire pregnancy.

The control group consisted of 204 pregnant women seen in a low-risk prenatal care unit. Those with obstetric risk were sent to specialized care, and those who did not agree to be interviewed were excluded from the control group. There was not known selection bias to include low risk care unit. At the time of study, the number of live births in the hospital was 15,359 babies. Many pregnant women had the prenatal care in different units though; at the outpatient clinic of the hospital, just 6,408 women were seen (low- and high-risk prenatal care, recurrent pregnancy loss, diabetes mellitus and sickle cell disease) in the covered period. The majority of these patients were seen for prenatal care.

The analyzed variables on reproductive outcome were: live-birth at term, preterm, miscarriages, number of prenatal consultations, gestational age at the beginning and end of the pregnancy, increase in weight during the pregnancy, the method of delivery and obstetric complications — mainly pre-eclampsia and gestational diabetes mellitus.

Women with RPL were considered as those who had two or more failed consecutive pregnancies confirmed by ultrasound and/or a beta-HCG pregnancy test at any gestational age. Reproductive Success Rate was considered as a live-birth, independent of gestational age at the birth, with survival of the baby after the neonatal period. Future pregnancies were defined as those pregnancies followed in the Recurrent Pregnancy Loss Clinic, and live birth is defined as newborns survival after the neonatal period (28 days after delivery), independent of the gestational age at the birth. The estimation of gestational age was performed either by the first day of the last menstrual period was recorded and/or first-trimester ultrasound. Miscarriages were defined as interruption of pregnancy prior to 22 weeks. The preterm birth subcategories definitions was the same used by World Health Organization[25]: extremely preterm – <28 weeks; very preterm – 28 to <32 weeks; moderate to late preterm – 32 to <37 weeks. Pre-natal care were made as proposed by the Health Ministry of Brazil[26], being one visit in the first, two in the second, and three in the third trimester. The pregnant women in the loss-group had their records opened and were encouraged to return as many times as necessary, when they were sent to the emergency room. The body mass index (BMI) was estimated for all patients. This was done through the Quetelet's formula[27] and blood pressure measurements, and was repeated at each consultation until the ending of prenatal care. Pre-gestational overweightness was considered when the first BMI (or up to 16 weeks gestation) was above 25 kg/m^2. The first BMI was utilized to estimate the increase of the maternal weight during the pregnancy, from what the allowed weight was classified into 3 categories: under, appropriate and above allowed. This corresponded to the the underweight, normal weight, overweight and obesity[28]. Pre-eclampsia was considered when the blood pressure (BP) during pregnancy was sBP≥140 mmHg or dBP≥90 mmHg after 20 weeks gestation, with new proteinuria. Pre-existing (chronic) hypertension was considered either when it was present, in pre-pregnancy or when detected in before 20 weeks gestation[29].

The screening cut-point for gestational diabetes mellitus was the fasting glucose measurements of ≥85 mg/dL, after the 20th week of pregnancy. The diagnosis of gestational diabetes mellitus was defined as: 2 fasting glucose measurements ≥126 mg/dL or glucose tolerance test with glucose levels >200 mg/dL or any fasting glucose ≥200 mg/dL or the presence of classic symptoms of diabetes[30].

The uterine cervix cerclage described by McDonald[13] was the treatment when the pregnant women had a history of mid-trimester pregnancy loss or when the transvaginal cervical ultrasound revealed a shortened endocervical canal length. Through interviews with patients and investigation of reference medical records, information was obtained on the outcome of pregnancies, mainly to low-risk prenatal patients, who had deliveries in hospitals other than in the university teaching hospital.

The Statistical Package for Social Sciences (SPSS) 18.0 program was used for statistical analysis. The means and standard deviations of continuous variables were compared using Student's *t*-test, and the proportions of nominal variables were compared by Pearson χ^2 test. Statistical association was considered for p-value<0.05. This Project was approved by the Ethics Committee of Maternidade Climério de Oliveira on September 2012, nº CAAE 06123412.0.0000.5543, and all subjects provided written Informed Consent for study participation.

Results

Of the 90 women who had their future pregnancy followed at the Recurrent Pregnancy Loss Clinic, 83 (91.2%) had reproductive success outcome rate. Among these women, 51 (61.4%) had full-term live births and 25 (30.1%) had late preterm babies. From the 204 patients of control group, we were able to obtain information on 187 women, and 181 (96.7%) had reproductive success, mainly with full-term live births (Table1).

The pregnant women in the loss group started the prenatal period with a higher BMI, and, even with a specialist support, they had a weight increased more than expected during the pregnancy, as can be seen in Table 2. Cervix cerclage was performed in 32 pregnant women in the loss group, and in 29 (90.6%) of them had term pregnancies. No surgery was needed in the control group. Seven women in the loss group had failed pregnancies due to miscarriages (weeks 13th, 16th,17th and 21st). One woman had an extremely preterm live birth (24th gestational week), who died soon after birth. Two women with SLE had preterm stillborns (28th and 30th gestational weeks). On the control group, there were two miscarriages and four extremely preterm (two neonatal deaths and two stillbirths).

Table 1. Pregnancy outcome in women with and without history of recurrent pregnancy loss

Subcategories of preterm birth base on week of gestational age	Women with losses (n=90)		Women without losses (n=187)		p-value
	n	%	n	%	
Miscarriage	4	4.4	2	1.1	
Extremely preterm (22 <28 weeks)	1	1.1	4	3.1	
Very preterm (28< 32 weeks)	7	7.8	0	0	
Moderate to late preterm (32 < 37 weeks)	27	30.0	7	3.7	
Full term (>37 weeks)	51	56.7	174	92.1	<0.01

p = Pearson χ^2 test.

Table 2. Clinical data on the pregnancy and delivery in women with and without history of recurrent pregnancy loss

Clinical data on pregnancy and delivery	Women with losses (n=90)		Women without losses (n=204)		p-value
	n	%	n	%	
Pre-pregnancy body mass index					
Normal	35	39.3	137	68.2	<0.01
Overweight	28	31.5	49	24.4	
Obesity	26	29.2	15	7.5	
Appropriateness of pregnancy weight gain					
Under	10	13.5	54	28	
Appropriate	21	28.4	47	24.9	
Above	43	58.1	88	46.6	0.04
Cesarean delivery	55*	64.7	73**	39.5	<0.01
Pre-natal care					
First clinical visit (weeks; mean and standard deviation)	13.3	4.2	19.6	6.9	<0.01
Last visit (weeks; mean and standard deviation)	34.8	5.6	39.3	1.6	<0.01
Number and percent of women with five or more visits	76	85.4	125	61.4	
Comorbidities					
Hypertension	28	31.1	9***	4.5	<0.01
Gestational diabetes mellitus	8	8.9	6	3.0	0.03

p = Pearson χ^2 test; *Only 85 were followed; **Only 185 were followed; ***Only 201 women.

Discussion

The reproductive success of 91.2% in this study was considered satisfactory and very stimulating for the couples and all the involved healthcare professionals. The result refers to all the subjects who had losses in several gestational ages, with predominance in the first trimester, as we showed in prior study of this group[6]. In seven of these cases, comorbidities that were not necessarily related to the recurrent loss were identified. The majority of cases were healthy pregnant women, a result that does not concur with published studies showing half of cases of RPL having an unexplained cause[1].

Additionally, two subjects who were considered healthy had an obstetrics history compatible with the pregnancy morbidity described in Antiphospholipid Syndrome[31,32]. These subjects were treated with enoxaparin 40 mg and aspirin, and had gestational success.

In this study, the group of 43 pregnant women who mainly had first trimester miscarriages had more reproductive success 42/43 (97.7%;95%CI 92.5–99.3). Other authors[8] who analyzed reproductive outcomes in 226 women with unexplained recurrent first trimester miscarriages related a success rate of 75%. The same was described[9] in women with mean age of 30 years, with significant decrease in those older than 40 years old. The high rate of success in this study can be related to the fact that the majority of the women had two or three miscarriages and the inclusion of biochemical losses. If only clinical pregnancy losses and not biochemical losses are considered as miscarriages, then recurrent miscarriage is less likely to be due to chance.

The favorable outcome in women with unexplained recurrent first trimester miscarriage has been largely related in literature[11,33] and, to explain it, two models are proposed: types I and II. Type I is the recurrent miscarriage (RM) which occurs mainly by chance, in women who have nounderlying pathology. There is a relatively good prognosis when compared with women of the same age, without pharmacological intervention, if supportive care alone is offered in the setting of a dedicated miscarriage clinic.

Type II unexplained recurrent first trimester miscarriage refers to miscarriages which occur due to an underlying pathology that is not easily identified by routine clinical investigations or is attributable to environmental and lifestyle risk factors. Women who had four or more miscarriages and a finding of a normal karyotype in products of conception in association presented a worse prognosis for the future pregnancy compared to women of the similar age. Women with four or more losses even with a thorough routine clinical investigations should be given:

- preconception genetic testing for evaluation of prospective parents before pregnancy;
- antenatal genetic testing to evaluate currently pregnant women to determine the genetic makeup of the developing fetus;
- preimplantation genetic testing to evaluate the embryo before uterine transfer, via an embryo biopsy during in vitro fertilization; and
- the genetic evaluation of the conception products following a failed pregnancy[34].

Six pregnant women in this study, out of 43 unexplained recurrent first trimester miscarriages, showed an endocervical canal length shortened by ultrasound and were treated with cerclage. Five, including one with bicornuate uteri, had a successful pregnancy. One presented amniorrexe, amnionitis and had a miscarriage at 21 weeks. An ultrasound screening[35] showed it to be effective in identifying the risk of preterm birth with evident decrease of costs. The women treated with curettages for prior miscarriages, even early miscarriages, can develop cervical incompetence, and these women can improve their odds of a successful pregnancy with the cerclage procedure, as it is related.

In 47 subjects of this study, the previous losses were predominantly mid-trimester pregnancy losses. Of these 47 subjects, 26 were treated with cerclage, and in 24 (92,3%) the surgery promoted the prolongation of the pregnancy, enough to bring the fetus up to the category of late preterm, in which all survived the neonatal period. The support of the neonatology hospital unit, which limits the time for viability at 28 weeks, was fundamental to the gestational success, which was not only in the neonatal period, because there was no notice of death of these children until the time of the interviews. In two patients, the miscarriages occurred at the 13th and 17th weeks, and were probably not related to anatomic factor, which is passive of surgical healing.

Of the 90 subjects in this study, 32 (35.5%) were treated with cerclage. In 51 (56.7%) cases, the pregnancies were full term; and 27 (30.0%) cases were late preterm, with a very favorable neonatal prognosis. A study[17] which evaluated 138 pregnant women treated with cerclage by the McDonald[13] method revealed a rate of 54.3% for full term pregnancies. The authors demonstrated the same pregnancy outcomes in women treated with elective versus ultrasound-indicated cervical cerclage. In this study, the two indicated the ways used in addition to a large prescription of progesterone. The majority of pregnancies were full term, and even the preterm pregnancies exceeded the viability bound, which reached the authors' and patients' objective.

In the control group, even though the majority had been full term pregnancies, there were two still-born with 26 weeks and two at 25th and 26th weeks, who died after birth. It is quite notable[36] that one of the factors that contributes to neonatal mortality is the number of prenatal consultations and the low-risk pregnant women had less than the loss group. This occurrence motivated the success and also presented significant difference in the gestational age at the beginning and ending of prenatal care, even when considering that 35 (38.9%) of the cases in the loss group had their pregnancies interrupted early because of obstetrical complications.

More women in the loss group started the prenatal care when they were overweight or obese and, despite the guidance of specialist, had more weight-gain during the pregnancy when compared with the low risk group.

These findings were associated with a greater risk of obstetrics complications[37] and the same finding was observed among the women with RPL in this study, who progressed more proportionally with pre-eclampsia and gestational diabetes mellitus, which contributed to the early interruption of pregnancies in these women. A study[38] that emphasized the effect of BMI on the outcome of pregnancy in women with recurrent unexplained miscarriages showed that maternal obesity significantly increased the risk of miscarriage. Another study[39] to verify the association between BMI and future pregnancy in 696 women with recurrent unexplained miscarriage showed obesity as an independent factor of risk for a future miscarriage in addition to the maternal age and number of previous miscarriages. In this study, about one-third of the subjects were in a group classified as overweight/obese, although very few were obese. These authors and others[40] recommend that all women with a history of RM should have their BMI recorded at their first clinic visit.

The favorable outcome, in women with recurrent unexplained miscarriages, who had more obstetrical complications[41], distinguishes the care the pregnant women received from the health group, even in a hospital for the training of medicine students. Prenatal consultations were scheduled, and patients were free to return to be seen by a doctor with a special interest in the RPL. It is also important that all staff members dealing with RPL couples are trained in the emotional aspects of pregnancy loss. This way, immediate support can be provided, and the couple will have direct access to specialized counseling and, when necessary, hospital care made available for mother and baby[40].

The majority of women with two or three first-trimester miscarriages, the inclusion of biochemical losses and women in the first pregnancy in control group, although the majority progressed to full term live-birth, represented the limitations of this study, compromising the comparison of reproductive outcome and obstetrics complications. The objective of the study, however, was achieved as we demonstrated the reality at a clinic for recurrent pregnancy loss in a public hospital, and how it is possible to change a history of failure and frustration in gestational success through attentive prenatal care and interventions with average complexity to the mother and baby.

Ackowledgment

To Mrs. Edvani Gomes da Silva for her diligent attention and patience in the specialized counseling to the overweight/obese pregnant women followed at a clinic for recurrent pregnancy loss and to the neonatal and obstetrician team.

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