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REVIEW

Recurrent Spontaneous Abortion

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Introduction

Recurrent spontaneous abortion (RSA) is a common clinical problem affecting approximately 1 in 300 women.[1] RSA is generally defined as three or more clinically detectable pregnancy losses before the 20th week of pregnancy. However, many physicians initiate an evaluation after two consecutive fetal losses, especially when the patient has not had a previous full-term pregnancy or is older than 35 years of age. Older terminology such as habitual abortion and repetitive miscarriage should be abandoned as these terms carry a negative connotation to the patient. Although an aetiology for recurrent fetal loss can be ascertained for approximately 40-60% of the couples evaluated,[2] the outcome after appropriate therapy is often successful. An important part of the clinical management of couples with recurrent pregnancy loss, apart from extensive investigation and treatment, is patient education and counseling, especially regarding the risk of subsequent losses. Older estimates of the risk of future losses based on the number of previous losses were calculated on incorrect assumptions and greatly exaggerated the risks. This review will describe the currently recognized aetiologic factors, diagnostic techniques, and therapeutic modalities being used for RSA.

Incidence

Between 12% and 20% of clinically recognized pregnancies end in spontaneous abortion. The true incidence of sporadic pregnancy loss is unknown, however, since a considerable number of early gestations may be lost prior to a missed menstrual period. Studies assaying for human chorionic gonadotropin after cycle day 20 suggest a much higher overall sporadic pregnancy loss rate of 30-60%.[3] The reported risk of successive losses varies in the literature. Patients who have had a prior livebirth with subsequent spontaneous losses have a risk for repeated abortion of less than 30%, regardless of the number of previous spontaneous abortions.[4] The risk that a first pregnancy will end in abortion is 10-15%. Without a previous successful birth, after one loss the chance for a second spontaneous abortion is 13-24%. After two spontaneous losses, the risk of a third loss increases to 20-38%. After a third consecutive spontaneous abortion, the risk for a

fourth loss rises to 20-45%.[5] In most studies, the number of patients experiencing more than four consecutive losses is too small to assess further risk accurately. Observation from these small cohorts suggest a further recurrence risk of 25-50%.[5] In couples with no identifiable problem associated with RSA approximately two-thirds will have a livebirth within 3 years.[2,6] Thus, it is useful to counsel couples with RSA who have had a previous liveborn that their chance for a successful term pregnancy is approximately 70%. For those with no liveborn offspring, the chance for a successful outcome is approximately about 50%.[5]

Aetiology

At least six major categories of disorders have been associated with RSA. These include genetic (25%), anatomic (10-15%), endocrinologic (15%), infectious, environmental toxins and drugs (5-10%), RSA remains unexplained in 40-60% of cases which includes immunologic abnormalities.[7,8]

Evaluation

Evaluation should be initiated after two or three spontaneous abortions. A complete history, including exposure to drugs, diethylstilbestrol (DES), radiation and previous cervical or uterine instrumentration should be obtained. A careful physical examination may reveal evidence of a metabolic illness, an endocrinologic disorder, or a genital tract abnormality such as mullerian anomalies, DES exposure, or leiomyomas. Laboratory studies recommended include peripheral blood karyotype of both partners, blood type and Rh factor, thyroid function studies, serum prolactin, and antiphospholipid antibody evaluation. Endocervical cultures for mycoplasma and ureaplasma may be obtained. Endometrial biopsy should be performed 1-3 days before the anticipated onset of the menstrual peroid to diagnose luteal phase defect (LPD). Hysterosalpingography (HSG) is performed prior to ovulation to evaluate the intrauterine cavity. Hysteroscopy and laparoscopy during the follicular phase may be indicated if a uterine anatomic defect is suspected.

Management

Genetic factors

Traditionally, it has been claimed that 50% of abortuses exhibit karyotypic anomalies. Only about 5% of the abnormal karyotypes are abnormalities in the structure of individual chromosomes, such as translocation. The vast majority are numerical abnormalities due to error occurring during gonadogenesis (chromosomal nondisjunction during meiosis), fertilization (triploidy due to digyny or dispermy) or the first division of the fertilized ovum (tetraploidy or mosaicism). Autosomal trisomy is the most common abnormal karyotype (50%), followed in decreasing frequency by monosomy 45 X (20%), triploidy (15%), tetraploidy (10%) and structural abnormalities (5%).[9]

Chromosomal anomalies account for approximately 25% of RSA. Increased incidence of fetal chromosomal abnormalities corresponds to increased maternal age. The incidence of genetic abnormalities in couples experiencing RSA is 3-5%, slightly higher than that observed in the general population (1%). Parental translocations, inversions, and mosaicisms account for 12% of RSA. If translocation is present in one parent, the chance for a successful pregnancy decreases to 20%.[10]

Genetic treatment at the current time is limited to counseling the couple regarding the potential for a successful pregnancy and

alternative approaches to building a family. If the genetic defect is paternal in origin then donor insemination should be mentioned as an alternative source of sperm. If the defect is maternal in origin, oocyte donation can now be considered since it is becoming increasingly available. Embryonic genetic diagnosis and therapy will not be available for sometime.

Anatomic factors

Uterine anomalies account for 10-15% of RSA. Clinically significant incomplete mullerian fusion or septum resorption occurs in 0.1% of females. Approximately 20-25% of women with unicornuate, bicornuate, didelphys, and or septate uteri will experience difficulty with reproductive functioning, including RSA.[11] Uterine fusion defects are generally associated with recurrent losses occurring in the second trimester. Implantation into an inadequately perfused septum can result in either first or second-trimester losses. The incidence of spontaneous abortion in a woman with a unicornuate uterus is 48% ; with uterine didelphys 43%; with bicornuate uterus 35% and with septate uterus 67%.[12] Successful pregnancy outcomes of 75-77% have been reported after Strassman metroplasty repair of bicornuate uteri.[13] Hysteroscopic resection is currently the treatment of choice for the patients with recurrent abortion and a uterine septum. The result of this treatment is as good as or better than an abdominal metroplasty. It has been reported that after hysteroscopic resection of the uterine septum the abortion rate decreased from 95% to 13%.[14]

Women exposed in utero to DES have an increased risk of reproductive difficulties. When stigmata of DES exposure, such as cervicovaginal ridges or a T-shaped uterus on HSG, are present the risk of spontaneous loss is 27-37% with each conception.[3] A smaller endometrial cavity, inadequate endometrial development, and increased incidence of incompetent cervix may contribute to the increased spontaneous loss rate. Documented cervical incompetence can be treated with cervical cerclage. Other therapies have not been found to be efficacious in decreasing spontaneous abortion risk in this population.

Cervical incompetence is characterized by an asymptomatic dilation of the internal cervical os leading to dilation of the cervical canal and external os during the second trimester of pregnancy. The consequent lack of support of the fetal membranes leads to their spontaneous rupture, which is usually followed by expulsion of the fetus and placenta. It has been estimated that about 20% of midtrimester pregnancy losses are due to cervical incompetence.[15] Cervical incompetence can result from trauma (multiple or excessive cervical dilation or wide cervical conization) or congenital defects (congenital collagen matrix abnormalities, DES exposure, or uterine didelphys). The best treatment of cervical incompetence is placement of a concentric, nonabsorbable silk or Mersilene suture at the level of the internal os (cerclage), utilizing the technique described by either Shirodkar or McDonald. These techniques yield a similar rate of success, with the rate of fetal survival increasing from about 20% before suture placement to 70% after cerclage procedure.[16]

Intrauterine adhesions (Asherman's syndrome) can result from traumatic endometrial curettage following an abortion or delivery, uterine surgery involving excision or cautery of submucous fibroids, postpartum endometritis, or pelvic tuberculosis. Symptoms include amenorrhea unresponsive to estrogen-progesterone administration, oligomenorrhea, infertility, or recurrent

pregnancy loss. Of the patients able to conceive, 40-80% will experience spontaneous abortion. Recurrent loss is attributed to inadequate endometrial growth and vascularization to support the pregnancy. Synechiae are visualized as intrauterine filling defects on a hysterosalpingogram. The diagnosis is best confirmed by hysteroscopy. The recommended treatment for intrauterine adhesions is lysis of the adhesions with miniature scissors during hysteroscopy. After adhesion lysis, either an intrauterine device or small foley cather is usually placed in the cavity. Hormonal therapy with 2.5 mg of conjugated estrogen daily for 2 months with 10 mg/d of Medroxyprogesterone acetate for the last 10 days of each month is administered to regenerate the endometrium, and then the foreign body is removed. It has been reported that the abortion rate decreased from 83% to 13% after hysteroscopic lysis of adhesion.[17]

Distortion of the endometrial cavity may also result from submucosal myomas. Abnormalities of the blood flow or endometrial development caused by myomas may lead to faulty implantation and early abortion. Later pregnancy, rapid tumour growth with or without degeneration can lead to premature labour. Nonetheless, myomas are uncommon as a cause of RSA. Myomectomy is indicated when all other aetiologies have been excluded. Hysteroscopic resection of submucous myomas can decrease the need for caesarean delivery in selected cases.

Endocrinologic factors

Luteal Phase Defect (LPD)

Maintenance of the endometrium for the first eight weeks of gestation depends on progesterone produced by the corpus luteum. The function of the latter depends on hCG produced by the trophoblast. When progesterone secretion from the corpus luteum is lower than normal, endometrial development may be inadequate to support the implanted blastocyst and may lead to spontaneous abortion. Thus it is reasonable to assume that defects in ovarian production of progesterone may result in either infertility, early abortion, or both. Yet controversy exists in the manner of diagnosis, the frequency of the abnormality in women with RSA, appropriate forms of therapy, and rate of success.

Endometrial biopsy during the late luteal phase is the most widely advocated method of diagnosing LPD. A single strip of endometrium from high in the uterine fundus is obtained with a curette, and the progesterone-induced effects determined according to published criteria.[18] If a discrepancy of 3 days or more is noted between the histologic date of the endometrium and that of the cycle, taking the onset of menses as day 28, the biopsy is repeated in a subsequent cycle. Correlation of histology with luteal length, as defined by the serum LH spike or ultrasound evidence of ovulation, has been suggested as being more accurate than timing by onset of menses. Delay of endometrial maturation in two cycles is taken as evidence of a corpus luteum defect.[19] The demonstration that serum progesterone levels are low throughout the luteal phase in women with this entity leads to a suggestion that serum sampling can be used as an alternative diagnostic test.[20] However, the need for multiple blood samples to accomplish this has inhibited its general use. Shortened length of the luteal phase on basal body temperature charts also has been suggested as evidence of the luteal phase defect. However, this abnormality has not been shown to correlate with repetitive abortion.[21] Several investigators have reported luteal deficiency to occur in as many as one-third of women with RSA, whereas others have

reported it to be an infrequent cause of abortion. This discrepancy may have occurred because the precision of endometrial dating by histologic examination varies among different observers.

Recommended treatment for LPD is progesterone supplementation administered intramuscularly (25 mg of progesterone in oil daily) or intravaginally (25 mg suppositories twice daily) or as micronized capsules in doses of 25-400 mg b.i.d. Treatment is initiated 3 days after ovulation and is discontinued with menses or after 10 weeks' gestation. Clomiphene citrate, which has weak estrogenic and antiestrogenic activity, has also been used as a treatment for LPD in doses of 50 to 150 mg daily for 5 days during the follicular phase of the conception cycle. It has been recommended for patients with biopsies more than 5 days out of phase. Successful therapy, as measured by pregnancy, occurs in about half of all those who are treated for infertility. Reports of treatment in patients with RSA are not as substantial. Tho et al used progesterone suppositories to treat 22 of 23 patients with LPD ; all conceived and 21 carried the pregnancy to term.[22] One patient was treated with Clomid and conceived but aborted. Stray-Pederson treated 4 patients with hCG injections from the 5th through the 14th week of pregnancy. All carried their pregnancies to term.[23] Although significant improvement in pregnancy outcome has already been reported after treatment of LPD, randomized double-blind studies have never been reported for either progesterone or clomiphene citrate or hCG therapies.

There is no evidence that progesterone administration is of value once signs of impending abortion appear. Furthermore, the use of progestins in threatened abortion patients has been abandoned because of the luteolytic effects ascribed to these compounds.

Other endocrinologic factors

Hyperprolactinemia may affect estradiol production, resulting in diminished luteal progesterone secretion. LPD associated with elevated prolactin levels should be treated with bromocriptine, which should be discontinued after a positive pregnancy.

Although abnormal maternal thyroid function has been implicated in pregnancy loss, an increased incidence of RSA has not been conclusively demonstrated in hypothyroid women. An increased risk of spontaneous abortion has been observed in diabetic women with elevated levels of haemoglobin A1c implying poor control. Diabetic women with good metabolic control have not been demonstrated to be at risk for RSA.

Reproductive tract infections

Maternal infections with mycoplasma (M. hominis), ureaplasma (U. urealyticum), toxoplasmosis, listeria, chlamydia, and group B hemolytic streptococci have been implicated in poor pregnancy outcome.[24] Most investigators have focused on M. hominis and U. urealyticum as possible causes of RSA. If positive cervical cultures are obtained, the recommended course of therapy is 100 mg of doxycycline twice daily for 10 days during the follicular phase. The patient' s partner should be also treated. Some studies have reported a higher incidence of infection by these two organisms in women with RSA compared to control women.[25,26] In addition, nonrandomized studies have reported improved pregnancy outcome following antibiotic treatment of M. hominis and U. urealyticum cultured in women with RSA.[27,28] However, due to poor study design a direct correlation with these organisms,antibiotic treatment, and RSA cannot

be made at present.[24] Although toxoplasmosis, listeria, and group B strepococcus are associated with septic abortion and sporadic cases of spontaneous abortion, a role in RSA is lacking. Studies investigating the role of chlamydia in early pregnancy loss cannot be clearly interpreted.[24]

Environmental factors

A number of environmental agents have been implicated in causing RSA. However, only ionizing radiation and teratogenic chemicals such as isotretinoin and mifepristone have been established as human abortion factors.[29] Alcohol use (1 drink/day) and cigarette smoking (10 cigarettes/day) are positively associated with pregnancy loss (relative risk 1.5-2). The exposure event must occur during a specific interval because most women who smoke or drink do not lose their pregnancies.[30] Other environmental agents and drugs have not been clearly proven to cause RSA.

Immunologic factors

The aetiology for RSA is undetermined in 40-60% of patients. Immunologic factors may have a role in up to 80% of otherwise unexplained RSA. Immunologic associations with RSA can be group into autoimmune and alloimmune causes. Autoimmunity as a source of recurrent abortions has been associated with the presence of antiphospholipid antibodies in the mother,[31-34] especially lupus anticoagulant (LA) or anticardiolipin antibody (ACA), resulting in a tendency to thrombosis with infarction of trophoblast and eventual pregnancy loss. Suggested treatments include low-dose aspirin, subcutaneous heparin, corticosteroid or various combinations of these agents, plasma exchange therapy, and intravenous immunoglobulins. Alloimmunity in RSA has been theorized to result from parental genetic similarity with failure of the mother to recognize the fetus as foreigner. Blocking antibodies do not develop to protect the pregnancy and it is subsequently lost due to the resultant cytotoxic maternal response. Therapy for alloimmune problems has generally involved attempts to establish blocking antibodies in the mother by immunization with paternal or third-party cells or tissue.

The exact relationship of alloimmunity to RSA has not been firmly established. The sharing of major histocompatibility locus antigens (HLA), which may cause the maternal immune system to fail to produce blocking antibodies, as mentioned above, as a cause of abortion was unable to be confirmed in several recent studies. Caudle et al[35] and Houwert-de Jong et al[36] found no difference in the degree of HLA antigen sharing in couples with RSA and a control group. Smith and Cowchock[37] and Dizon et al[38] likewise found no difference in the incidence of HLA sharing between a group of couples with RSA and the aetiology of which could not be determined. Sargent et al[39] performed a prospective study on couples with recurrent abortion prior to and following conception and found no difference in the incidence of HLA sharing among the couples who subsequently had a successful pregnancy and those whose pregnancies aborted. Futhermore, they were unable to confirm that after pregnancy occurred in these women, as well as in normal controls, there was an increase in production of maternal immunologic factors to fetal (paternal) HLA antigens. However, Mowbray et al[40] performed a randomized treatment trial on a group of women with recurrent abortion, and no detectable antibody against paternal lymphocytes was found. Women injected with paternal white cells had a significantly greater chance of subsequent successful pregnancy (78%) than did those injected with their own white cells (37%).

However, in the study by Smith and Cowchock,[37] after paternal white cells immunization of women with recurrent abortion of unknown aetiology, the rate of successful pregnancy was only 50%, similar to the 62% rate reported by Houwert-de Jong et al[36] for a group of women with a history of recurrent abortion who received no treatment. Furthermore, in the former study after immunization, the outcome of pregnancy was not related to the development of blocking antibodies. Thus, the data regarding an immunologic cause of abortion are conflicting. Leukocyte transfusion therapy also carries the risk of anaphylaxis and transmission of infectious disease. For this reason, at present it is not cost effective or necessary to perform expensive HLA typing on each member of the couple with a history of recurrent abortion. Immunization of the woman and the man' s white blood cells should be performed only under experimental protocols with informed consent since the procedure has not been proven to be beneficial.

Autoimmunity as a cause of recurrent abortions has been related to the presence of antiphospholipid antibodies in the mother especially LA and ACA. Antiphospholipid antibodies are present in up to 40% of patients with otherwise unexplained RSA. Although some patients whose test positive for LA and ACA will have uncomplicated pregnancies, higher levels of antiphospholipid antibodies present in the maternal serum correlate with increased incidences of spontaneous abortion and intrauterine fetal demise. These antibodies are immunoglobulins of the IgG or IgM class. Although in vitro these immunoglobulins have anticoagulant activity by interfering with activation of the prothrombin activator complex and thus prolonging the partial thromboplastin time, clinically the presence of these antibodies is associated with thrombosis. Although the exact mechanisms of an increased incidence of thrombosis is not known, some investigators have shown that when the antibody is present, it inhibits prostacyclin production from endothelial tissues, leading to a relative excess of thromboxane, which could enhance thrombosis. Additionally, decreased antithrombin III activity, deficient prekallikrein factor production, inhibition of antiendothelial cell thrombomodulin, and decreased protein C and S also contribute to thrombus formation.[41] Up to 95% of pregnancies in untreated women with LA result in pregnancy loss.[42] Laboratory tests used to diagnose the presence of LA include the activated partial thromboplastin time, the kaolin clotting time, and the dilute Russell viper venum time. A standardized enzyme-linked immunosorbent assay is available to detect ACA. Several therapeutic regimens have been proposed for women with RSA and elevated levels of antiphospholipid antibodies. These therapies are aimed at decreasing the autoimmune response and reducing the risk of thrombotic events. Aspirin has been used because of its ability to inhibit thromboxane synthetase and decrease platelet aggregation. Corticosteroids posses immunosuppressive effects, thereby decreasing antiphospholipid activity. Immunoglobulins may act through feedback inhibition of antibody synthesis, competitive binding of macrophage receptors, or stimulation of suppressor cells. The most widely used therapeutic regimen is daily ingestion of 20-60 mg of prednisolone with 75-80 mg of aspirin. It has been reported that the overall livebirth rate with this therapy was about 80%.[43] Recent studies have shown that patients with RSA could benefit from heparin and aspirin administration[44] as well as intravenous immunoglobulin administration.[45,46] Complications associated with corticosteroid use include

induction of diabetes, cushinoid facies, poor wound healing, and infections. Prolonged heparin use is associated with thrombocytopenia and osteoporosis. Immediate allergic reactions and vasomotor symptoms including nausea, chest tightness, and wheezing have been reported with immunoglobulin administration.

Prognosis

Prognosis for successful pregnancy in patients with RSA depends on the determined aetiology. Couples diagnosed with a chromosome anomaly in one of the partners have a 20% chance per conception for a viable pregnancy. Genetic counseling is indicated for these patients. Amniocentesis or chorionic villus sampling may be recommended, as there is a 3-5% risk for transmission of an unbalanced chromosomal arrangement to the fetus that does not result in spontaneous abortion.[47] Patients with mullerian anomalies have a 60-70% chance for a viable pregnancy. After surgical correction of a uterine septum, successful pregnancy rates between 80-87% have been reported.[14,48] The best prognosis has been reported for patients diagnosed with LPD. After hormonal treatment, successful pregnancy rates of more than 90% have been observed. An 80% viable pregnancy rate was reported in patients with U. urealyticum cervical infections.[47] Livebirth rates of 70-90% have been reported in patients with antiphospholipid syndrome receiving antenatal therapy. When an aetiology cannot be identified for the recurrent spontaneous losses, reassurance and counseling are critical. Subsequent successful pregnancy and delivery rates as high as 85% have been observed in patients who receive frequent feedback and emotional support during early gestation.

Conclusion

Couples who have experienced RSA want to know the cause of miscarriage. They should be informed that a cause can be identified in 60% of couples. Unexplained reproductive failure can lead to anger, guilt, and depression. Feelings of grief and guilt are often as intense as those following a stillbirth, and patients may experience a grief reaction similar to that associated with the death of an adult. The women should be assured that exercise, intercourse, and dietary indiscretions do not cause abortions. Any questions or concerns that she may have about her personal habits should be discussed. Women who undergo recurrent early pregnancy loss have already begun to prepare for their babies, emotionally and physically, as compared to infertile patients who have never conceived. When a miscarriage occurs, a couple may have great difficulty informing friends and families about the loss. Feeling of hopelessness may continue long after the loss. Patients may continue to grieve and have episodes of depression on the expected due date or the date of the pregnancy loss. Anger may be directed toward their physicians for not being able to solve their problem.

Treatment should be directed at correcting any identifiable causes of early pregnancy losses. In these cases, therapy can significantly increase the probability of carrying a subsequent pregnancy to term. In those couples where no cause can be identified, it is essential for the physician to provide continuing emotional support because 70% of couples in this group will eventually carry a pregnancy to term whether or not they receive treatment.

References

1. Edmonds DK, Lindsay KS, Miller JF, Williamson E, Wood PJ. Early embryonic mortality in women. Fertil Steril 1982 ; 38 : 447-53.
2. Katz, Kuller JA. Recurrent miscarriage. Am J Perinatol 1994 ; 11 : 386-97.
3. Hill JA, Ravnikar VA. Recurrent abortion. In : Ryan KJ, Barbieri RL, Berkowitz RS, editors. Kistner's Gynecology Principles and Practice. 5th ed. New York : Year book medical publishers, 1990 : 406-30.
4. Warburton D, Fraser FC. On the probability that a woman who has a spontaneous abortion will abort in subsequent pregnancies. Br J Obstet Gynaecol 1961 ; 68 : 748-87.
5. Stirrat GM. Recurrent miscarriage 1: definition and epidemiology. Lancet 1990 ; 336 : 673-5.
6. Parazzini F, Acaia B, Ricciardiello O, Fedele L, Liati P, Canadiani GB. Short-term reproductive prognosis when no cause can be found for recurrent miscarriage. Br J Obstet Gynaecol 1988 ; 95 : 654-8.
7. Hatasaka HH, Varner NW. Recurrent pregnancy loss. Curr Opin Obstet Gynecol 1994 ; 6 : 503-9.
8. Cook CL, Pridham DD. Recurrent pregnancy loss. Curr Opin Obstet Gynecol 1995 ; 7 : 357-66.
9. Hassold T, Chen N. A cytogenetic study of 1000 spontaneous abortions. Ann Human Genet 1980 ; 44 : 151-78.
10. Khudr G. Cytogenetics of habitual abortion : a review. Obstet Gynecol 1974 ; 29 : 299-310.
11. Patton PE. Anatomic uterine defects. Clin Obstet Gynecol 1994 ; 37 : 705-21.
12. Buttram VC Jr, Gibbons WE. Mullerian anomalies : a proposed classification (an analysis of 144 cases). Fertil Steril 1979 ; 32 : 40-6.
13. Rock JA, Jones HW Jr. The clinical management of the double uterus. Fertil Steril 1977 ; 28 : 798-806.
14. March CM, Israel R. Hysteroscopic management of recurrent abortion caused by septate uterus. Am J Obstet Gynecol 1987 ; 156 : 834-42.
15. Mann EC. Habitual abortion. Am J Obstet Gynecol 1959 ; 77 : 706.
16. Ayers J, Peterson E, Ansbacher R. Early therapy for the incompetent cervix in patients with habitual abortion. Fertil Steril 1982 ; 38 : 177-81.
17. March CM, Israel R. Gestational outcome following hysteroscopic lysis of adhesions. Fertil Steril 1981 ; 36 : 455-9.
18. Noyes RW, Hertig AT, Rock J. Dating the endometrial biopsy. Fertil Steril 1950 ; 1 : 3.
19. Shapiro SS, Dumesic DA. Corpus luteum defects. Curr Opin Obstet Gynecol 1990 ; 2 : 159-65.
20. Horta JLH, Fernandez JG, deLoen BS, Cortes-Gallegos V. Direct evidence of luteal insufficiency in women with habitual abortion. Obstet Gynecol 1977 ; 49 : 705-8.
21. Smith SK, Lenton EA, Landgren B,Cooke ID. The short luteal phase and infertility. Br J Obstet Gynaecol 1984 ; 91 : 1120-2.
22. Tho PT, Bryd JR, McDonough PG. Etiologies and subsequent reproductive performance of 100 couples with recurrent abortion. Fertil Steril 1979 ; 32 : 389-95.
23. Stray-Pedersen B, Stray-Pedersen S. Etiologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion. Am J Obstet Gynecol 1984 ; 148 : 140-6.
24. Riley LR, Tuomala RE. Infectious disease and recurrent pregnancy loss. Infert Reprod Med Clin North Am 1991 ; 2 : 165-8.
25. Stray-Pederson B, Eng J, Reikvam T. Uterine T-mycoplasma colonization in reproductive failure. Am J Obstet Gynecol 1978 ; 130 : 307-11.
26. Quinn PA, Schwchuk AB, Shuber J, Lie KI, Ryan E, Sheu M, et al. Serologic evidence of ureaplasma urealyticum infection in women with spontaneous pregnancy loss. Am J Obstet Gynecol 1983 ; 145 : 245-50.
27. Quinn PA, Schwchuk AB, Shuber J, Lie KI, Ryan E, Sheu M, et al. Efficacy of antibiotic therapy in preventing spontaneous pregnancy loss among couples colonized with genital mycoplasmosis. Am J Obstet Gynecol 1983 ; 145 : 239-44.
28. Toth A, Lessen ML, Brooks-Toth CW, Feiner C. Outcome of subsequent pregnancies following antibiotic therapy after primary or multiple spontaneous abortions. Surg Gynecol Obstet 1986 ; 163 : 243-50.
29. Polifka JE, Friedman JM. Environmental toxins and recurrent pregnancy loss. Infert Reprod Med Clin North Am 1991 ; 2 : 195.
30. Verp MS. Environmental causes of repetitive spontaneous abortion. Sem Reprod Endocrinol 1989 ; 7 : 188.
31. Matzner W, Chong P, Xu G, Ching W. Characterization of antiphospholipid antibodies in women with recurrent spontaneous abortions. J Reprod Med 1994 ; 39 : 27-30.

32. Harris EN, Pierangeli SS. Antiphospholipid antibodies and the antiphospholipid syndrome. Springer Semin Immunopathol 1994 ; 16 : 223-45.
33. Yetman DL, Kutteh WH. Antiphospholipid antibody panels and recurrent pregnancy loss: prevalence of anticardiolipin antibodies compared with other antiphospholipid antibodies. Fertil Steril 1996 ; 66 : 540-6.
34. Oshiro BT, Silver RM, Scott JR, Yu H, Branch DW. Antiphospholipid antibodies and fetal death. Obstet Gynecol 1996 ; 87 : 489-93.
35. Caudle MR, Rote NS, Scott JR, Dewitt C, Barney MF. Histocompatibility in couples with recurrent spontaneous abortion and normal fertility. Fertil Steril 1983 ; 39 : 793-8.
36. Houwert-de Jong MH, Termijtelen A, Eskes TK, Mantingh A, Bruinse HW. The natural course of habitual abortion. Eur J Obstet Gynecol Reprod Biol 1989 ; 33 : 221-8.
37. Smith JB, Cowchock FS. Immunological studies in recurrent spontaneous abortion : Effects of immunization of women with paternal mononuclear cells on lymphocytotoxic and mixed lymphocyte reaction blocking antibodies and correlation with sharing of HLA and pregnancy outcome. J Reprod Immunol 1988 ; 14 : 99-113.
38. Dizon TD, Nelson L, Scott JR, Branch DW, Ward K. Human leukocyte antigen DQ alpha sharing is not increased in couples with recurrent miscarriage. Am J Reprod Immunol 1995 ; 34 : 209-12
39. Sargent IL, Wilkins T, Redman CW. Maternal immune responses to the fetus in early pregnancy and recurrent miscarriage. Lancet 1988 ; 2 : 1099-104.
40. Mowbray JF, Giggins C, Liddell H, Reginald PW, Underwood JL, Beard RW. Controlled trial of treatment of recurrent spontaneous abortion by immunization with paternal cells. Lancet 1985 ; 1 : 941-3.
41. Hadi HA, Treadwell EL. Lupus anticoagulant and anticardiolipin antibodies in pregnancy : a review II : diagnosis and management. Obstet Gynecol Surv 1990 ; 45 : 786-91.
42. Hadi HA, Treadwell EL. Lupus anticoagulant and anticardiolipin antibodies in pregnancy : a review I : immunochemistry and clinical implications. Obstet Gynecol Surv 1990 ; 45 : 780-5.
43. Reece EA, Gabrielli S, Cullen MT, Zheng XZ, Hobbins JC, Harris EN. Recurrent adverse pregnancy outcome and antiphospholipid antibodies. Am J Obstet Gynecol 1990 ; 163 : 162-9.
44. Sher G, Feinman M, Zouves C, Kuttner G, Maassarani G, Salem R, et al. High fecundity rates following in vitro fertilization and embryo transfer in antiphospholipid antibody seropositive women treated with heparin and aspirin. Hum Reprod 1994 ; 9 : 2278-83.
45. Coulam CB. Immunotherapy with intravenous immunoglobulin for treatment of recurrent pregnancy loss : American experience. Am J Reprod Immunol 1994 ; 32 : 286-9.
46. Coulam CB, Krysa L, Stern JJ, Bustillo M. Intravenous immunoglobulin for treatment of recurrent pregnancy loss. Am J Reprod Immunol 1995 ; 34 : 333-7.
47. Mishell DR. Recurrent abortion. J Reprod Med 1993 ; 38 : 250-9.
48. DeCherney AH, Russell JB, Graebe RA, Polan ML. Resectoscopic management of mullerian fusion defects. Fertil Steril 1986 ; 45 : 726-8.