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DEBATE

Recurrent miscarriage: Does any treatment help?

Comment by: **El Sayed El Badawy Awad,** M.D.
Alexandria, Egypt

Recurrent pregnancy loss is emotionally frustrating for couples experiencing loss and often is a frustrating challenge for their medical teams. This dual frustration usually results in recommendation of unsubstantiated test that are not necessarily useful or adopting therapies of dubious efficacy.

This perhaps reflects dilemmas and controversies which surround this subject starting from definition up to advanced research, passing through etiology, investigations and treatment modalities. The diversity and complexity of known etiologies and the wide spectrum of unknown etiologies add to the frustration of both couples and physicians. After every single case of miscarriage, the physician is usually asked, "what was wrong??" a simple a logic question for which- in many instances- the answer may be impossible.

Most textbooks define recurrent pregnancy loss (RPL) as three or more consecutive spontaneous abortions. This definition can be further subdivided into primary (all pregnancies lost) or secondary (after a successful pregnancy). In many clinical situations, the definition is altered to two or more consecutive spontaneous abortions. If by chance alone, RPL should occur in 0.3-0.4% of women. However, RPL affects almost 1% of women suggesting a specific underlying cause in more than half such cases. Usually little clinical importance is gained from extensive investigations of otherwise healthy couples who suffered from only two spontaneous abortion, and their likelihood of having a subsequent successful pregnancy is not less than 80%. On the other hand, the likelihood of extensive and expensive investigations finding any relevant cause is less than 10%. It appears that a clear and consistent definition of three consecutive losses is necessary to allow sensible questions to be asked and arrange cost-effective investigations. This is also important to provide prognosis, suggest possible remedies and guide further research.

The situation regarding etiological factors is not far being complex. The incidence of chromosome abnormality in spontaneously aborted conceptuses is more than 50% in first trimester and 20% in 2nd trimester. Parental chromosomal rearrangements could be found in 10% of couples of RPL in the form of translocations, inversions and mosaicism. The woman is twice as likely as the man to be the carrier of these chromosomal rearrangements. On the other hand, autosomal trisomies are the most common defects found in 1st trimester miscarriages in addition to molecular mutations.

Anatomical etiological disorders include congenital uterine fusion abnormalities, cervical incompetence or acquired uterine factors like fibroids, polyps or synechiae. The controversy relating diagnosis and management of cervical incompetence is well discussed in obstetric textbooks.

Other important etiological factors include endocrinal, immunological, infectious, environmental factors as well as thrombophilic defects.

An evident link is well established between immunologic factors and adverse pregnancy outcome including RPL but the main controversies lie in the validity and usefulness of different investigations and modes of therapy. A long list of investigational tests should not be applied in view of their limited experimental nature. Moreover, the efficacy of therapies of disorders of materno-fetal

alloimmune relationships is doubtful at most or of limited value at best. These therapies include allogenic leukocyte immunization and intravenous immunoglobulin administration and other less tested therapies.

Different microbial agents may be related to pregnancy loss, these include bacteria, viruses, parasites and spirochetes. The theory that microbial infections can cause pregnancy loss is present in literature since the turn of the 20th century with discovery of brucellosis. Despite that, few studies to confirm that exist and their results are inconsistent. In fact, infection is viewed as a rare of RPL, hence the validity of famous infections screen is of little significance. Equally important the use of empiric antibiotic therapy should be abandoned.

The impact of environmental toxins and pollutants on pregnancy is unmistakable. This accounts for more than 10% of adverse pregnancy outcome including RPL, malformations and preterm birth. Occupational hazards like exposure to lead, mercury, ethylene oxide, ionizing radiation, anesthetic gases are examples of environmental factors. Social habits like smoking and alcohol consumption are additional hazards for RPL. Moreover domestic factors like exposure to electromagnetic fields, use of cellular phones, and video terminals should not be overlooked. Identification of a single and definitive environmental factor as a cause of RPL may be difficult in designing research but several caveats are to be considered, such as gestational age at the time of exposure, amount, duration, and frequency of exposure, genetic differences and susceptibility and establishing a clear plausible cause-effect relationship.

Many cases of RPL are characterized by defective placentation and the presence of microthrombi in the placental vascular tree. This tendency for clotting or procoagulant state prior to conception which is aggravated by pregnancy is well recognized as a cause of adverse pregnancy outcome.

Since reproductive failure is a continuum depending on the severity of the cause, this thrombophilic defect may impair fertility, cause RPL, IUFD, growth retardation, PIH or fetal distress at labor. The association between RPL and acquired thrombophilic defects like antiphospholipid antibody syndrome (APLA) is now firmly established. In recent years, the role of inherited thrombophilia and RPL is under investigation. This deficiency of natural anticoagulants include activated protein C resistance, antithrombin III deficiency, protein C & protein S' deficiency.

Despite complexity of pathways for clot formation, the therapy is now well defined in the form of low dose aspirin and subcutaneous heparin with successful outcomes.

The complexity of the situation made famous scientific bodies like ALOG and RCOG propose guidelines for workup and management of cases of RPL. It is noteworthy to mention that each local committee can propose local guidelines based on special relevant local etiological factors and service provision available. But to sum up these workups should be of maximum clinical usefulness to avoid unnecessary, expensive and experimental investigations. Moreover, definitive therapies for definitive causes should be preferred to empiric therapies.

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Prof. Dr. El Sayed El Badawy Awad
Professor of Obstetrics and Gynecology
Faculty of Medicine, University of Alexandria,
Alexandria, Egypt

Comment by: **Aboubakr Elnashar**, M.D.
Benha, Egypt

Recurrent miscarriage (RM) is defined as the loss of three or more consecutive pregnancies before viability. Some clinician favor changing the definition to two or more consecutive losses (1), but the efficacy of commencing investigations after two losses has not been established.

Causes of RM are different from those of single sporadic miscarriage. Causes of RM should be persistent & proved each time. Treatment of RM depends widely on whether a definite cause has been found or whether it is finally classified as idiopathic or unexplained. A definite cause can be established in only 50% (2) of cases & several alleged causes are controversial & doubtful. In management of RM many investigations are requested but few specific treatments are available. So it is crucial for management of RM to define the cause & then to treat depending on level-one evidence therapies.

Doubtful causes (poor correlation between the cause & RM) of RM include uterine anatomic abnormalities (retroversion or backward tilting of the uterus, mild intrauterine adhesions, subserous fibroid, intramural fibroid less than 7 cm, arcuate uterus), infections (toxoplasmosis, mycoplasma, chlamydia trachomatis, L. monocytogenes, HSV, CMV), endocrine abnormalities (endometriosis, luteal phase defect) & occupational exposure (herbicide spraying, electromagnetic fields, chemical inhalation, anesthetic gases). So, the following investigations are of no value in normal females with RM: cultures for bacteria or virus; GTT or thyroid function tests, other antiphospholipid antibodies other than anticardiolipn & lupus anticoagulant antibodies, antinuclear antibodies, antithyroid antibodies, tests for thrombophilia, human leukocytes antigen, maternal antipaternal antibodies (2). The following treatments are of no value: leukocyte immunization, intravenous immunoglobulin & luteal phase support with progesterone.

Possible causes (good correlation between the cause & RM) of RM include genetic abnormalities, uterine cavity abnormalities (congenital uterine malformation, submucous fibroid, cervical incompetence, severe intrauterine adhesions), endocrine abnormalities (uncontrolled diabetes mellitus, uncontrolled thyroid dysfunction, PCOS), antiphospholipid syndrome, cigarette smoking & alcohol consumption. So, the following investigations are required: peripheral blood karyotyping of the parents, karyotyping of the abortus, pelvic ultrasonography or hysteroscopy, anticardiolipn & lupus anticoagulant antibodies (2). Treatment of antiphospholipid syndrome is low dose aspirin & low dose heparin (3). Women with uterine septum should undergo hysteroscopic evaluation & resection (2). Cervical cerclage should not be offered to women at low or medium risk of mid trimester loss, regardless of cervical length by ultrasound (4). The role of cervical cerclage for women who have short cervix on ultrasound remains uncertain, as the number of randomized women are too few to draw firm conclusions. No known therapy for decreasing the risk of RM in women with PCOS (2). Suppression of LH secretion with GnRH agonist prior to stimulation induction yielded no difference in outcome (5). Metformin has been continued during pregnancy to prevent RM in polycystic ovary syndrome (6).

Unexplained RM is diagnosed if the basic investigations (karyotyping, HSG or hysteroscopy, anticardiolipn & lupus anticoagulant antibodies) are normal (2). Causes of unexplained RPL include thrombophilia, hyperhomocystenemia, poor ovarian reserve, thyroid autoantibodies, selenium deficiency and vitamin B12 deficiency. Heparin therapy may prevent RM in thrombophilia (7). No treatment options have been proved beneficial in cases thyroid autoantibodies (8).

In absence of any cause, it is difficult to propose a particular treatment regimen. Empirical therapy is unnecessary (2). Reassurance, attendance at a dedicated early pregnancy assessment clinic & informative & sympathetic counseling are associated with successful pregnancy in 35-85% of cases. Often, the patient, who is not prepared to accept that the chance of having successful pregnancy next time is higher without pharmacological intervention, does not share this opinion. Immunotherapy is not beneficial (9) & there is insufficient evidence to support use of HCG in unexplained RM (10).

Empirical treatment is usually prescribed with aspirin, 75 mg/day, folic acid 0.5 mg/day & heparin in case of an obstetric history of fetal death (7). Low dose aspirin did not improve pregnancy outcome in unexplained RM (11).

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Aboubakr Mohammed Elnashar, M.D.
Prof. of Obstetrics & Gynecology
Benha University Hospital, Egypt
E-mail: elnashar53@hotmail.com

Comment by: **Khaled R. Gaber, Ph.D**.
Cairo, Egypt

Miscarriage occurs in 10-15 % of pregnant women (1), with a percentage of them at risk to lose their next pregnancy. This risk rises to near 20 % after one miscarriage and approaches 40 % after 3 consecutive losses (2). The repetition of this tragedy, recurrent pregnancy loss (RPL), magnifies the problem and may have serious far-reaching consequences on the patient and her family. Hence, it necessitates the establishment of an effective treatment protocol.

In daily medical practice, rigidity is not recommended. It may be wise to start the evaluation panel after the second loss, or even once it occurs. The start of evaluation and the order of request for the tests greatly depend upon the objective data in the couple and their family's medical history. Waiting for another loss may not clarify the etiology, and may even aggravate the psychological condition of the couple.

RPL is a heterogeneous syndrome. Several factors are involved in the etiology, with different modalities of treatment. These factors may be related to the conception itself and are mostly genetic/chromosomal (preventive treatment). Or, factors involved in the process of implantation and development of the fetus: anatomic (surgical treatment), hormonal and immunologic factors (medical therapy). The later group of factors is usually associated with maternal medical complications. It should be noted that more than one factor might have a role in the occurrence of pregnancy loss (PL) (3). The risk of miscarriage is also increased by multiple pregnancy, poorly controlled diabetes, infection, exposure to toxins and smoking.

Preventive treatment

Chromosomal abnormalities tend to cause abortion early in pregnancy. Over 50 % of abortuses in the first trimester are chromosomally abnormal, whereas after 20 weeks only 10 % are abnormal (4, 5). If fetal tissues reveal abnormal karyotype, parental studies are requested. Preventive treatment may be offered if a partner shows chromosomal rearrangement. This may include: preimplantation genetic diagnosis and transfer of only chromosomally normal embryos or through prenatal diagnosis (amniocentesis, chorionic villous sampling) and counseling for the risk of a live birth with serious birth defect.

Surgical treatment

The prevalence of uterine malformations in RPL is between 1.8 and 37.6 % (6). Recently, three dimensional ultrasound and magnetic resonance imaging appear promising in evaluating the anatomic factor. These techniques when coupled with hysteroscopic surgery can have a role to overcome the complications associated with open uterine surgery (post-operative infertility, uterine scar rupture) in such abnormalities (6, 7). I believe that starting evaluation following the first miscarriage can greatly benefit this group of patients, both in counseling and early treatment.

Traumatic lesions are usually reported as the main cause of cervical incompetence. Although cerclage operation is best performed by the end of the first trimester, emergency cerclage with indomethacin, antibiotics and bed rest appear a successful therapy if the condition is detected even by the end of the second trimester with bulging membranes (8).

Medical therapy

The debate concerning the role of follicular phase hormonal defect treatment and its role in RPL is mostly due to lack of controlled studies. The common regimen of treatment in luteal phase defect (LPD) is medical, and includes: Progesterone supplementation or induction with clomiphene citrate and supportive doses of human chorionic gonadotrophin during the luteal phase. A meta-analysis reported the existence of LPD as a clinically significant entity first trimester miscarriage, and can be successfully treated with progesterone administration (9). Several investigators reported failure of exogenous progesterone administration after conception to show any benefit (10). However, we have detected that nearly 20 % of the RPL in our clinic have LPD (based on endometrial biopsy &/or hormonal evaluation), and that they benefited from progesterone supplementation. Progesterone supplied during the luteal phase of the cycle preceding conception gave better results than when started following a positive pregnancy test.

Women with polycystic ovaries (PCO) are at increased risk of RPL compared with regularly cycling women in the general population. Studies revealed that pituitary desensitization with gonadotrophin releasing hormone analogues has no effect on pregnancy outcome in women with PCO c". Recently, it was reported that metformin administration during pregnancy reduces first trimester PL in women with PCO.

RPL related to immune dysfunction is increasingly recognized and is mostly related to blood clotting disorders. Women with RPL associated with prior maternal or fetal complications (preeclampsia, abruption, growth retardation) should be screened for congenital thrombocytopenia and antiphospholipid antibodies (APLAs). The chance of having successful pregnancy decreases with each PL. With proper treatment the live birth rate reach 80 % (13). Treatment protocol for RPL associated with immune dysfunction is completely empirical. The most commonly used medications include different combination of: antiplatelets, anticoagulants, and immunosuppressant therapy. Although the safety of low-dose aspirin (LDA) during the first trimester of pregnancy is still a matter of debate, it appears to be safe, with no reported major complications (maternal or fetal) at this dose (60 - 150 mg/day). Treatment with LDA is usually advised before conception and in combination with heparin when pregnancy test is positive. The safety of heparin makes it the thromboprophylaxis of choice. The low molecular weight heparin (LMWH) is now more accepted and safe than the unfractionated heparin (UFH). This is due to the lower risk of associated bone loss, bleeding and induced thrombocytopenia. Also, its once-day subcutaneous injection makes it more accepted by the patient (14).

Most reports now agree that the combination of heparin and LDA is the standard treatment and is superior to LDA alone (15, 16). The live birth rate rises from 40 % in the single treatment to over 70 % in the combination type (16).

Prednisone was one of the first medications used for APLAs positive pregnant women (17). Due to the associated maternal and fetal complications from its long term use (diabetes, hypertension, prematurity) prednisone is no more recommended by most investigators. Similar maternal complications were reported during the

study performed in our center (18). However, prednisone cannot be excluded from the treatment protocol, as some of the cases may be associated with active systemic lupus erythromatosis. Prednisone treatment should be prescribed in centers where physicians experienced in its use for such indications, with close follow-up of the maternal condition during pregnancy for both the disorder and the complications of the therapy.

CONCLUSION AND RECOMMENDATION

An important component in the management of couples with RPL is the establishment of a correct diagnosis. It is important to remember that several factors may be integrated in the etiology at the same time. Therefore, it is advised not to stop the evaluation protocol as soon as the first factor has been detected.

For a significant proportion of RPL couples, no definite cause can be reached. For these, reassurance is important, as with care and sympathy, pregnancy can reach term in near 70 % of these cases.

As technical, diagnostic, and therapeutic approaches to RPL continue to improve, it is a hope that the millions of couples who live this tragedy will have the opportunity to overcome it. This also emphasizes the need, in our country, for special clinics to deal with a special area of obstetrics, the couple with recurrent pregnancy loss.

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Dr. Khaled R. Gaber, Ph.D.
Assistant Professor and Head of
Prenatal Diagnosis and Fetal Medicine Department
National Research Center,
Cairo, Egypt