

CLINICAL ASSISTED REPRODUCTION

EDITORIAL

Does Endometriosis Have an Adverse Effect on the Fertilization In Vitro and the IVF Outcome?

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In an article in this issue of the journal, Bergendal *et al.* report lower rates of fertilization in women with endometriosis than in controls with tubal factor infertility. The authors further indicate that other parameters of the in vitro fertilization (IVF) cycle were unaffected by the disease, the quality of the embryos in both groups was comparable, and with the same number

of embryos transferred, so were the implantation and pregnancy rates. In this retrospective analysis, the authors were unable to investigate the cause of decreased fertilization. They postulate, however, based on prior reports in the literature, a gametotoxic effect of monocyte/macrophages or their secretory products, which are known to be present in peritoneal, follicular, or other body fluids of women with endometriosis.

There is no general consensus regarding the effect of endometriosis on fertility. Moreover, the cause-and-effect relationship between endometriosis and infertility has recently been questioned. Nevertheless, endometriosis has become a frequent clinical indication for IVF, and the literature abounds with contradictory reports of the effect of this disease on IVF parameters and outcome.

Past studies have generally agreed that for most patients endometriosis has no adverse effects on the ovarian response to stimulation as evidenced by similar peak estradiol levels and similar numbers of mature follicles as well as oocytes retrieved in women with and without the disease. The only exception are women with advanced endometriosis where ovarian function can be clearly compromised. Fertilization rates, oocyte and embryo quality, and implantation as well as pregnancy rates have, however, remained more controversial. Published studies have been almost exclusively retrospective and observational. Their results are, therefore, highly dependent on proper selection of sub-

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jects and controls. Some reports, in agreement with the study by Bergendal *et al.*, indicate lower fertilization rates but no other adverse effects of the disease. Others report lower fertilization, lower oocyte/embryo quality, and lower implantation as well as pregnancy rates. Yet others report no changes in fertilization or oocyte/embryo quality, but decreased implantation and pregnancy rates. All are contradicted by reports of similar fertilization and oocyte/embryo quality and similar implantation/pregnancy rates in women with and without endometriosis.

The quality of oocytes/embryos, as well as fertilization and implantation rates, is affected not only by the disease but also by a multitude of clinical and laboratory-related factors. To achieve meaningful conclusions, the same clinical and laboratory protocols should be strictly followed by both subjects and controls. The decrease in the fertilization rates in endometriosis reported by Bergendal *et al.* was observed in spite of matched contemporaneous controls undergoing the same IVF protocol.

There is no question that modifications in the clinical and laboratory protocols, some minor, all seldom reported, determine the variability in the IVF implantation and pregnancy rates. In tubal disease alone, implantation rates as low as 8% and as high as 23% have been reported by the major programs. In endometriosis, this "between-program variability" ranges between 2.8 and 22%. It is possible that some of the modifications in the IVF protocol modulate the adverse effect(s) that endometriosis may have on the reproductive processes. The variability in the implantation and pregnancy rates in endometriosis may be, therefore, secondary to a factor(s) that is (are) variable within every endometriosis population and/or may be affected by clinical IVF protocols and/or laboratory techniques.

Abnormal autoantibodies may be such factors. They have been demonstrated in varying concentrations in the peripheral circulation and in the peritoneal, follicular, and other body fluids in approximately 60% of women with endometriosis. In women with autoimmune diseases such as systemic lupus erythematosus, the presence of abnormal autoantibodies has been associated with a high incidence of pregnancy wastage. In healthy women with abnormal autoantibodies there is also a high prevalence of various forms of reproductive failure such as recurrent spontaneous abortions, intrauterine death, intrauterine growth retardation, and pregnancy-induced hypertension leading to preeclampsia. In such patients thrombosis in placental vessels and thrombo-

cytopenia are frequent findings. It has been suggested that autoantibodies induce thrombosis in spiral arteries of the endometrium and in the placenta, causing infarctions and decreased blood supply to the conceptus. Others have proposed that abnormal autoantibodies bind to the trophoblast and alter its function. Several studies indicate that suppression of abnormal autoantibodies with corticosteroids as well as anticoagulant therapy such as aspirin and/or heparin may improve reproductive performance in affected women.

A high prevalence of abnormal autoantibodies has been reported in failed IVF cycles, and several studies indicate that the presence of autoantibodies adversely affects the IVF outcome. Furthermore, the use of corticosteroids or anticoagulants during the IVF protocol in autoantibody-positive patients improves pregnancy rates according to several reports. However, there are no prospective data to demonstrate an adverse effect of autoantibodies on gametes or embryos, or on fertilization, implantation, or pregnancy rates, in IVF cycles, and the beneficial effects of corticosteroids and anticoagulants have not been correlated with autoantibody suppression. On the contrary, a recent prospective study in a large population of 793 consecutive IVF patients was unable to demonstrate the adverse effect of antiphospholipid antibodies on implantation or pregnancy rates (1). The patients in that study did not receive corticosteroids or anticoagulants during the IVF cycle. Interestingly, however, that IVF laboratory is known to routinely strip cumulus-corona cells after oocyte retrieval. Our personal experience at two independent institutions indicates that abnormal autoantibodies adversely affect the IVF outcome. Yet one of us (N.G.), in a blinded, collaborative study, was unable to demonstrate the adverse effect of autoantibodies when IVF was performed at another institution which also routinely removes cumulus-corona cells from the oocyte.

It is possible that abnormal autoantibodies produced by some women with endometriosis and present in the follicular fluids interfere with oocyte fertilization *in vitro* and with early embryo development, while those in the peripheral circulation may cause implantation failure. This concept is supported by two recent reports. One indicates that antiphospholipid antibodies bind to the zona pellucida and to mouse preembryos, interfering with their subsequent development to the blastocyst stage (2). The other demonstrates that antiphospholipid antibodies bind to the human trophoblast and interfere with its function (3). Abnormal autoantibodies can be

suppressed with corticosteroids, used routinely during the IVF cycle by some programs, or rendered ineffective by the use of aspirin and/or heparin. They can be diluted or removed from the oocyte/embryo environment by follicular/oocyte washing, cumulus–corona cell removal, changes of media, etc. It is, therefore, possible that the individual variability in autoantibody levels in women with endometriosis, differences in clinical protocols, and different laboratory procedures determine the presence and concentration of autoantibodies in vivo and in vitro and their binding to the oocytes and embryos. These differences may be responsible for the contradictory reports.

It would be of interest in future studies to control for the above-mentioned variables in order to identify

factors affecting oocyte/embryo quality and implantation in endometriosis.

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