18 Infertility and Antiphospholipid Antibodies

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Whether antiphospholipid antibodies (aPL) play a pathogenic role in infertility is highly controversial. aPL have been suggested to represent one potential etiology of infertility, specifically in patients with unexplained implantation failure following in vitro fertilization (IVF). The rationale is appealing, as it represents a logical extension of the demonstrated pathogenicity of aPL in contributing to recurrent spontaneous abortion, where mechanisms other than placental thrombosis and infarction seem to be at play. aPL in this setting are postulated to bind to phospholipids on trophoblast tissue, impairing trophoblast development and preventing normal placentation. Unexplained infertility in patients found to have aPL may represent the earliest form of aPL-mediated obstetric pathology: a disturbance of implantation, leading to failure to achieve biochemical or clinical pregnancy. What evidence supports this? More importantly, is there convincing evidence that makes this clinically relevant, that is, data to support use of current aPL pregnancy therapy to treat patients with failed IVF cycles?

The field of reproductive medicine, like the study of antiphospholipid syndrome (APS), has experienced explosive growth over the last 20 years. Infertility is a common problem, affecting 15% to 20% of couples. By definition, infertility represents the inability of a couple practicing frequent intercourse and not using contraception to conceive a child within 1 year. Causes of infertility are fairly evenly distributed between males and females, and usually fall into one of three major groups: male factor, ovulatory dysfunction, and tubal–peritoneal disease. For this reason, initial work-up includes evaluation of both the male and the female partner. For women, this means hormone tests and direct visualization of the reproductive tract. Routine tests include day-three follicle stimulating hormone (FSH), prolactin, thyroid function tests, cervical cultures, and evaluation of ovulatory function (basal body temperature, urinary lutenizing hormone, transvaginal ultrasound, and/or endometrial biopsy). Tubal patency and uterine morphology are evaluated with a hysterosalpingogram; hysteroscopy and laparoscopy may be required. Low serum progesterone 1 week post-ovulation suggests a luteal phase defect. A postcoital test is sometimes performed to assess cervical mucous and presence of antisperm antibodies [1]. Tests for male factors include semen analysis, specific tests for spermatozoal function such as the hamster egg penetration assay, and hormone levels [2].

A probable etiology for infertility is often uncovered. In general, ovulatory dysfunction accounts for 15% cases, pelvic factors (including endometriosis and adhesions) for 35%, male factors (oligospermia, decreased sperm motility, or abnormal sperm function) for 35%, and abnormal sperm–cervical mucus penetration or

antisperm antibodies for 5%. Despite extensive testing, etiology remains unexplained in about 10% to 15% of cases. Importantly, two or more factors are identified in 20% to 40% of couples. Although IVF is an assisted reproductive technique originally developed for patients with Fallopian tube pathology, it is now routinely used for infertility patients with a wide range of etiologies, including those with unexplained infertility [3]. The mechanics of IVF can bypass many potential steps that may be defective.

Briefly, the usual IVF protocol includes ovarian stimulation, retrieval of multiple oocytes, in vitro fertilization, and embryo placement in the uterus. Gonadotropin-releasing hormone (GnRH) analogs are often used to desensitize pituitary gonatotropes to endogenous GnRH and downregulate gonadotropin secretion. Controlled ovarian hyperstimulation is accomplished by administering human menopausal gonadotropin, and ovulation is triggered with human chorionic gonadotropin (hCG) when multiple follicles are mature. Oocytes are usually retrieved through transvaginal ultrasound-guided follicular puncture.

After separation of motile spermatozoa and in vitro capacitation, spermatozoa are added to oocytes and cultured to achieve fertilization. Gamete micromanipulation is used for male factor infertility, usually intracytoplasmic sperm injection (ICSI). Fertilized oocytes are re-examined after incubation to confirm embryonic cleavage has occurred and to assess embryo quality. If indicated, embryo biopsy with prenatal genetic diagnosis may be done to rule out aneuploidy or other genetic defects. Embryo placement (usually 2 to 3 per procedure) is through transcervical transfer to the uterus, and the luteal phase is then maintained with low dose hCG or exogenous progesterone. Within 10–12 days of embryo transfer, implantation can be detected by an increase in serum hCG levels. Diagnosis of clinical pregnancy depends on visualization by ultrasound of a gestational sac containing a fetus with fetal heart activity within the uterine cavity 4–6 weeks after transfer.

Many factors affect IVF outcome. Age is one of the most critical: female fertility begins to decline naturally in the mid-30s and becomes marked after age 40. As patients age, oocyte quality decreases, negatively impacting likelihood of IVF success. In addition, the reported outcomes – including those in many of the aPL studies described below – are often expressed in a number of different ways. *Biochemical pregnancy* is implantation identified by a transient production of hCG but with early loss before sonographic documentation of a fetus. *Clinical pregnancy* is when fetal heart activity is seen. *Ongoing pregnancy* represents currently viable gestations, and *live birth rate* or *deliveries* describes successfully completed pregnancies. Outcome may be expressed as pregnancy rate per cycle or per transfer procedure, or as pregnancy rate per embryo transferred. Control patients are of particular importance in studies of outcome because even in optimal cycles implantation rates per embryo differ between IVF and spontaneous pregnancy. Likelihood of embryo implantation in an IVF cycle is 10%, versus about 25% for a natural cycle. In addition, there are increased rates of ectopic pregnancy and first trimester spontaneous abortion in IVF pregnancies [3].

Recent research has focused on the role of a variety of immunologic factors in reproductive failure, both infertility and recurrent spontaneous abortion (RSA). While alloimmune factors (including T cell embryotoxic cytokines and CD56 natural killer cells) are postulated to play a role primarily in RSA, autoimmune humoral abnormalities (including antiphospholipid, antithyroid, and other autoantibodies), have been suggested to play a role in both RSA and in infertility.