Assisted Reproduction

Human Reproduction Archives

ISSN 2595-0711

REVIEW ARTICLE

Recurrent Pregnancy Loss: reviewing therapeutic approaches

Elaine Cristina Fontes de Oliveira[1]*, Mariana Seabra Leite Praça[1], Gabriela Martins Perez Garcia[1], Ines Katerina Damasceno Cavallo[1]

[1] Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brasil

Abstract:

Objetive: to discuss recurrent pregnancy loss (RPL) causes and shed light on the current evidence in the management of each one. **Methods:** A comprehensive and non-systematic search of the theme was carried out through online databases (PubMed and *Cochrane* database), using the terms "recurrent pregnancy loss", "treatment", "genetic or chromosomal abnormalities", "uterine factor", "uterine septum", "fibroid", "myoma", "cerclage", "endocrine causes", "polycystic ovary syndrome", "thyroid", "hypothyroidism", "hyperprolactnemia", "antiphospholipid syndrome", "hereditary thrombophilia", "inherited trombophilia", "obesity", "lifestyle", "unexplained miscarriages", "progestogens", "vaginal progesterone", "assisted reproductive technologies", "in vitro fertilization", preimplantation genetic screening", "obstetric complications" and variants as keywords. **Results:** Couples with structural chromosomal rearrangements should be advised of the good reproductive prognosis after natural conception, so that in vitro fertilization plus preimplantation genetic diagnosis should not be offered as first-line treatment for them. Treatment of women with subclinical hypothyroidism may reduce the risk of miscarriage. Bromocriptine treatment can be considered in women with hyperprolactinemia. There is insufficient evidence to recommend metformin supplementation in pregnancy to prevent pregnancy loss in women with glucose metabolism defect. Treatment of Antiphospholipid Syndrome with low-dose aspirin started preconceptionally and heparin started after the first positive pregnancy test is recommended. The evidence to recommend the use of progesterone to improve live birth rate in women with RPL and luteal phase insufficiency is insufficient. **Conclusion:** The treatment for RPL should be directed to the cause of the miscarriages. Since the outcomes for most couples with unexplained RPL are favorable without treatment, therapy interventions that have not been proven are not recommended.

Keywords: Abortion. Abortion habitual. Thrombophilia. Obesity. Clinical protocols.

Introduction

Recurrent pregnancy loss (RPL) is a clinical condition that affects around 3% of the couples trying to conceive when considering at least two losses and about 1% when above three losses.[1] It is classically defined as three or more consecutive miscarriages before 20 weeks of gestation.[2] The latest definition comprehends both spontaneous pregnancies and those after assisted reproductive technologies (ART), excluding molar and ectopic pregnancies, as well as implantation failures.[3] Due to the similar prevalence of changes found in patients with two or more miscarriages, testing for evidence-based factors it has been suggested after the second loss.[4]

The RPL has been associated with genetic or chromosomal abnormalities in the couple, or in the embryo; maternal thrombophilia; uterine structural abnormalities; maternal immune diseases; endocrine disorders; and environmental factors.[5-7] About 50% of women will have no identifiable abnormalities with the current investigative protocols.[8] Nevertheless, by associating the analysis of miscarriage tissue with the evaluation of 24-chromosome pairs by microarray combined with the standart American Society for Reproductive Medicine (ASRM) evaluation for recurrent miscarriage, a definite cause was identified in over 90% of cases.[9] The incidence of aneuploidy in the genetic evaluation of products of conception (POC) does not rule out the presence of other associated pathologies.[7,9]

Financial support: None
Conflicts of interest: The authors declare no conflicts of interest
Submitted: November 10, 2021.
Accepted: October 25, 2022.
The study was carried out at Hospital das Clínicas da Universidade Federal de Minas Gerais.

Factors that influence future successful pregnancy involve: maternal age, number of previous losses, and genetic evaluation of POC.[1,10,11] The risk of aneuploidy increases directly with increasing the maternal age, with a risk of miscarriage more than 75% in patients over 45 years.[1,10] Increasing maternal age is a risk factor for sporadic losses, just as for repeated losses.[1] Despite that risk, the chance of an euploid miscarriage grows with the number of previous losses, whereas the occurrence of aneuploidy remains constant.[12]

Most therapeutic recommendations in RPL are based in clinical experience and observational studies. There are few prospective and randomized studies. The therapeutic interventions are determined by the cause. However, there is no treatment proven effective on patients with losses without apparent cause. Table 1 summarizes the key therapeutic interventions proposed by the main international entities.[13-15]

The purpose of this review is to discuss RPL causes and shed light on the current evidence in the management of each one, reviewing the therapeutic options and their gestational impacts assessed throughout different systematic reviews and meta-analyses.

Table 1- Therapeutic interventions for recurrent pregnancy loss according to different guidelines[13-15]

	ESHRE(2017)	ASRM(2013)	RCGO(2011)
Genetic factors	Genetic counseling; Limited evidence for PGT	Genetic counseling; consider IVF + PGT, amniocentesis and chorionic villus biopsy	Genetic counseling; IVF + PGT optional
Antiphospholipid syndrome	Low dose aspirin (75-100 mg/day) before conception + unfractionated heparin or LMWH after positive pregnancy test	Low dose aspirin before conception + unfractionated heparin or LMWH	Low dose aspirin + heparin
Anatomic factors	Insufficient evidence on benefit from surgery	Consider uterine septum resection	Insufficient evidence on benefit of uterine septum resection
Inherited Thrombophilia	Unfractionated heparin or LMWH not empirically recommended	Unfractionated heparin or LMWH not empirically recommended unless personal or family history of thromboembolism	Insufficient evidence to recommend the use of heparin
Hormonal and metabolic factors			
Hypothyreoidism	levothyroxine	levothyroxine	levothyroxine
Glucose Metabolism Defects	Metformin not recommended	Metformin	Insufficient evidence for metformin recommendation
Hyperprolactinemia	Dopamine agonists	Dopamine agonists	Insufficient evidence for recommendation
Luteal phase defect	Progesterone not recommended	Progesterone can be beneficial	Insufficient evidence to recommend progesterone or hCG
Psychological factors	Supportive care	Supportive care	Supportive care
Lifestyle modifications	Quit smoking; normal body weight; limit alcohol consumption; healthy diet; normal exercise pattern	Quit smoking; normal body weight; limit alcohol consumption; limit caffeine consumption	
Unexplained loss	Empirical treatments not recommended	Empirical treatments not recommended	

ASRM: American Society for Reproductive Medicine; ESHRE: European Society of Human Reproduction and Embriology; RCGO: Royal College of Obstetricians and Gynaecologists; IVF: *in-vitro* fertilization; PGT: Preimplantation genetic testing; LMWH: Low molecular weight heparin; hCG: human Chorionic Gonadotropin

Methods

A comprehensive and non-systematic search of the theme was carried out through online databases (PubMed and *Cochrane database*), using the terms recurrent pregnancy loss, treatment, genetic or chromosomal abnormalities, uterine factor, uterine septum, septate uterus, fibroid, myoma, cerclage, endocrine causes, polycystic ovary syndrome, thyroid, hypothyroidism, hyperprolactnemia, antiphospholipid syndrome, hereditary thrombophilia, inherited trombophilia, obesity, lifestyle, unexplained miscarriages, progestogens, vaginal progesterone, assisted reproductive technologies, in vitro fertilization, preimplantation genetic screening, obstetric complications and variants as keywords. Approximately 200 articles had the title and abstract readed by authors. The selection criteria were: articles in English, articles published in the last five years, articles that adressed the treatment of causal factors in recurrent pregnacy loss, with preference for randomized controlled trials, meta-analyses, systematic review and review articles. Clinical protocols from the main internacional societies of Reproductive Medicine were also selected. After a complete reading of the selected articles, articles of interest cited in their references were also used.

Results/Discussion

To facilitate the discussion, the authors chose to categorize the results into sections: genetic or chromosomal abnormalities, uterine abnormalities, polycystic ovary syndrome, thyroid disorders, hyperprolactnemia, antiphospholipid syndrome, hereditary thrombophilia, obesity and lifestyle, unexplained miscarriages, assisted reproductive technologies and obstetric complications.

Genetic or chromosomal abnormalities

Around 12% of couples may exhibit structural rearrangements of their chromosomes, with only 40% of these being identified by the traditional karyotypes.[16]

Although carriers of the chromosome alterations may undergo *in-vitro* fertilization (IVF) plus preimplantation genetic diagnosis (PGD) as a way of reducing the miscarriage rates and increase the live birth rates, recent studies reveal no differences of the live birth rate when compared to the natural conception.[17,18] Couples with structural chromosomal rearrangements should be advised of the good reproductive prognosis after natural conception, so that IVF plus PGD should not be offered as first-line treatment for them.[18]

The ESHRE and others entities recommend that all couples with results of an abnormal foetal or parental karyotype should receive genetic counselling.[13-15] Furthermore, the limited evidence for preimplantation genetic testing in couples with RPL shows no clear benefit of treatment.[15]

Uterine abnormalities

The prevalence of anatomical uterine abnormalities in women with RPL varies between 15% and 42% in different studies.[19] The structural uterine anomalies may be divided in congenital and acquired. The congenital anomaly more often associated with repeated losses is the uterine septum.[20] The acquired anomalies include polyps, uterine myomas and intrauterine adhesions.[19]

In patients with RPL and structural uterine malformations, repair of normal anatomy appears to improve gestational prognosis. The hysteroscopic resection of uterine septum and submucosal leiomyomas, when indicated, should be performed.[21]

Retrospective studies reported reduced abortion rates and increased live birth rates in patients who underwent hysteroscopic metroplasty compared to untreated patients.[22] Recentely, a meta-analysis involving seven observational studies found that surgical removal of the septum was associated with a low rate of miscarriage (OR 0.25, 95% CI 0.07-0.88), yet there was no difference regarding the live birth rate (OR 1.92, 95% CI 0.37-9.99).[22] The TRUST trial, a multicentre randomized controlled trial published in 2021, also measured the effect of surgical resection of the septum for pregnancy outcomes in women with septate uterus. Eighty patients were randomized to undergo surgical septum resection (n=40), or expectant management (n=40). The live birth rate was 31% in the septum resection group versus 35% in the expectant management group (RR 0.88, 95% CI 0.47-1.65). There was no difference in live birth rates, the primary outcome of the trial. The results could lead to changes in the septate uterine standard treatment.[23] The surgery is not recommended in other uterine malformations, like bicornuate and didelphic uterus.[19]

Thus, in relation to uterine malformation, the ESHRE points out that whether hysteroscopic septum resection has beneficial effects, this should be evaluated in the context of surgical trials in women with RPL and septate uterus. Metroplasty is not recommended for bicorporeal uterus with normal cervix and RPL. Uterine reconstruction is not

recommended for hemiuterus and RPL. There is insufficient evidence in favour of metroplasty in women with bicorporeal uterus and double cervix and RPL.[15]

While there is a recommendation to remove the submucosal myomas and those that distort the endometrial cavity (types 0-2 according to The International Federation of Gynecology and Obstetrics/FIGO) by the ASRM, the same recommendation is not supported by the European Society for Human Reproduction and Embryology (ESHRE).[14,15,19,24]

Regardless of the association between myomas and miscarriages, there is no solid evidence that myomectomy in RPL patients improves pregnancy prognosis.[24] A retrospective study by Saravelos *et al*. examined the impact of different types of fibroids on the pregnancy outcome of women with RPL and investigated to what extent resection of fibroids distorting the uterine cavity affects the outcome of a future pregnancy. It was demonstrated that the miscarriage rates decreased from 21.7% to 0%, while the live birth rate increased from 23.3% to 52% in women with intracavitary distortion and undergoing myomectomy. However, since there was no control group and considering the good outcomes achieved without intervention, it is not possible to know if the surgeries were responsible for these results.[25] The removal procedure for intramural myomas and those that do not distort the uterine cavity is not indicated.[24] The ESHRE guideline also points out that there is insufficient evidence supporting hysteroscopic removal of submucosal fibroids in women with RPL, and surgical removal of intramural fibroids is not recommended in these women.[15]

The prevalence of endometrial polyps in RPL patients is from 1.6% to 6%, still there is no clear evidence of their association with repeated losses. The prevalence of intrauterine adhesions varies from 1.3% to 9.6% in these patients. The data is insufficient to support the benefits of the removal of polyps and intrauterine adhesions for pregnancy outcome.[15] Given that most surgeons opt to remove anomalies distorting the uterine cavity, due to their possible interference in the embryo implantation, the realization of randomized clinical trials become more difficult.[26] Both the removal of endometrial polyps and intrauterine adhesions should be performed by hysteroscopic.[19]

A meta-analysis by Alfirevic *et al*. assessed the performance of cerclage to prevent preterm birth in singleton pregnancies women with a history of prior losses, ultrasound finding of short cervix or physical exam recommendation. Patients who underwent cerclage presented a reduced risk of perinatal death when compared to those with no cerclage, even though the confidence interval (CI) crossed the line of no effect (RR 0.82, 95% CI 0.65-1.04). Moreover, patients with cerclage were less likely to have a preterm birth when compared to the control groups (RR 0.88, 95% CI 0.69-0.95). It remains unanswered if the cerclage was more effective than the alternative treatments (progesterone and pessary).[27]

The ESHRE recommends women with a history of second-trimester pregnancy losses and suspected cervical weakness should be offered serial cervical sonographic surveillance. In women with a singleton pregnancy and a history of recurrent second-trimester pregnancy loss attributable to cervical weakness, a cerclage could be considered.[15]

Polycystic ovary syndrome

Although Polycystic Ovary Syndrome (PCOS) is associated with an increase number of miscarriages, probably due to hyperinsulinemia and the hyperandrogenism, there is no clear evidence that this condition is associated with RPL.[28] The PCOS incidence appears to be the same in patients with or without history of recurrent losses.[29]

To elucidate the possible effect of pregestacional metformin use in patients with PCOS and the risk of miscarriage, seventeen randomized controlled trials were included in a sistematic review and meta-analysis. The results did not show any benefit of pregestational metformin use, combined with other drugs or not, on the abortion risk in PCOS patients (OR 0.89, 95% CI 0.65-1.21; p = .452).[30]

Concluding, there is insufficient evidence to recommend metformin supplementation in pregnancy to prevent pregnancy loss in women with RPL and glucose metabolism defect.[15]

Thyroid disorders

The treatment of patients with hypothyroidism or hyperthyroidism during pregnancy is undoubted.[15] Otherwise, subclinical hyperthyroidism (SCH) and euthyroid women with high levels of thyroid antibodies treatment is not recommended since there is no evidence of enhanced obstetric outcomes. Seeing that high-quality studies are lacking in literature, the treatment of women with subclinical hypothyroidism is still controversial.[7,31-33] The absence of sufficient evidence that subclinical hypothyroidism, defined as serum thyroid stimulating hormone (TSH) levels above 2.5 mIU/ml and free thyroxine level within the reference range, is a predisposing factor to miscarriage in patients with RPL or that thyroxine use in these women improves pregnancy outcomes.[7,31]

A systematic review and meta-analysis found that levothyroxine did not improve the subsequent live birth rate in women with subclinical hypothyroidism with or without thyroid antibodies. There was a statistically significant association between RPL and thyroid autoimmunity (OR 1.94, 95% CI 1.43-2.64), however there was no benefit from administering levotyroxine in euthyroid patients with thyroid autoimmunity.[34]

A recent cohort study involving 1,418 pregnancies evaluated the prevalence of subclinical hypothyroidism in 1,014 patients with a history of two or more miscarriages and their gestational outcomes. The prevalence of subclinical hypothyroidism in these patients was 14.4% (146/1014). Delivery rates were 75% (33/44) in the tyroxine group, 68.6% (72/105) in the untreated subclinical hypothyroid group, and 70.1% (606/865) in the euthyroid group. After excluding miscarriages with karyotype abnormalities, biochemical pregnancies and ectopic pregnancies, the live birth rate was 89.2% (33/37), 90.0% (72/80) and 91.1% (606/665), respectively. There was no statistically significant difference in birth rates between these 3 groups. In conclusion, levothyroxine did not improve live birth rates in RPL patients with subclinical hypothyroidism. Treatment of subclinical hypothyroidism with TSH levels between 2.5-10.0 mUI/l may have no benefit in increasing live birth rates.[32]

Now, the cohort study by van Dijk et al.[33] evaluated if the subclinical hypothyroidism was associated with the decrease of live birth rates in women with RPL. Women with RPL and normal thyroid function were the control group. A number of 848 women were assessed: 96% had euthyroidism, 2.4% had subclinical hypothyroidism and 1.2% had hypothyroidism. The live birth rate was 45% in women with subclinical hypothyroidism versus 52% in euthyroid women (OR 0.69, CI 95% 0.28-1.71).

In relation to tyroid disease, the ESHRE states that evidence is limited regarding treatment effect of levothyroxine for women with subclinical hypothyroidism and RPL. Treatment of women with SCH may reduce the risk of miscarriage, but the potential benefit of treatment should be balanced against the risks. The evidence to support treatment with levothyroxine in euthyroid women with thyroid antibodies and RPL is insufficient.[15]

Hyperprolactinemia

A small randomized clinical trial measured the use of bromocriptine in patients with RPL and symptomatic or occult hyperprolactinemia. Forty-six patients who had between 2 to 4 miscarriages were included in the analysis. Bromocriptine was administered in doses of 2.5–5.0 mg/day depending on individual response, starting before pregnancy and continued until the end of the 9th week of gestation. The patients in the bromocriptine group were allowed to become pregnant as soon as their serum prolactin levels normalized. The percentage of successful pregnancies was higher in the group of patients treated with bromocriptine than in those not treated (85.7% versus 52.4%, $p < .05$). The serum bromocriptine level during early pregnancy (5-10 weeks' gestation) was significantly higher in patients who miscarried (31.8-55.3 ng/ml) than in patients who had a successful pregnancy (4.6 -15.5 ng/ml. $p < .01$ or $p < .05$).[35]

A 2016 meta-analysis evaluating the use of dopamine agonists to prevent miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage found only 2 studies for evaluation, with only the study cited above being included.[36] Larger studies are therefore needed to assess the benefit of dopamine agonists in patients with RPL and idiopathic hyperprolactinemia.

So, bromocriptine treatment can be considered in women with RPL and hyperprolactinemia to increase live birth rate.[15]

Antiphospholipid Syndrome (APS)

Treatment of APS with low-dose aspirin started preconceptionally and low molecular weight (LMWH) or unfractionated heparin (UFH) started after the first positive pregnancy test is recommended by several international entities.[13-15] The criteria for APS[37] are described in Table 2.

A meta-analysis compared the use of aspirin alone with LMWH plus aspirin and with unfractionated heparin plus aspirin. The use of aspirin alone was related to lower live birth rates when compared to the use of LMWH plus aspirin (OR=0.37; 95%CrI, 0.17-0.71). The use of unfractionated heparin plus aspirin also had high live birth rates when compared to the use of aspirin alone (OR=2.63; 85% CrI, 1.04-5.39). Treatment with LMWH plus aspirin or unfractionated heparin plus aspirin did not differ. Unfractionated heparin plus aspirin improved the birth weight of newborns compared to the use of LMWH plus aspirin. There was no statistically significant difference in gestational age at delivery, rates of preterm delivery, vaginal delivery, cesarean delivery, or restricted intrauterine growth (IUGR) between these 2 associations.[38]

Another recent meta-analysis evaluated the use of aspirin or heparin or both in improving gestational outcomes in patients with persistent levels of antiphospholipid antibodies (anticardiolipin, lupus anticoagulant or anti-β2-glycoprotein-I antibodies) and RPL. The authors concluded that the combination of heparin plus aspirin may increase the birth rate (RR 1.27, 95% CI 1.09-1.49) when compared to aspirin alone.[39]

The ESHRE guideline suggests administration with low dose aspirin (75–100 mg/day), starting before conception, and a prophylactic dose heparin (UFH or LMWH) starting at date of a positive pregnancy test, for these women.[15]

Table 2: Sapporo classification criteria for Antiphospholipid Syndrome - International Consensus[37]

Confirmed diagnosis: 1 clinical criteria + 1 laboratory criteria	
Clinical criteria:	
1. Vascular thrombosis	
2. Pregnancy morbidity	One or more unexplained deaths of a morphologically normal fetus after the 10th week of gestation
	One or more premature births of a morphologically normal newborn before 34 weeks' gestation, because of severe preeclampsia or eclampsia or placental insufficiency
	Three or more miscarriages before 10 weeks of gestation after excluding maternal and paternal morphological and hormonal alterations
Laboratorial criteria:	
1. Presence of lupus anticoagulant in plasma on 2 occasions, at least 12 weeks apart	
2. Presence of IgG and IgM anticardiolipin antibody in plasma in medium or high titers on two or more occasions, at least 12 weeks apart	
3. Presence of IgG or IgM anti-β2-glycoprotein-I antibody in plasma serum at medium or high titers on two or more occasions, at least 12 weeks apart	

Hereditary thrombophilia

Women carrying factor V Leiden mutation (OR 2.44, 95% CI 1.96-3.03), prothrombin gene mutation (OR 2.08, 95% CI 1.61-2.68) and protein S deficiency (OR 3.45, 95% CI 1.15-10.35) had high risk of RPL in a meta-analysis and systematic review.[40]

There are insufficient data to support the use of thromboprophylaxis to reduce miscarriage in patients with RPL. The use of LMWH to improve the live birth rates in pregnant women with hereditary thrombophilia was assessed in a systematic review by Tan et al.[41] Despite the favorable outcomes for the LMWH treatment in these patients (RR 2.40, 95% CI 0.73-7.83), there was no statistically significant difference (p=0.15).

Maternal risk of thromboembolic events should determine the indication for thromboprophylaxis in pregnancy in women with inherited thrombophilia.[42]

According to the ESHRE, antithrombotic prophylaxis for women with hereditary thrombophilia and a history of RPL should only be used in the context of research, or if indicated for venous thromboembolism (VTE) prevention.[15]

Obesity and lifestyle

Obesity is evidently associated with the increase risk of RPL in two meta-analyses.[43,44] A systematic review and meta-analysis analyzed the effects of lifestyles on RPL. Body mass index (BMI), tobacco, alcohol and caffeine intake were evaluated. BMI > 25 was clearly associated with the risk of RPL, but larger studies are needed to assess the effect of alcohol, cigarettes and caffeine.[43]

Couples with RPL should be informed that smoking, alcohol use, obesity and excessive physical activity can have a negative impact on the pregnancy outcome, and it is recommended that smoking cessation and alcohol consumption, maintenance of body weight within the normal range and normal practice of physical exercise before pregnancy.[13-15]

Unexplained miscarriages

Progesterone is essential to establishment and maintenance of pregnancy, and some researchers hypothesize that its deficiency would be cause some miscarriages. The use of progestogens has been attemped for more than 70 years with the aim of preventing new abortions in women with unexplained RPL.[45,46]

Two recent meta-analyses who evaluated the use of progestogens in patients with unexplained RPL concluded that there may be some benefit in the routine administration of synthetic progestogens in this group of women, culminating in lower miscarriage rates and higher live birth rates. However, in these meta-analyses, the types (natural or synthetic), doses and route of administration (oral, vaginal or intramuscular) of the progestins varied, as well as the time of initiation and duration of the intervention.[47,48]

The treatment with micronized vaginal progesterone (Utrogestan®) in women with RPL was evaluated in the study PROMISE (PROgesterone in recurrent MIScarriagE). Women with idiopathic RPL were randomized to receive 400 mg

of micronized vaginal progesterone twice daily or placebo, started with a positive pregnancy test and maintained until 12 weeks gestation. The total live birth rate was 65.8% (262 of 398 women) in the progesterone group and 63.3% (271 of 428 women) in the placebo group (RR 1.04, CI 95% -4.0-9.0). There was also no statistically significant difference between the groups in the rates of clinical pregnancy, miscarriage, ectopic pregnancy, stillbirth, neonatal outcomes, mean age at abortion and preterm birth.[49]

The PRISM (PRogesterone In Spontaneous Miscarriage) randomized clinical trial evaluated the use of micronized vaginal progesterone in patients with vaginal bleeding in the first 12 weeks of pregnancy. Progesterone was maintained until 16 weeks of gestation. The live birth rate was 75% (1513/2025 patients) in the progesterone group and 72% (1459/2013 patients) in the placebo group (RR 1.09, 95% CI 1.0-1.07; p=0.08). When the groups were subdivided by number of previous miscarriages, the group that had 3 or more previous miscarriages benefited from the use of progesterone (72% in the progesterone group vs. 57% in the placebo group; RR 1.28, 95% CI 1.08-1.51; $p = 0.004$).[50]

A critical evaluation of these two large clinical trials (PROMISE and PRISM) concluded that the effectiveness of micronized vaginal progesterone in preventing new miscarriages in women with idiopathic RPL increases with the number of previous miscarriages. For the subgroup with a history of 1 or more previous miscarriages and pregnancy bleeding, the live birth rate was 75% (619/914) with progesterone versus 70% (619/886) with placebo (5% difference; RR 1.09, 95% CI 1.03-1.15; p=0.003). The benefit was greatest in the subgroup of women with 3 or more previous losses and current bleeding; the live birth rate was 72% (98/137) with progesterone versus 57% (85/148) with placebo (15% difference; RR 1.28, CI 95%, 1.08-1.51; p=0.004). The outcomes from these clinical trials should not be generalized to other progestogens, such as dydrogesterone or 17-hydroxyprogesterone. The study does not suggest any benefits of progesterone in women with bleeding and no history of a previous loss.[51]

A meta-analysis by Devall *et al*. evaluated the effectiviness and safety profile for the different progestogen treatments for threatened and recurrent miscarriage. In patients with RPL, the result of a single trial (826 women) evaluating the use of vaginal micronized progesterone versus placebo showed no effect on the live birth rates (RR 1.04, CI 95% 0.95-1.15). The evidence for dydrogestone compared with placebo for women with RPL is very low and its benefits remain unclear. The authors conclude that there is little or no difference in the use of progestogens in the live birth rate for women with threatened miscarriage or RPL. However, vaginal micronized progesterone could increase the live birth rate in women with threatened miscarriage and history of one or more previous abortions. No other type of progestogens has been effective in treating these patients.[52]

The ESHRE guideline states that the evidence to recommend the use of progesterone to improve live birth rate in women with RPL and luteal phase insufficiency is insufficient.[15]

RPL and the Assisted Reproductive Technologies

When a clear etiology in RPL is not identified, some couples and doctors start considering the ART as an option to reduce the time to pregnancy, increase pregnancy chances and improve embryonic quality.[53]

Mean time to conception and delivery in women with unexplained RPL was assessed in a prospective cohort study: 56% after 6 months, 74% after 12 months and 86% after 24 months, with a total live birth rate of 65%. Of these, 13% got pregnant after ART, whereas the others conceived spontaneously. The only factor associated with the increased time for a live birth was the number of previous losses (OR 0.83, 95% CI 0.74-0.94).[54]

A retrospective cohort study compared the time to the next pregnancy in women with unexplained RPL who conceived naturally to those who underwent any infertility treatment. For patients who became pregnant spontaneously, 88% of pregnancies occurred within the first 6 months, with a mean time of 2 (1-10) months. Patients who underwent intrauterine insemination (IUI), IVF and pre-implantation genetic screening (PGS) conceived at a mean time of 3 (1-9), 4 (1-12) and 5 (2-10) months, respectively. A statistically significant difference (p<0.01) was observed in these patients regarding the increased time to the next pregnancy. There was no difference as to the miscarriage rates between the two groups (18% in the spontaneous pregnancy group versus 16% in the ART group without PGS; p=0.76).[55]

Another retrospective study compared the pregnancy outcomes in patients who underwent PGS to those with expectant management (spontaneous attempt to conceive) for a period of 6 months. The median time to pregnancy was of 6.5 months in the PGS group versus 3 months in the expectant management group. The author concluded that PGS should not be offered to couples with an urgency to conceive.[56]

Obstetric complications

A prospective cohort study evaluated pregnancy complications in women with RPL. There were a total of 1092 women divided between women with RPL (431) and control group (661). Women with pregnancy loss history had a higher rate of complications (53.6%) than healthy women without RPL (20.9%) (OR= 4.37; 95% CI 3.345-5,714; p < 0.0001).

The prevalence of the following complications is observed: abortion, cervical insufficiency, genetic alterations, fetal anomalies, oligohydramnios, polyhydramnios, restricted intrauterine growth, gestational diabetes, pre-eclampsia, placenta previa, placental abruption, liver disorders related to pregnancy, premature rupture of membranes. The risk was also higher in those patients with multiple gestations. Women with 3 losses were at greater risk of complications than women with 2 losses (OR = 1,269; CI 1,112-2,386, p < 0.02). There was no difference according to the type of loss (explained or unexplained). Women with RPL had an increased risk of not having a live birth when compared to the control group (OR=5.77, CI 3.359-9,933, p<0.0001). In this work, the increase in the number of previous abortions was related to a reduction in pregnancy rates and an increase in pregnancy complications. When patients were stratified according to the causes of RPL, an increased risk of preeclampsia and placental abruption was observed in women with unexplained loss. Women with secondary loss had a higher risk of gestational diabetes mellitus, probably due to greater exposure to the diabetogenic effect of previous pregnancies.[57]

Conclusion

The treatment for RPL should be directed to the cause of the miscarriages. Since the outcomes for most couples with unexplained RPL are favorable without treatment, therapy interventions that have not been proven are not recommended, especially the expensive and invasive ones. The explanation and emotional support are two of the main factors to treatment success.

References

1. Rai R, Regan L. Recurrent miscarriage. Lancet. 2006;368(9535):601-11. **http://dx.doi.org/10.1016/S0140-6736(06)69204-0**. PMid:16905025.
2. Kolte AM, Bernardi LA, Christiansen OB, Quenby S, Farquharson RG, Goddijn M, et al. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. Hum Reprod. 2015;30(3):495-8. **http://dx.doi.org/10.1093/humrep/deu299**. PMid:25376455.
3. Tulandi T, Al-Fozan HM. Definition and etiology of recurrent pregancy loss. Up to date [Internet]. 2021 [cited 2021 Nov 2]. Available from: https://www.uptodate.com/contents/definition-and-etiology-of-recurrent-pregnacy-loss
4. Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two versus three or more recurrent pregnancy loss. Fertil Steril. 2010;93(4):1234-43. **http://dx.doi.org/10.1016/j.fertnstert.2009.01.166**. PMid:19338986.
5. Porter TF, Scott JR. Evidence-based care of recurrent miscarriage. Best Pract Res Clin Obstet Gynaecol. 2005;19(1):85-101. **http://dx.doi.org/10.1016/j.bpobgyn.2004.11.005**. PMid:15749068.
6. Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Hum Reprod. 2006;21(9):2216-22. **http://dx.doi.org/10.1093/humrep/del150**. PMid:16707507.
7. Homer HA. Modern management of recurrent miscarriage. Aust N Z J Obstet Gynaecol. 2019;59(1):36-44. **http://dx.doi.org/10.1111/ajo.12920**. PMid:30393965.
8. Saravelos SH, Regan L. Unexplained recurrent pregnancy loss. Obstet Gynecol Clin North Am. 2014;41(1):157-66. **http://dx.doi.org/10.1016/j.ogc.2013.10.008**. PMid:24491990.
9. Popescu F, Jaslow CR, Kutteh WH. Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definitive cause of pregnancy loss in over 90% of patients. Hum Reprod. 2018;33(4):579-87. **http://dx.doi.org/10.1093/humrep/dey021**. PMid:29538673.
10. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ. 2000;320(7251):1708-12. **http://dx.doi.org/10.1136/bmj.320.7251.1708**. PMid:10864550.
11. Maquard Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in women over the age of 35 years. Hum Reprod. 2010;94(4):1473-1477. PMID: 19643401.
12. Sugiura-Ogasawara M, Ozaki Y, Kitaori T. Diagnosis and treatment methods for recurrent miscarriage cases. Reprod Med Biol. 2009;8(4):141-4. **http://dx.doi.org/10.1007/s12522-009-0029-6**. PMid:29699318.
13. Royal College of Obstetricians and Gynecologists. Recurrent miscarriage, investigation and treatment of couples. London: RCGO; 2011. (Greentop Guideline; no. 17).
14. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103-11. **http://dx.doi.org/10.1016/j.fertnstert.2012.06.048**. PMid:22835448.
15. Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, et al. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open. 2018;2018(2):hoy004. **http://dx.doi.org/10.1093/hropen/hoy004**. PMid:31486805.
16. de Ziegler D, Frydman RF. Recurrent pregnancy losses, a lasting cause of infertility. Fertil Steril. 2021;115(3):531-2. **http://dx.doi.org/10.1016/j.fertnstert.2020.12.004**. PMid:33581853.
17. Munné S, Howles CM, Wells D. The role of preimplantation genetic diagnosis in diagnosing embryo aneuploidy. Curr Opin Obstet Gynecol. 2009;21(5):442-9. **http://dx.doi.org/10.1097/GCO.0b013e32832fad73**. PMid:19606031.

18. Iews M, Tan J, Taskin J, Alfaraj S, AbdelHafez FF, Abdellah AH, et al. Does preimplantation genetic diagnosis improve reproductive outcome in couple with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review. Reprod Biomed Online. 2018;36(6):677-85. **http://dx.doi.org/10.1016/j.rbmo.2018.03.005**. PMid:29627226.
19. Carbonnel M, Pirtea P, de Ziegler D, Ayoubi JM. Uterine factors in recurrent pregnancy losses. Fertil Steril. 2021;115(3):538-45. **http://dx.doi.org/10.1016/j.fertnstert.2020.12.003**. PMid:33712099.
20. Rackow BW, Arici A. Reproductive performance of women with müllerian anomalies. Curr Opin Obstet Gynecol. 2007;19(3):229-37. **http://dx.doi.org/10.1097/GCO.0b013e32814b0649**. PMid:17495638.
21. Turocy JM, Rackow BW. Uterine factor in recurrent pregnancy loss. Semin Perinatol. 2019;43(2):74-9. **http://dx.doi.org/10.1053/j.semperi.2018.12.003**. PMid:30683511.
22. Krishnan M, Narice BF, Ola B, Metwally M. Does hysteroscopic resection of uterine septum improve reproductive outcomes: a systematic review and meta-analysis. Arch Gynecol Obstet. 2021;303(5):1131-42. **http://dx.doi.org/10.1007/s00404-021-05975-2**. PMid:33550465.
23. Rikken JFW, Verhorstert KWJ, Emanuel MH, Bongers MY, Spinder T, Kuchenbecker WKH, et al. Septum resection in women with a septate uterus: a cohort study. Hum Reprod. 2020;35(7):1578-88. **http://dx.doi.org/10.1093/humrep/dez284**. PMid:32353142.
24. Penzias A, Bendikson K, Butts S, Coutifaris C, Falcone T, Fossum G, et al. Removal of myomas in asymptomatic patients to improve fertility and/or reduce miscarriage rate: a guideline. Fertil Steril. 2017;108(3):416-25. **http://dx.doi.org/10.1016/j.fertnstert.2017.06.034**. PMid:28865538.
25. Saravelos SH, Yan J, Rehmani H, Li TC. The prevalence and impact of fibroids and their treatment on the outcome of pregnancy in women with recurrent miscarriage. Hum Reprod. 2011;26(12):3274-9. **http://dx.doi.org/10.1093/humrep/der293**. PMid:21954281.
26. Shahine L, Lathi R. Recurrent pregnancy loss: evaluation and treatment. Obstet Gynecol Clin North Am. 2015;42(1):117-34. **http://dx.doi.org/10.1016/j.ogc.2014.10.002**. PMid:25681844.
27. Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. Cochrane Database Syst Rev. 2017;6(6):CD008991. **http://dx.doi.org/10.1002/14651858.CD008991.pub3**. PMid:28586127.
28. Amrane S, McConnell R. Endocrine causes of recurrent pregnancy loss. Semin Perinatol. 2019;43(2):80-3. **http://dx.doi.org/10.1053/j.semperi.2018.12.004**. PMid:30665726.
29. Shahine L, Lathi R. Recurrent pregnancy loss evaluation and treatment. Obstet Gynecol Clin North Am. 2015;42(1):117-34. **http://dx.doi.org/10.1016/j.ogc.2014.10.002**. PMid:25681844.
30. Palomba S, Falbo A, Orio F Jr, Zullo F. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2009;92(5):1646-58. **http://dx.doi.org/10.1016/j.fertnstert.2008.08.087**. PMid:18937939.
31. Vissenberg R, van den Boogaard E, van Wely M, van der Post JA, Fliers E, Bisschop PH, et al. Treatment of thyroid disorders before conception and early pregnancy: a systematic review. Hum Reprod Update. 2012;18(4):360-73. **http://dx.doi.org/10.1093/humupd/dms007**. PMid:22431565.
32. Yoshihara H, Sugiura-Ogasawara M, Goto S, Kitaori T. Levothyroxine and subclinical hypothyroidism in patients with recurrent pregnancy loss. Am J Reprod Immunol. 2021;85(3):e13341. **http://dx.doi.org/10.1111/aji.13341**. PMid:32894608.
33. van Dijk MM, Vissenberg R, Bisschop PH, Dawood F, van Wely M, Goddijn M, et al. Is subclinical hypothyroidism associated with lower live birth rates in women who have experienced unexplained recurrent miscarriage? Reprod Biomed Online. 2016;33(6):745-51. **http://dx.doi.org/10.1016/j.rbmo.2016.09.002**. PMid:27720162.
34. Dong AC, Morgan J, Kane M, Stagnaro-Green A, Stephenson MD. Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril. 2020;113(3):587-600. **http://dx.doi.org/10.1016/j.fertnstert.2019.11.003**. PMid:32192591.
35. Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. Fertil Steril. 1998;70(2):246-52. **http://dx.doi.org/10.1016/S0015-0282(98)00164-2**. PMid:9696215.
36. Chen H, Fu J, Huang W. Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history. Cochrane Database Syst Rev. 2016;7(7):CD008883. **http://dx.doi.org/10.1002/14651858.CD008883.pub2**. PMid:27455388.
37. Chaturvedi S, McCrae KR. Diagnosis and management of the antiphospholipid syndrome. Blood Rev. 2017;31(6):406-17. **http://dx.doi.org/10.1016/j.blre.2017.07.006**. PMid:28784423.
38. Liu X, Qiu Y, Yu ED, Xiang S, Meng R, Niu K, et al. Comparison of therapeutic interventions for recurrent pregnancy loss in association with antiphospholipid syndrome: a systematic review and network meta-analysis. Am J Reprod Immunol. 2020;83(4):e13219. **http://dx.doi.org/10.1111/aji.13219**. PMid:31872490.
39. Hamulyák EN, Scheres LJ, Marijnen MC, Goddijn M, Middeldorp S. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. Cochrane Database Syst Rev. 2020;5(5):CD012852. PMid:32358837.
40. Liu X, Chen Y, Ye C, Xing D, Wu R, Li F, et al. Hereditary thrombophilia and recurrent pregnancy loss: a systematic review and meta-analysis. Hum Reprod. 2021;36(5):1213-29. **http://dx.doi.org/10.1093/humrep/deab010**. PMid:33575779.

41. Tan WK, Lim SK, Tan LK, Bauptista D. Does low-molecular-weight heparin improve live birth rates in pregnant women with thrombophilic disorders? A systematic review. Singapore Med J. 2012;53(10):659-63. PMid:23112017.
42. Davenport WB, Kutteh WH. Inherited trombophilias and adverse pregnancy outcomes: a review of screening patterns and recommendations. Obstet Gynecol Clin North Am. 2014;41(1):133-44. **http://dx.doi.org/10.1016/j.ogc.2013.10.005**. PMid:24491988.
43. Ng KYB, Cherian G, Kermack AJ, Bailey S, Macklon N, Sunkara SK, et al. Systematic review and meta-analysis of female lifestyle factors and risk of recurrent pregnancy loss. Sci Rep. 2021;11(1):7081. **http://dx.doi.org/10.1038/s41598-021-86445-2**. PMid:33782474.
44. Cavalcante MB, Sarno M, Peixoto AB, Araujo Júnior E, Barini R. Obesity and recurrent miscarriage: A systematic review and meta-analysis. J Obstet Gynaecol Res. 2019;45(1):30-8. **http://dx.doi.org/10.1111/jog.13799**. PMid:30156037.
45. Devall AJ, Coomarasamy A. Sporadic pregnancy loss and recurrent miscarriage. Best Pract Res Clin Obstet Gynaecol. 2020;69:30-9. **http://dx.doi.org/10.1016/j.bpobgyn.2020.09.002**. PMid:32978069.
46. Coomarasamy A, Dhillon-Smith RK, Papadopoulou A, Al-Memar M, Brewin J, Abrahams VM, et al. Recurrent miscarriage: evidence to accelerate action. Lancet. 2021;397(10285):1675-82. **http://dx.doi.org/10.1016/S0140-6736(21)00681-4**. PMid:33915096.
47. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. Cochrane Database Syst Rev. 2019;2019(11):CD003511. **http://dx.doi.org/10.1002/14651858.CD003511.pub5**. PMid:31745982.
48. Saccone G, Schoen C, Franasiak JM, Scott RT Jr, Berghella V. Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials. Fertil Steril. 2017;107(2):430-8.e3. **http://dx.doi.org/10.1016/j.fertnstert.2016.10.031**. PMid:27887710.
49. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, et al. A randomized trial of progesterone in women with recurrent miscarriages. N Engl J Med. 2015;373(22):2141-8. **http://dx.doi.org/10.1056/NEJMoa1504927**. PMid:26605928.
50. Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. N Engl J Med. 2019;380(19):1815-24. **http://dx.doi.org/10.1056/NEJMoa1813730**. PMid:31067371.
51. Coomarasamy A, Devall AJ, Brosens JJ, Quenby S, Stephenson MD, Sierra S, et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol. 2020;223(2):167-76. **http://dx.doi.org/10.1016/j.ajog.2019.12.006**. PMid:32008730.
52. Devall AJ, Papadopoulou A, Podesek M, Haas DM, Price MJ, Coomarasamy A, et al. Progestogens for preventing miscarriage: a network meta-analysis. Cochrane Database Syst Rev. 2021;4(4):CD013792. PMid:33872382.
53. Kirshenbaum M, Orvieto R. Should we offer in vitro fertilization to couples with unexplained recurrent pregnancy loss? J Clin Med. 2019;8(11):2001. **http://dx.doi.org/10.3390/jcm8112001**. PMid:31744073.
54. Kaandorp SP, van Mens TE, Middeldorp S, Hutten BA, Hof MH, van der Post JA, et al. Time to conception and time to live birth in women with unexplained recurrent miscarriage. Hum Reprod. 2014;29(6):1146-52. **http://dx.doi.org/10.1093/humrep/deu052**. PMid:24682612.
55. Perfetto CO, Murugappan G, Lathi RB. Time to next pregnancy in spontaneous pregnancies versus treatment cycles in fertile patients with recurrent pregnancy loss. Fertil Res Pract. 2015;1(1):5. **http://dx.doi.org/10.1186/2054-7099-1-5**. PMid:28620510.
56. Murugappan G, Shahine LK, Perfetto CO, Hickok LR, Lathi RB. Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss. Hum Reprod. 2016;31(8):1668-74. **http://dx.doi.org/10.1093/humrep/dew135**. PMid:27278003.
57. Ticconi C, Pietropolli A, Specchia M, Nicastri E, Chiaramonte C, Piccione E, et al. Pregnancy-related complications in women with recurrent pregnancy loss: a prospective cohort study. J Clin Med. 2020;9(9):2833. **http://dx.doi.org/10.3390/jcm9092833**. PMid:32882985.

***Correspondence**

Elaine Cristina Fontes de Oliveira
Avenida Professor Alfredo Balena, no 110, Centro, CEP 30130-100, Belo Horizonte, MG, Brasil
E-mail: emedmg@gmail.com

Authors information

ECFO: Master´s Degree in Women Health, Hospital das Clínicas, Universidade Federal de Minas Gerais. **MSLP:** Ph.D. in Women Health, Hospital das Clínicas, Universidade Federal de Minas Gerais. **GMPG:** resident doctor in Gynecology and Obstetrics, Hospital das Clínicas, Universidade Federal de Minas Gerais. **IKDC:** Ph.D. in Women Health, Hospital das Clínicas, Universidade Federal de Minas Gerais.

Authors contribution

ECFO: Conceptualization; Investigation; Writing – original draft

MSLP: Writing- original draft (supporting)

GMPG: Writing- original draft (supporting)

IKDC: conceptualization (supporting); review & editing (lead)