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Evidence-based investigations and treatments of recurrent pregnancy loss

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Objective: To give an overview of currently used investigations and treatments offered to women with recurrent pregnancy loss (RPL) and, from an evidence-based point of view, to evaluate the usefulness of these interventions.

Design: Ten experts on epidemiologic, genetic, anatomic, endocrinologic, thrombophilic, immunologic, and immunogenetic aspects of RPL discussed methodologic problems threatening the validity of research in RPL during and after an international workshop on the evidence-based management of RPL.

Conclusion(s): Most RPL patients have several risk factors for miscarriage, and an extensive investigation for all major factors should always be undertaken. There is an urgent need for agreement concerning the thresholds for detecting what is normal and abnormal, irrespective of whether laboratory tests or uterine abnormalities are concerned. A series of lifestyle factors should be reported in future studies of RPL because they might modify the effect of laboratory or anatomic risk factors. More and larger randomized controlled trials, including trials of surgical procedures, are urgently needed, and to achieve this objective multiple centers have to collaborate. Current meta-analyses evaluating the efficacy of treatments of RPL are generally pooling very heterogeneous patient populations and treatments. It is recommended that future meta-analyses look at subsets of patients and treatment protocols that are more combinable. (Fertil Steril® 2005;83:821–39. ©2005 by American Society for Reproductive Medicine.)

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There is no doubt that the introduction of a series of new assisted reproduction technologies (ART) has recently greatly improved the treatment options available for infertile couples. Most of these couples will now be offered treatments that are generally accepted and often evidence-based. Unfortunately, the situation is much less clear regarding couples with recurrent pregnancy loss (RPL), who are often treated as second-class infertility patients in the health care system. Accurate prevalence figures are not available, but it has been estimated that 2%–5% of women have RPL, defined as three or more consecutive losses of intrauterine pregnancies before the 28th gestational week (1, 2).

Although the array of diagnostic tests and possible therapeutic interventions in the management of RPL have grown significantly, in 1992 a U.S. study (3) showed that the total live birth rate had not increased in a cohort of RPL patients from 1987 to 1991 as compared with a similar group from 1968 to 1977.

The motivation for organizing a workshop under the auspices of the European Society for Human Reproduction and Embryology with the title "Evidence-Based Investigations and Treatments of Recurrent Pregnancy Loss" was the fact that many of the large number of diagnostic tests that have become available for the investigation of patients with RPL are probably of doubtful value and need proper evaluation and standardization. Furthermore, many treatments also need

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proper evaluation concerning their therapeutic value and possible risks.

One reason for the slow progress in RPL research might be related to the fact that RPL is a complex area in which information from many disciplines, such as gynecology, genetics, epidemiology, occupational medicine, immunology, hematology, and endocrinology, are to be integrated to ensure that the research is valid. This collaboration among many disciplines unfortunately has only been established infrequently, with the result that most investigations in this area have been narrowly focused, lacking an integrated approach to the subject.

A key element in this workshop was to let experts from the different disciplines present their specific views on the causes and treatments of RPL and engage the audience in discussion to attempt a clarification on what is the state-of-the-art knowledge and where consensus can be reached.

Gynecologists, obstetricians, and fertility specialists from 18 countries participated in the 3-day workshop held in Denmark in 2002. The following review summarizes the conclusions from the discussions undertaken between the participants during the workshop and the extensive follow-up discussions between the authors that have continued until now.

RESEARCH METHODOLOGY AND EPIDEMIOLOGY OF RELEVANCE IN RPL STUDIES

Readers of the extensive literature about RPL often become confused owing to the contradictory and ever-changing views and results that are being published. Many of these controversies are caused by the very different estimates of the frequencies of RPL risk factors in patients and controls, of the effect of these risk factors on pregnancy outcome, and of the efficacy of various treatments. An important reason for the controversy in this area is the apparent lack of appreciation of the many methodologic pitfalls threatening valid research in the area of RPL. Following is a review of some of the pitfalls inherent in this area of research with different study designs.

Case–Control Studies

In case–control studies, flaws can occur during the sampling of cases and controls. Patients can be incorrectly sampled because of an incorrect RPL diagnosis or ascertainment bias. Furthermore, flaws can occur in relation to the tests carried out.

Incorrect RPL Diagnosis. Women can be diagnosed erroneously as having RPL owing to faulty recall of the pregnancy history, classification of biochemical pregnancies as miscarriages, and the investigator's failure to adhere to the generally accepted criteria for RPL.

An example of information (recall) bias is that, owing to their increased attention on pregnancy and miscarriage, women with only two previously confirmed miscarriages might be more prone to interpret and report delayed menstruations in the past as early miscarriages. More miscarriages might also be reported owing to the woman's wish to be offered investigations and treatment. Only 71% of miscarriages reported by non-RPL women in a questionnaire could be verified in hospital records (4).

Biochemical pregnancies (pregnancies documented only by a positive urine or serum hCG test) constitute a considerable proportion of some RPL patients' previous pregnancy history. Some of these pregnancies might be spontaneous resorbed ectopic pregnancies or very early implantation failures due to genetically abnormal embryos, according to currently available tools. The etiologies of recurrent biochemical pregnancies might thus be different from those of clinical pregnancy losses. Thus, inclusion of patients with a large proportion of biochemical pregnancies in clinical studies of RPL would be expected to diminish the estimate of a maternal risk factor in case–control studies and the treatment effect in controlled clinical trials.

Many studies have included women with only two previous miscarriages, which often might be a chance phenomenon caused by de novo fetal chromosome abnormalities rather than a recurrent maternal factor (5). Including women with only two early miscarriages in the study will in most cases "dilute" the estimate of the risk factor (in case–control and cohort studies) or the treatment effect in controlled clinical trials. This is supported by findings that the frequency of many immunologic risk factors (6, 7) and the possible effect of immunotherapy increases (8) and the frequency of chromosomally abnormal abortions declines (9) with the number of previous pregnancy losses.

Ascertainment Bias. Ascertainment bias occurs when patients referred to clinics with special interests are deliberately or unconsciously selected because of that clinical feature on which the clinic's interest is focused. Such patients therefore are not representative of the general RPL population. For example, RPL patients investigated in clinics with expertise in coagulation and antiphospholipid antibodies might comprise an excess of women with antiphospholipid antibodies (10) because referring centers preferentially refer patients who in addition to obstetric problems also have suffered thromboembolic episodes or expressed "lupus-like" symptoms.

Sampling of Controls. In case–control studies, the quality of the control group is just as important as that of the case group. Sampling of controls is subject to confounding, mismatch with regard to pregnancy-related variables, and ascertainment bias. Age is typically an important confounding factor because it is associated with both the risk of developing RPL and the occurrence of many serologic abnormalities (e.g., autoantibodies).

Blood parameters are often investigated at different stages of pregnancies in patients and controls but still compared by statistical methods. Many immunologic (11–14) and coagulation factors change during pregnancy and after a pregnancy