Management of Recurrent Pregnancy Loss

Sana N. Khan

Abstract

Recurrent pregnancy loss (RPL) defined as two pregnancies diagnosed on ultrasound or histopathologic examination or any three consecutive pregnancy losses. Approximately 2% of reproductive aged women experience RPL in contrast to the 15% of women who experience sporadic losses. Etiologies are varied and research continues to further understanding of the unknown. Management of recurrent pregnancy loss depends largely on the etiology, keeping in mind that approximately 50% of cases will be unexplained. Improved outcomes are achieved when this condition is managed by a specialist, who can provide psychological support throughout diagnosis and management. Briefly, when karyotype abnormalities are encountered, the couple will need genetic counseling and may be offered prenatal genetic screening or even assisted reproductive techniques to largely ensure a euploid fetus. Anatomic abnormalities of the uterus are often managed surgically. When antiphospholipid antibody syndrome is encountered, treatment with aspirin and heparin has been shown to improve outcomes. Treatment of overt thyroid disease, diabetes mellitus, or hyperprolactinemia is warranted to normalize hormone values. Anticoagulation may be warranted for inherited conditions; however testing and treatment of acquired conditions are not advised. Given that a large percentage of cases are unexplained, treatment options for this subset have also been proposed including lifestyle modifications, or as last resort oocyte donation or gestational surrogacy.

Keywords

Recurrent pregnancy loss • Recurrent miscarriage • Habitual aborter • Unexplained pregnancy loss • Idiopathic pregnancy loss

Contents

S.N. Khan (✉)
Wayne State University, Detroit, MI, USA
e-mail: snkhan@med.wayne.edu

D. Shoupe (ed.), *Handbook of Gynecology*,
DOI 10.1007/978-3-319-17798-4_39

1 Introduction

Recurrent pregnancy loss (RPL) can be a challenging and complicated problem, defined as two or more failed clinical pregnancies diagnosed ultrasonographically or histopathologically or any three consecutive pregnancy losses. This problem is encountered by approximately 2% of reproductive aged women, in contrast to 15% of reproductive aged women who experience sporadic **miscarriage**. **RPL** is complex because of the fact that an etiology is often not encountered, in approximately 50% of cases, and because of the fact that the problem is psychologically very taxing for couples (Li et al. 2002). **RPL**, defined as three or more **miscarriages**, is thought to affect 1% of reproductive aged couples (Stirrat 1990; Salat-Baroux 1988). This condition is further complicated by the lack of randomized clinical data, and most recommendations are based on meta-analysis, observational studies, and expert opinions (Practice Committee of the American Society for Reproductive Medicine 2012). However, patients can be reassured that live birth rates after normal and abnormal diagnostic testing are 71% and 77%, respectively (Harger et al. 1983). It has been reported that patients have improved outcomes when managed by a specialist with experience in the treatment of RPL.

2 Causes and Management of Recurrent Pregnancy Loss

2.1 Karyotypic Abnormalities

When chromosomal abnormalities are discovered in one or both parents, it is essential that comprehensive genetic counseling be offered to the patient. The reasons for this are twofold, one to understand the abnormalities and the rates of abnormal gametes and risk for future loss events as well as to understand the rate of transmission to future generations (Laurino et al. 2005).

Unfortunately, when products of conception are evaluated, the majority have sporadic chromosomal abnormalities. Balanced reciprocal translocations in one or both parents make up approximately 2–5% of RPL cases, and genetic counseling is strongly encouraged to identify breakpoints, which can help couples determine their future risks and chances for success. This data, as well as the fact that RPL is approximately six times higher in first cousins, supports the suggestion that RPL may be associated with nonrandom genetic errors (Christiansen et al. 1990).

One option for these couples as well as those with RPL is embryo evaluation with preimplantation genetic screening (PGS); however, some couples opt for gamete or embryo donation. This information may be of particular importance considering that fetal chromosomal abnormalities are found in >70% of products of conception in women greater than 35 years of age (Marquard et al. 2010).

2.2 Other Genetic Causes

A variety of other genetic causes including single or multiple gene defects or polymorphisms have also been associated with RPL. These include methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms (Chen et al. 2016). Other etiologies include skewed X chromosome inactivation and Y chromosome microdeletion in the male partner (Agarwal et al. 2015).

2.3 Uterine Abnormalities

When uterine abnormalities are encountered, which can include congenital or mullerian abnormalities, adhesive disease, or submucosal myomata, these are surgically resected with improved pregnancy rates (Mollo et al. 2009; Tomazevic et al. 2010). Various techniques have been employed to restore normal anatomy including hysteroscopy, laparoscopic and open depending on the lesion encountered. The use of prophylactic cerclage is controversial in patients receiving uterine reconstruction for a mullerian anomaly.

2.4 Immunologic Factors

Some preliminary data suggests that in addition to immunologic disease entities, paternal antigens in the embryo may trigger a rejection response. Others postulate that abnormal expressions of normal signaling mediators such as cytokines or integrins may play a role (Saito et al. 2016).

2.4.1 Antiphospholipid Syndrome

Testing for antiphospholipid antibody syndrome (APAS) includes laboratory detection of high levels of anticardiolipin, lupus anticoagulant, or anti-β-2 glycoprotein-1 antibodies on two separate occasions in addition to the clinical criteria of vascular thrombosis of a deep vessel or unexplained death of a morphologically normal fetus >10 weeks, or premature delivery <34 weeks secondary to preeclampsia, eclampsia, or placental insufficiency, or three or more **unexplained losses** <10 weeks.

Treatment depends on the individual clinical scenario, but typically involves the use of heparin or low molecular weight heparin (LMWH) to prevent venous thromboembolic events and/or a combination of low-dose aspirin and heparin or LMWH to prevent arterial events. Therapy can begin either with conception or some groups report conception attempt for patient with history of early losses.

2.4.2 Celiac Disease

Data has suggested that untreated celiac disease is associated with infertility and pregnancy loss. This data, although not always consistent, reminds us to optimize a woman's heath ensuring that all medical conditions are treated prior to attempting pregnancy.

2.5 Endocrine Dysfunction

Patients may present with endocrine abnormalities including diabetes mellitus, thyroid disease, or hyperprolactinemia. Overt endocrine dysfunction requires prompt treatment and normalization of the underlying condition, ideally prior to conception.

2.5.1 Thyroid Dysfunction

In addition to the correction of overt thyroid disease, euthyroid patients with thyroid peroxidase antibodies appear to benefit from low-dose levothyroxine supplementation. Limited data suggests that benefits may include decreased miscarriage and preterm delivery rates (Negro et al. 2006).

2.5.2 Hyperprolactinemia

Elevated prolactin levels have been associated with increased miscarriage rate, and treatment with dopamine agonists appears to decrease rates of adverse outcomes. High prolactin levels have been suggested to cause or potentially contribute to a luteal phase defect. Treatment may include either bromocriptine or cabergoline depending on the side effect panels and cost to patients (Hirahara et al. 1998). It is also usually recommended that treatment be continued into pregnancy.

2.5.3 Luteal Phase Defect

Luteal phase abnormality was previously considered to play a role in the disruption of early pregnancies; however there is no strong evidence to suggest that exogenous progesterone supplementation prevents early miscarriage, leading to in 2015 a statement from the American Society for Reproductive Medicine, stating no need for exogenous progesterone after a pregnancy has been established. However, it has been demonstrated that progesterone supplementation is very important in assisted reproductive cycles as high steroid secretion for multiple corpora lutea negatively feeds back on the hypothalamic-pituitary axis causing decreased LH secretion and premature luteolysis (Pluchino et al. 2014).

2.6 Polycystic Ovarian Syndrome

Previous literature has shown that miscarriage rates are higher in patients with polycystic ovarian

syndrome as compared with the general population. Mechanisms for this are postulated to include elevated luteinizing hormone, testosterone, or insulin resistance. Therefore, therapies should focus on normalization of hormone and insulin/glucose levels. Prior research has suggested that the use of metformin may decrease the rates of pregnancy loss; however, larger studies have failed to confirm these findings (Okon et al. 1998). Some studies suggest that a subgroup of PCOS patients with insulin resistance and obesity may benefit from anticoagulation therapy (Chakraborty et al. 2013).

2.7 Infectious/Microbial

In the past a variety of infectious agents such as *Listeria monocytogenes*, *Toxoplasma gondii*, *cytomegalovirus*, and primary genital herpes have been found to be associated with sporadic pregnancy loss however not with RPL. More recently, however, CMV has been correlated with RPL rates, and it is unclear whether the underlying etiology is any exposure to the virus or a reactivation or recurrence is responsible for adverse outcomes (Sherkat et al. 2014). Other studies have more closely examined products of conception for infections such as *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis* as well as *human papillomavirus* (HPV) and only found HPV to be more prevalent and of uncertain significance (Matovina et al. 2004).

2.8 Unexplained

As previously mentioned, in nearly the majority of patients with RPL, no etiology is found. Many patients question the role that lifestyle choices such as tobacco, alcohol, exercise, and diet play in RPL. No data clearly suggests definitive improvement with these changes. Therefore, recommendations should be based to optimize overall health.

Progesterone supplementation has long been prescribed for a variety of situations involving assisted reproductive technologies and infertility treatments. Data from meta-analysis suggests improved outcomes in patients with RPL; however given concerns and limitations, governing regulatory bodies do not recommend the use of progesterone after a pregnancy has been established (Practice Committee of the American Society for Reproductive Medicine 2015).

A variety of therapies have been tested and found to be ineffective, or the efficacy has not been proven.

The use of aspirin and/or heparin or LMWH in the absence of the diagnosis of antiphospholipid antibody syndrome.

Glucocorticoid use has not found to be effective.

There are currently no recommendations to test for inherited thrombotic disease in the evaluation of RPL.

Currently, no immunologic treatments are recommended for RPL patients.

Given the relatively good success rates of patients with RPL, PGS should not be an initial option for these patients as advised by the major organization guidelines (Thornhill et al. 2005; Practice Committee of the American Society for Reproductive Medicine and Practice Committee of the Society for Assisted Reproductive Technology 2006).

Interestingly, several studies have suggested that adequate psychological support for patients suffering from **unexplained RPL** significantly improved outcomes. Treatments included specific antenatal counseling and psychological support techniques and being managed by dedicated pregnancy loss providers (Clifford et al. 1997).

2.9 Miscellaneous

Some literature has noted that poor egg quality alone may be the cause of recurrent pregnancy loss, but further investigation is needed (Remohi et al. 1996). The oocyte may not be the only gamete implicated in RPL, as a recent meta-analysis noted that DNA fragmentation in sperm was statistically significantly related to

Table 1 Summarizing RPL

Categories of RPL	Percentage	Specific etiologies	Management
Anatomic	22	Congenital/mullerian anomalies Leiomyomata Polyps Intrauterine adhesions Abnormal endometrial receptivity	Surgical management of surgical abnormality Endometrial receptivity testing
Immunologic	25	APAS Cytokine/integrin factor	Anticoagulation therapy with aspirin and heparin
Endocrine	20	Diabetes mellitus Polycystic ovarian syndrome Thyroid dysfunction Hyperprolactinemia	Treatment of underlying condition
Infectious/ microbial	6	Infectious etiologies mostly responsible for sporadic not recurrent pregnancy loss	
Genetic	3	Aneuploidy Chromosomal rearrangement	Testing of products of conception, possible embryo biopsy
Unknown	40		

miscarriage and recommended utilizing sperm selection techniques to improve outcomes (Robinson et al. 2012).

Timing of implantation has been the focus of some researchers as they question the adage that the window of implantation is constant in all women. New data suggests that the timing of transfer may need to be individualized, and this has resulted in increased implantation and pregnancy success in the setting of RPL with euploid embryos. Endometrial receptivity testing based on these findings is being developed for clinical use (Ruiz-Alonso et al. 2014).

Integrins are now being studied in various tissues as biomarkers for a variety of both physiologic and disease processes. Beta3 integrin has been studied as a marker of implantation, and it has been shown that in patients with RPL, the expression of this integrin is significantly decreased. Reasons for this remain unclear; however the use of endometrial receptivity testing may overcome these issues or educate patients and physicians to move in other directions such as surrogacy or uterine transplantation (Germeyer et al. 2014). Table summarizing percentages, causes and management of various causes of RPL (Table 1).

3 Conclusion

RPL is a complex problem, which can be devastating to the patients experiencing this condition. Management, performed by a specialist, should focus on psychological support while underlying etiologies are diagnosed and treated. Patients should be assured that most do go on to have live births.

References

Agarwal S, Agarwal A, Khanna A, Singh K. Microdeletion of Y chromosome as a cause of recurrent pregnancy loss. J Hum Reprod Sci. 2015;8(3):159–64.

Chakraborty P, Banerjee S, Saha P, Nandi SS, Sharma S, Goswami SK, et al. Aspirin and low-molecular weight heparin combination therapy effectively prevents recurrent miscarriage in hyperhomocysteinemic women. PLoS One. 2013;8(9):e74155.

Chen H, Yang X, Lu M. Methylenetetrahydrofolatereductase gene polymorphisms and recurrent pregnant loss in China: systematic review and meta-analysis. Arch Gynecol Obstet. 2016;293(2):283–90.

Christiansen OB, Mathiesen O, Lauritsen JG, Grunnet N. Idiopathic recurrent spontaneous abortion. Evidence of a familial predisposition. Acta Obstet Gynecol Scand. 1990;69(7–8):597–601.

Clifford K, Rai R, Regan L. Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Hum Reprod. 1997;12(2):387–9.

Germeyer A, Savaris RF, Jauckus J, Lessey B. Endometrial beta3 integrin profile reflects endometrial receptivity defects in women with unexplained recurrent pregnancy loss. Reprod Biol Endocrinol. 2014;12:53.

Harger JH, Archer DF, Marchese SG, Muracca-Clemens-M, Garver KL. Etiology of recurrent pregnancy losses and outcome of subsequent pregnancies. Obstet Gynecol. 1983;62(5):574–81.

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.

Laurino MY, Bennett RL, Saraiya DS, Baumeister L, Doyle DL, Leppig K, et al. Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2005;14(3):165–81.

Li TC, Iqbal T, Anstie B, Gillham J, Amer S, Wood K, et al. An analysis of the pattern of pregnancy loss in women with recurrent miscarriage. Fertil Steril. 2002;78(5):1100–6.

Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in women over the age of 35 years. Fertil Steril. 2010;94(4):1473–7.

Matovina M, Husnjak K, Milutin N, Ciglar S, Grce M. Possible role of bacterial and viral infections in miscarriages. Fertil Steril. 2004;81(3):662–9.

Mollo A, De Franciscis P, Colacurci N, Cobellis L, Perino A, Venezia R, et al. Hysteroscopic resection of the septum improves the pregnancy rate of women with unexplained infertility: a prospective controlled trial. Fertil Steril. 2009;91(6):2628–31.

Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab. 2006;91(7):2587–91.

Okon MA, Laird SM, Tuckerman EM, Li TC. Serum androgen levels in women who have recurrent miscarriages and their correlation with markers of endometrial function. Fertil Steril. 1998;69(4):682–90.

Pluchino N, Drakopoulos P, Wenger JM, Petignat P, Streuli I, Genazzani AR. Hormonal causes of recurrent pregnancy loss (RPL). Hormones (Athens). 2014;13(3):314–22.

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.

Practice Committee of the American Society for Reproductive Medicine. Current clinical irrelevance of luteal phase deficiency: a committee opinion. Fertil Steril. 2015;103(4):e27–32.

Practice Committee of the American Society for Reproductive Medicine, Practice Committee of the Society for Assisted Reproductive Technology. Preimplantation genetic diagnosis. Fertil Steril. 2006;86(5 Suppl 1):S257–8.

Remohi J, Gallardo E, Levy M, Valbuena D, De los Santos MJ, Simon C, et al. Oocyte donation in women with recurrent pregnancy loss. Hum Reprod. 1996;11(9):2048–51.

Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S, et al. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Hum Reprod. 2012; 27(10):2908–17.

Ruiz-Alonso M, Galindo N, Pellicer A, Simon C. What a difference two days make: "personalized" embryo transfer (pET) paradigm: a case report and pilot study. Hum Reprod. 2014;29(6):1244–7.

Saito S, Shima T, Nakashima A, Inada K, Yoshino O. Role of paternal antigen-specific treg cells in successful implantation. Am J Reprod Immunol. 2016; 75(3):310–6.

Salat-Baroux J. Recurrent spontaneous abortions. Reprod Nutr Dev. 1988;28(6B):1555–68.

Sherkat R, Meidani M, Zarabian H, Rezaei A, Gholamrezaei A. Seropositivity of cytomegalovirus in patients with recurrent pregnancy loss. J Res Med Sci. 2014;19 Suppl 1:S22–5.

Stirrat GM. Recurrent miscarriage. Lancet. 1990; 336(8716):673–5.

Thornhill AR, De Die-Smulders CE, Geraedts JP, Harper JC, Harton GL, Lavery S, et al. ESHRE PGD Consortium "Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)". Hum Reprod. 2005;20 (1):35–48.

Tomazevic T, Ban-Frangez H, Virant-Klun I, Verdenik I, Pozlep B, Vrtacnik-Bokal E. Septate, subseptate and arcuate uterus decrease pregnancy and live birth rates in IVF/ICSI. Reprod Biomed Online. 2010;21(5): 700–5.