

Editorial

## Recurrent pregnancy loss and thrombophilia in women with PCOS

In this issue Kazerooni and colleagues have authored an interesting article entitled “Correlation between thrombophilia and recurrent pregnancy loss in patients with polycystic ovary syndrome (PCOS): A comparative study”.<sup>1</sup> Based on the absence or presence of recurrent pregnancy loss (RPL) and polycystic ovary syndrome (PCOS), the authors have tried to determine the association of thrombophilia and RPL in patients with and without PCOS, using a case-controlled comparative study, and separating the subjects into four groups.<sup>1</sup> This study attempted to shed light on two medically challenging areas in obstetrics and gynecology—RPL and PCOS—the etiology of both of which is still uncertain.

RPL is defined by two or more failed pregnancies, and up to 50% of cases of RPL will not have a clearly defined etiology.<sup>2</sup> The potential etiologic factors in the association and causation of RPL can be separated into three categories: definite, probable, and doubtful. Factors that have a definite association with RPL include parental genetics, uterine abnormalities, PCOS, antiphospholipid syndrome (APS), and factor V Leiden (FVL) mutation.<sup>3</sup> Probable associations with RPL include uncontrolled thyroid disease, uncontrolled diabetes, T-helper type 1 (Th1) cell cytokine bias, increased natural killer (NK) cell cytotoxicity, and maternal human leukocyte antigen (HLA) levels.<sup>3</sup> The only definite causation of RPL has been found to be parental genetics. Other causes of RPL include uterine abnormalities, uncontrolled thyroid disease, uncontrolled diabetes, PCOS, APS, FVL mutation, Th1 cytokine bias, increased NK cell cytotoxicity, and maternal HLA alleles.<sup>3</sup>

One of the challenges for most researchers is how to identify those limited RPL cases with genetic defects who are destined to miscarry, from other treatable ones.<sup>4–6</sup> In addition, screening for inherited or acquired thrombophilias (especially FVL and prothrombin gene mutations, such as prothrombin G20210A gene mutations, and protein C, protein S, and antithrombin deficiencies, as noted by Kazerooni et al, might be reasonably acceptable when patients have personal history of venous thromboembolism in a nonrecurrent risk factor setting, or if there is a first-degree relative with a known or suspected high-risk thrombophilia. However, any association between hereditary thrombophilias and RPL has not been supported by two prospective cohort studies.<sup>2,7</sup> In addition, it is acknowledged that APS is the only thrombophilia known to have a direct influence on pregnancy loss, although much

research has been devoted to better ascertain the role of thrombophilia in RPL.<sup>8</sup>

PCOS, a common endocrinopathy characterized by oligo- or anovulation, clinical or biochemical hyperandrogenemia, and polycystic ovaries on ultrasonography, affects 5–10% of women of reproductive age.<sup>9,10</sup> The search for a specific endocrine abnormality or hematologic parameter as a predictor of pregnancy failure remains elusive.<sup>11</sup> Extensive and evidence-based study in this group of patients related to RPL and thrombophilia is supposed to be more efficient and valuable than sporadic case reports.

In their research, Kazerooni and colleagues studied this particular group of patients (with a combination of PCOS and RPL), and showed an elevated level of thrombophilic parameters in this population.<sup>1</sup> As predicted, this group of patients also had higher levels of testosterone and dehydroepiandrosterone sulfate, a higher fasting insulin level, and increased homocysteine levels. It is interesting to find a higher prevalence of FVL mutations in this specific group of patients compared to those PCOS patients without RPL. Therefore, the authors concluded that hyperinsulinemia, hyperandrogenemia, hypofibrinolysis, hyperhomocysteinemia, activated protein C ratio, and FVL mutations are associated with an increased ratio of RPL in patients with PCOS. This study supports the previously published concept that complicated alterations in endocrinologic, metabolic, and thrombophilic status are associated with RPL in patients with PCOS.<sup>11–13</sup> As for detectable genetic disorders, Kazerooni et al’s study also supports the fact that FVL mutation is associated with RPL in women with PCOS.

However, Kazerooni and his colleagues failed to ultimately provide convincing information, because they did not provide any reliable and strict criteria to identify these patients with genetic disorders. Consequently, the heterogeneity of the study population and the absence of a medication history compromised the value of this article, although the underlying issue remains controversial.

In fact, extensive studies related to genetic mutations including FVL, the methylene tetrahydrofolate reductase gene, prothrombin, and the presence or absence of homozygosity in this specific group of patients have been conducted in different countries, with varying results and conclusions.<sup>7,12,13</sup> A combination of multiple inherited thrombophilia mutations from both parents rather than one specific defect of maternal origin was

believed to be the possible reason for an adverse pregnancy outcome, similar to prenatal genetic consultation,<sup>4–6</sup> which contains many issues to be considered, including ethical, social, and medical problems, since it is hard to make a decision only based on these still uncertain data. To provide proper and cost-effective preconception genetic testing or even a preimplantation embryonic genetic diagnosis for infertile couples with an adverse pregnancy experience, a more detailed division of RPL into embryonic or post-embryonic stages, first or second trimesters, and an idiopathic or otherwise cause could more effectively aid in identifying the correct and sufficient combination of genetic defects for different categories of pregnancy loss.

In conclusion, the cause of RPL is multifactorial, and recent guidance on the investigation and management of women with RPL has been issued by the Royal College of Obstetricians and Gynecologist and the American College of Obstetricians and Gynecologists.<sup>13</sup> These recommendations reflect the lack of an evidence base in favor of thrombophilia testing and anticoagulant-based intervention.<sup>13</sup> Progressively more extensive testing is being performed, which leads, on many occasions, to results of questionable value. And although these vulnerable patients often look forward to receiving any intervention at all, unless they are fully informed of the evidence it may be still difficult for them to accept “no treatment,”<sup>14</sup> although thromboprophylaxis with aspirin or heparin combined with metformin seems to be safe in pregnancy. The supportive delicate care and the need to intervene with medication to reduce guilt and anxiety may be ultimately provided.<sup>8</sup>

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