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The Importance of an Evidence Based Workup for Recurrent Pregnancy Loss

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Basic Epidemiology of Recurrent Pregnancy Loss

Failure of the conceptus to survive beyond the mid-second trimester is common, affecting 10% of clinically recognized pregnancies and 20% of unrecognized conceptions(1). Recurrent pregnancy loss (RPL), usually defined as two or more consecutive losses (2), is also a frequent reproductive problem, with 5% of couples attempting pregnancy suffering two or more losses, and 0.5% to 1% having three or more(2). Most losses that occur after the pregnancy is clinically recognized occur in the preembryonic or embryonic period (<10 weeks gestation). Death of the conceptus alive at or beyond 10 weeks, or fetal death, is a less common type of pregnancy loss. Silver et al. have proposed a useful algorithm for nomenclature of pregnancy loss, which is more specific than previous iterations (Table 1) (3). These definitions use developmental phase to define stages of pregnancy loss. By grouping pregnancy losses by specific time frames, etiology may be easier to elucidate. When RPL is unexplained, losses tend to occur at the same gestational age period, suggesting some undefined factor specific to that period of embryonic or fetal development (4, 5).

Most practitioners recognize that among sporadic, e.g. non-recurrent pregnancy loss, the majority of losses during the preembryonic or embryonic periods are due to spontaneous (and non-recurrent) aneuploidy. However, aneuploidy is less commonly found in abortuses of women with RPL, suggesting that other etiologic factors are at play (6, 7). Most experts agree that uterine malformations, parental karyotype abnormalities, and antiphospholipid antibodies, if present, are important etiologic factors. In otherwise healthy women, the possible roles of endocrinologic, immune, and thrombophilic factors are debated. In fact, it is very likely that most cases of RPL are multifactorial in etiology and include male partner, female partner, and embryonic factors or variables, most of which are yet to be elucidated. Clearly, advancing maternal age is a risk factor for pregnancy loss. More recently, obesity also has been identified as increasing the chances for miscarriage (8). In one study of women with RPL, obese women had increased odds of having yet another pregnancy loss when compared to nonobese women (OR 1.73, 95% CI 1.06–2.83) (9). Women with history of pregnancy loss are also at increased risk of cardiovascular disease(10) and both renal and

cardiovascular atherosclerotic morbidity(11). Might some common risk factors be at play here? Some experts even suggest RPL may be due to a failure of embryonic “quality control,” with the endometrium allowing poor quality embryos to implant and become a clinically recognized pregnancy destined to be lost (12).

It is critically important to recognize that among women with recurrent preembryonic and embryonic losses, the outcomes of subsequent pregnancies are quite positive when compared to subsequent pregnancy outcomes in women of similar age without RPL. Indeed, live birth rates exceed 70% in most couples with RPL, with even better outcomes once embryonic cardiac activity is visualized (13–15). Both maternal age and number of previous losses alter the prognosis for the subsequent pregnancy, as well outlined by Brigham, et al (Table 2) (16). For example, in this dataset, a 25 year old woman with two previous losses has a 89% predicted success rate in a subsequent pregnancy, whereas a 40 year year old woman with 5 previous losses has an only 42% predicted success rate. Increasing maternal age is associated with increase in embryo aneuploidy, which is the likely reason for the worsening prognosis with advancing years.

Challenges in RPL Research

Except for parental structural karyotype abnormalities, the factors usually considered in the evaluation of couples with RPL, and thus thought by at least some experts to be associated with RPL, lack well understood causative mechanisms. These include autoimmune disorders, endometrial dysfunction and endometritis (17, 18), endocrine dysfunction, thrombophilias (19), and uterine malformations (20, 21). A 2002 workshop by the European Society for Human Reproduction and Embryology noted only a small number of truly evidence-based tests for RPL. Extant studies exhibit abundant flaws, including study design, phenotype definition, choice of controls, and failure to account for possible variation in biomarkers.

Much of the research in the field of RPL has consisted of case-control studies, where women with RPL (cases) are compared to their unaffected counterparts (controls). Exposures are then assessed (e.g. demographic factors, genetic mutations, and biomarkers) and rates of exposures are compared between groups and reported as an odds ratio (OR). Case-control studies are strictly observational and are easily biased if (a) cases are not well selected, (b) controls are not appropriately defined, and (c) confounders are not accounted for (22). Confounders are notoriously difficult to predict and account for in observational analysis, but some are well established. Maternal age, for example, is a confounder that can lead to perturbations in a variety of biomarkers while also being a direct risk factor for pregnancy loss. When evaluating RPL studies, it is crucial to note whether cases are defined by two or three previous pregnancy losses and if any live births are permitted in the case group. One should question whether controls are selected from the same population as women with RPL, and whether there is something intrinsically different about them, e.g., availability for study or of a higher or lower socioeconomic status. Given the difficulty assessing and controlling for confounders in case-control trials, some experts in study design recommend considering any OR less than 3 to possibly be due to confounding and thus not a true association(22). This should be kept in mind when assessing case-control studies of RPL.

Consider for example, the case of skewed X-linked inactivation. The theory is that increase in skewed X-inactivation (>90% or >95% skewed) is suggestive of X-linked recessive traits in the mother, which could be lethal in a male embryo or fetus. One study found a 14% rate of highly skewed X-inactivation in women with history of two or more previous losses of unexplained etiology compared to only 1% of controls(23). Another study with similarly chosen cases and controls found no difference in skewed X-linked inactivation (2.3% in cases versus 4.1% in controls)(24). Further work indicated that skewed X-linked inactivation becomes more common as women age(25). Thus, maternal age is a likely confounder to any association between skewed X-linked inactivation and RPL. To their credit, the authors of the original study (which found an association between skewed X-linked inactivation and RPL) published a follow up study controlling for maternal age and reported that, in fact, skewed X-linked inactivation was not associated with RPL(26). In this case, then, an association was found, studied further and ultimately found to be a confounder, not a causative factor.

In RPL studies involving biomarkers, it is important (yet challenging) to note the timing of specimen acquisition, particularly the proximity to pregnancy (for both RPL subjects and controls) and timing in the menstrual cycle. All too often in studies, samples are drawn at a time of a convenient office visit. While understandable, this is a notable confounder for any study of biomarkers affected by cyclical hormonal changes. Another potential confounder for many biomarkers often ignored in RPL studies is whether the patient was fasting or postprandial at the time of blood draw.

In older studies an all too common methodological flaw in RPL research was the use of historic controls. Often a patient is used as her own control, with her personal history used as the control group outcome. This biases the study to find the intervention to be effective. By definition, RPL patients have a history of more miscarriages than live births. However, most of them also are more likely than not to have a successful live birth in their subsequent pregnancy, with or without intervention. (13). Thus, when rates of live birth are compared before and after intervention, the intervention is almost certainly going to appear successful (unless it is, in fact, significantly harmful). Success was already likely. The error inherent in using historic controls has been demonstrated in studies of uterine septum resection and preimplantation genetic diagnosis (27–29). This is not to say that these two therapies might not, indeed, be efficacious. However, use of historic controls is not appropriate and should not be used to support the use of these therapies (which are both costly and potentially morbid).

To be sure, randomized clinical trials are difficult to conduct in the RPL population. Patients are averse to being randomized, and clinicians have a strong desire to “do something,” leading to poor acceptance of randomization to placebo. Given the lack of proven, standard-of-care therapies, control subjects might be expectantly managed. Additionally, it is easy for patients to gain access to unproven treatments outside of well-conducted, randomized clinical trials. Even with regard to factors most compellingly associated with RPL, e.g., uterine malformations or antiphospholipid antibodies, a solid understanding of causative mechanisms is lacking. This, in turn, has hampered the identification of candidate treatments. Even for proposed treatments, the elephant in the room is the relative lack of

well-designed, properly-powered trials. An excellent recent trial of vaginal progesterone in women with RPL is a welcome exception. This randomized women with RPL to 400mg micronized progesterone or placebo twice a day from time of positive pregnancy test until 12 week's gestation and found no difference in live birth rate (65.8% in placebo group versus 63.3% in the progesterone group (30). Vaginal progesterone is frequently used in women with RPL, and now we have strong evidence that this is unnecessary.

The Study and Use of Screening and Diagnostic Tests

When choosing demographic and obstetric risk factors to consider clinically relevant, it is important to recall that risk factors are only useful in predicting future outcomes if they are strongly associated with the outcome. Typically, risk factors are assessed by studying the odds of finding the risk factor in a population with the outcome or disease compared to the odds of finding the risk factor in a population without the outcome or disease. As a general rule, in order to be useful as a screening test the factor must be strongly associated with the disease(31). When the affected and unaffected populations have much overlap in factor values (rates of the risk factor), the predictive value is limited.

Screening tests should be evaluated by the detection rate (DR), i.e., the percentage of affected individuals with a positive result, and the false-positive rate (FPR)(32). The DR and the FPR are intrinsic to the test and how a positive result is defined. The DR and FPR are unaffected by the incidence of the condition (36). In contrast to screening tests, diagnostic tests are evaluated using the same parameters but may have different cutoffs for DR and FPR depending on the disease in question.

Wald et al. propose a series of questions for evaluating tests (Table 3)(32). These questions are based in part on the classic book Principles and Practice of Screening for Disease, an outline of what public health practitioners and clinicians should consider when embarking on evaluations(33). Important questions to consider pertinent to RPL evaluation include: what are the medical costs and benefits? What are the financial costs and benefits? What therapeutic intervention will follow a positive result? What is the justification of this therapy? Although RPL is not a disease in the classic sense, nor do we screen an asymptomatic population, these questions can still guide us when determining the appropriate evidence based workup and treatment for RPL.

Cost and Commercialization

All medical evaluations, as well as treatments, have costs. *Value* in health care is defined as health outcomes achieved per dollar spent(34). One website lists costs of common tests used to evaluate women with RPL(35). Using the low end of the range quoted for each test, the total comes to \$5,637. A recent cost effectiveness analysis estimated that an evidence-based workup would cost \$3,551 for a self-pay patient(36). Insurance (for those who have it) will cover some but not all of the costs of evaluation in the U.S. (parental karyotypes, for example, are frequently not covered). At the end of the costly workup, odds remain high that the woman will be left in the unexplained RPL category without a reason for her losses that

she was searching for. If her subsequent pregnancy outcome is not meaningfully changed, the value of this evaluation is low.

If one types “recurrent pregnancy loss” into a popular online search engine, eight out of ten results on the first page are patient and clinician considered resources – national organizations, academic institutions, and patient created support groups. Two are private clinicians offering services. By the second page, there are more clinicians seeking patients as well as laboratories marketing proprietary tests for RPL. One such clinician website opens with a listing of many expensive and therapies with no proof of efficacy such as immunotherapy. In the upper right hand corner, there is a prominent tab for online bill pay.

There has been a proliferation of for-profit RPL centers, with many tests available on site. Given that much of the services rendered in these centers have not been shown to improve outcomes, these practices are predatory in nature and do not improve medical care.

Science and the Media

The media owns a large responsibility in the propagation of false hope or hope before its time for women with RPL. Recently, a robust analysis of human endometrial stromal cells (HESCs) showed that in women with RPL, the epigenetic signature of HESCs is different than that in women with normal pregnancies (37). The authors speculate that HESCs in women with RPL are less pluripotent and conclude that this combines with deficiency of mesenchymal stem cells to diminish endometrial plasticity and lead to RPL. The popular press published this finding as the answer to miscarriage treatment, titling articles “Scientists identify cause of multiple miscarriages for first time(38)” and “Lack of stem cells to blame for recurrent miscarriages(39).” One of the primary study’s authors is quoted as saying: “I can envisage that we will be able to correct these defects....In fact, this may be the only way to really prevent miscarriages in these cases(40).” These articles (all of which appear to be sourced from the same press release) paint this study of HESCs as the one, final answer to the problem of RPL. Of course it is unclear whether this test truly predicts RPL or whether effective treatments can be developed. Although these data are novel and interesting, sensationalist journalism does not make for good science or patient care. In fact, it causes harm by creating false hope and expectations among couples with RPL.

In our experience, one of the first things women with RPL (or really any medical condition) is an online search. Given the current state of the search results, it is not surprising that many RPL patients find the results of their search hopeful. Many then ask their clinicians if they could receive, for example, therapeutic stem cell treatments for their RPL. This is in the absence of compelling, evidence-based, proof of effectiveness and promotes costly and potentially risky medical care. Other fields have already seen commercialization of expensive stem cell treatments without evidence of clinical benefit(41, 42).

Dangers of Overdiagnosis

Pursuing evaluations of uncertain association, especially in the absence of credible treatments to improve outcomes adds incremental financial cost, as well as diminishes the value of healthcare provided. Such practices also have the potential to cause harm. Although

the concept of *overdiagnosis* typically is defined as diagnosis with an asymptomatic disease that will not ultimately lead to significant morbidity, it is starting to be expanded(43). There are many motivators that lead to overdiagnosis – a desire for “an answer,” the belief that our patients want us to “do something” (and the idea that ordering a test is “doing something),” and the availability of commercialized, new technology. But our being able to tell a woman with RPL that her level of some biomarker is slightly high or slightly low is not useful if that knowledge does not improve her ability to have a live birth - our goals in diagnosis should be to obtain useful information that will improve treatment.

Preventing overdiagnosis is the basis of the Choosing Wisely campaign. Choosing Wisely was started by the American Board of Internal medicine in 2012 with a goal of “avoiding wasteful or unnecessary medical tests, treatments and procedures(44).” As part of Choosing Wisely, multiple medical specialty and subspecialty societies have submitted lists of five to ten recommendations of things to avoid. Relevantly, one of the recommendations by the Society for Maternal-Fetal Medicine is, “Don’t do an inherited thrombophilia evaluation for women with histories of pregnancy loss...(45)” They go on to say that data linking inherited thrombophilia and adverse pregnancy outcomes are not substantial enough to warrant this testing.

What does the evidence support?

The evidence for and against evaluations and treatments for RPL is the subject of this issue of Clinical Obstetrics and Gynecology. We posit that choosing an evidence-based workup and treatment for RPL is imperative, in order to provide best patient care and to create a culture that permits rigorous research into potential (not yet evidence-based) tests and therapeutics. An article in the New York Times said it well: “Affected couples, often desperate for a solution, sometimes grasp at unproven or useless remedies. What they need instead is factual information, emotional support and, if possible, treatment based on a medically established cause(46).” The evidence supporting (and questioning) this evaluation and treatments will be presented in following chapters in detail. We recognize that as health sciences technologies become more sophisticated, (hopefully) more precise, and (hopefully) less expensive, we may develop new tools that allow us to better evaluate and treat couples with RPL. As exciting as the future of reproductive medicine is, the goal must remain optimizing value and adhering to evidence based care.

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Table 1.

Glossary of terms and early pregnancy events [adapted from Silver et al., 2011]

PREFERRED NOMENCLATURE	OLD NOMENCLATURE	DEFINITION	DEVELOPMENTAL PHASE
Voluntary termination of pregnancy	Medical abortion, legal abortion		
Recurrent pregnancy loss	Recurrent abortion, habitual abortion	2 or more consecutive losses	
Early pregnancy loss	Spontaneous abortion	Pregnancy loss before 10 wk with no documentation of an embryo on ultrasonogram; Can include losses greater than 10 wk from LMP if there is no evidence of passing a formed fetus	Morula, blastocyst, gastrula, embryo
Peri-implantational loss	Spontaneous abortion, biochemical pregnancy	Pregnancy loss before 5 wk of gestation with no gestational sac visible on ultrasonogram	Morula, blastocyst, gastrula
Pregnancy of unknown location including ectopic pregnancy	Ectopic pregnancy	A pregnancy that is not clearly in the uterus; includes definite ectopic pregnancy, probable ectopic pregnancy, and probable failing intrauterine pregnancy	N/A
Pre-embryonic loss	Spontaneous abortion	Pregnancy loss at 5 0/7–5 6/7 wk gestation with visible gestational sac and/or yolk sac but no visible embryo on ultrasonogram	Morula, blastocyst, gastrula
Embryonic loss	Spontaneous abortion	Pregnancy loss at 6 0/7–9 6/7 wk gestation of an embryo with CRL less than 10 mm and no cardiac activity visible on ultrasonogram	Embryo
Fetal death Early fetal death 10 0/7–15 6/7 wk Late fetal death 16 0/7–19 6/7 wk	Spontaneous abortion	10 0/7–19 6/7 wk of gestation, either 1) passage of a conceptus measuring at least 30 mm CRL, 2) ultrasonographic documentation of a dead conceptus with CRL at least 30 mm, or 3) loss of conceptus after documented fetal cardiac activity at or beyond 10 wk gestational age; the fetus is dead at time of delivery	Fetal

Table 2.

Predicted percentage success rate of subsequent pregnancy according to age and previous pregnancy loss history.

Age (years)	Number of previous pregnancy losses			
	2	3	4	5
20	92 (86–98)	90 (83–97)	88 (79–96)	85 (74–96)
25	89 (82–95)	86 (79–93)	82 (75–91)	79 (68–90)
30	84 (77–90)	80 (74–86)	76 (69–83)	71 (61–81)
35	77 (69–85)	73 (66–80)	68 (60–75)	62 (51–74)
40	69 (57–82)	64 (52–75)	58 (45–71)	52 (37–67)
45	60 (41–79)	54 (35–72)	48 (29–67)	42 (22–62)

Values are percentages with 95% confidence intervals (CI) shown in parentheses. Adapted from Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum Reprod. 1999;14(11):2868–71 (permission for use pending).

Table 3.**Wald's checklist for the assessment of screening or diagnostic tests***The test:*

- Is the test a screening test or diagnostic test?
- Is it one of several tests or enquiries?
- If so, are the tests carried out in series (e.g. only those whose first result is positive have a second test and so on) or in parallel (everyone has all tests)?

The disorder:

- What is the disorder that the test is designed to detect?
- Can the disorder be defined without reference to the test?
- What is its natural history?
- Is the natural history of those with positive tests similar to the natural history of those with negative tests?

Prevalence of the disorder:

- What is the prevalence of the disorder in the population to be tested?
- What method was used to determine prevalence?

Therapeutic intervention

- If it is a screening test, what diagnostic test will follow and what therapeutic intervention if that test is also positive?
- If it is a diagnostic test, what therapeutic intervention will follow a positive result?
- What is the justification for this therapy?

Test results

- Is the test or inquiry quantitative or qualitative?
- If it is quantitative (e.g. maternal serum AFP level) what is the distribution of screening test results in affected and unaffected subjects?
- If it is qualitative (e.g. cervical smear test) what are the possible definitions of a positive result?

Test performance

- What is the detection rate?
- Has this been determined from a complete series of affected individuals in which any with negative results were not overlooked?
- What is the false-positive rate?
- What are the odds of being affected given a positive result? How will this vary according to the prevalence of the disorder?
- For quantitative tests, what is the effect of changing the cut-off level on the detection rate, false-positive rate and the odds of being affected given a positive result?
- Can a flow diagram be constructed starting with 100000 individuals and ending with the final outcome, segregating affected from unaffected at the outset?

Cost and benefit analysis

- What are the medical costs and benefits?
- What are the financial costs and benefits?
- Can a balance sheet be drawn up for each, including any suffering that will be alleviated through the application of the whole testing process and at what cost and medical intervention?

Evaluation of the tests

- Is the test better than other tests when comparison is made of their respective detection rates and false-positive rates?
- Does it offer an advantage over other tests to such an extent that it should replace an existing test or be added to it and used in combination?

Practical problems

- What are the practical problems in implementing the test as a screening or diagnostic procedure?
- Are special facilities required?

- If so, what is their availability or ease of installation?
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