

A Brief Review of Stroke associated with Assisted Reproductive Technology

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Abstract

Strokes related to assisted reproductive technology are rare, but can be devastating. In order to understand how stroke can occur as a complication of assisted reproductive technology, both the normal physiology of ovulation and the hormonal manipulations used to maximize pregnancy will be examined. In particular, the danger of thrombotic complications related to ovarian hyperstimulation syndrome will be reviewed including the pathophysiology, clinical features, risk factors and treatment.

Keywords: Assisted reproductive technology; Stroke; *In vitro* fertilization; Ovarian hyperstimulation syndrome; Cerebral venous thrombosis

Introduction and Definitions

Assisted reproductive technology (ART) is the generic term referring to the methods used to achieve pregnancy including fertility medication, artificial insemination, *in vitro* fertilization (IVF) and surrogacy. IVF refers to the procedure where the ovaries are stimulated by fertility medications to produce follicles; the oocytes are aspirated from the follicles and fertilized in the lab and then transferred to the uterine cavity. The process involves the use of exogenous hormones to achieve cycle control, stimulate the ovaries and support implantation. During this process, supra physiological estradiol levels can result. High estradiol levels alone increase thrombotic risk [1].

One major complication of this intervention, ovarian hyperstimulation syndrome (OHSS) can be associated with significant arterial and venous thrombotic complications [2]. OHSS is a rare iatrogenic complication that occurs when the ovaries are hyper stimulated and enlarged related to fertility treatments. The incidence of OHSS can occur in up to 10% of IVF cycles, but only a small number of these cases are severe [3,4]. It has two clinical forms both of which are related to human chorionic gonadotrophin (HCG). The most common early form occurs in the first eight days after exogenous HCG administration and the late form is related to pregnancy induced HCG production [5,6]. Thrombotic complications related to ART are rare, but neurologists need to understand the risks and pathophysiology.

Incidence

The incidence of thrombosis varies from 0.2% of all IVF cycles to up to 10% in OHSS [7]. This is a small percentage, but the absolute number of those affected is considerable given the number of women who undergo fertility treatment. Seventy five percent of the thrombotic events are venous including cerebral venous thrombosis; the remainders of events are almost all ischemic strokes [8].

Normal physiology

A normal menstrual cycle is divided into three phases either based on what occurs in the ovary; the follicular phase, ovulation and the luteal phase or the correlating phases in the uterus; proliferative, secretory and menstruation. Follicle stimulating hormone, FSH, released from the pituitary gland stimulates follicular growth. The growing follicles produce estradiol which has a negative effect on the pituitary release of luteinizing hormone, LH and at a threshold causes release of gonadotropin-releasing hormone (GnRH) which stimulates the pituitary release of LH, the LH surge which triggers ovulation. FSH and LH cause the remaining parts of the dominant follicle to transform into the corpus luteum, which produces progesterone [9].

Controlled ovarian stimulation

ART uses hormonal manipulation of this normal physiology to increase the odds of fertilization and pregnancy. Estrogen receptor modulators, such as clomiphene, can stimulate follicular development. They have rarely been associated with OHSS [10]. Most infertility regimens use daily FSH injections for follicular stimulation [11]. FSH is used in conjunction with a low dose of a GnRH analog to prevent the LH surge until the follicles are judged to be mature. Either human chorionic gonadotropin (HCG) or a GnRH agonist can be used to trigger the LH surge and the ovulatory cascade. The oocytes can then be harvested, fertilized and implanted.

Pathophysiology of OHSS

HCG which naturally rises during pregnancy following ovarian stimulation or when it is given for follicular maturation to trigger ovulation appears to be pivotal in the development of the increased vascular permeability which is the core feature of OHSS [12]. High levels of HCG are felt to cause an over expression of vascular endothelial growth factor in the developing follicles leading to a release of vasoactive substances [13,14]. The result is ovarian enlargement as well as capillary hyperpermeability with fluid extravasation causing ascites, pleural and pericardial effusions. The resultant fluid shifts are also responsible for electrolyte disturbances, oliguria, hypovolemia and hemoconcentration [15].

Elevated estrogen levels alone cause a hypercoagulable state. In studies of oral contraceptives or hormone replacement therapy, high estrogen levels are associated with an increased risk of both arterial and venous thrombosis [16]. In a study of seven women undergoing ovarian stimulation, endogenous estrogen levels (other hormonal changes were not investigated) and the associated changes in coagulation parameters were evaluated. These women showed a predictable rise in fibrinogen which correlated with the marked rise in estrogen during the cycle, thus producing a prothrombotic state [17]. This thrombotic risk is magnified in OHSS. In addition to high estradiol levels, hypercoagulability is worsened by the hypovolemia and hemoconcentration both which result from the increased capillary permeability [18]. Ascites and increased ovarian size promote venous stasis further exacerbating the hypercoagulable state [19].

Clinical features

The clinical signs and symptoms of OHSS are varied. The increase in ovarian size can cause abdominal pain, nausea and vomiting. Increased vascular permeability occurs leading to a shift of fluid from the intravascular to extravascular space resulting in third spacing with subsequent hypotension, edema, ascites, pericardial and pleural effusions. A complex cascade ensues which may include hypotension, hemoconcentration, tachycardia and hypercoagulability. The latter problem results in thrombotic complications. These events (especially venous thrombosis) have been reported to occur even weeks after OHSS has resolved. Thrombotic complications are primarily venous, 66% [19]. The venous complications related to OHSS have been reported in axillary, mesenteric, jugular, subclavian and cerebral venous sinuses. In fact, venous thromboembolic complications preferentially occur in the neck and upper limbs in particular the internal jugular and subclavian veins [20,21]. The arterial events are almost always ischemic stroke [18].

Risk factors

A number of risk factors for thrombotic complications from ART have been defined. The risk is particularly prominent in women who are more likely to develop OHSS. The defined primary risk factors include young age, history of polycystic ovary syndrome, PCOS, a prior history of OHSS and any underlying thrombophilia [22]. Younger patients are more likely to have a robust response to ovarian stimulation increasing the risk for complications and development of OHSS. A prior history of OHSS as well as a history of PCOS also increases the risk of OHSS [22,23]. Women with PCOS are also more likely to suffer this complication as they tend to produce more follicles.

The secondary risk factors include features related to treatment response including absolute estradiol level as well as the number and size of follicles produced. If pregnancy follows this exuberant response to IVF, that will also increase the risk of OHSS due to the stimulation of HCG.

Treatment

Prevention and recognition of OHSS are the key elements to patient safety as no direct treatment exists. One strategy would be to identify women at risk for OHSS and in these high risk individuals to carefully follow the ovaries response to stimulation using both estrogen levels and ultrasounds. Additionally, cancelling the IVF cycle if there is concern for OHSS is prudent [13,23,24]. Currently, there is a movement away from using HCG as an ovulatory trigger as it seems to

be important in the pathogenesis of OHSS. For women with PCOS the use of metformin during controlled ovarian hyperstimulation has been shown to decrease the relative risk of OHSS by 0.2; 95% CI without changes the clinical outcomes of implantation rate, pregnancy or live birth rate [25].

The key features of treatment once OHSS has occurred are supportive. These measures include fluid replacement, pain control, avoiding non-steroidal anti-inflammatory medications (as these may worsen renal function) and maintenance of adequate blood pressure. Women with severe OHSS require hospitalization to manage hypotension, poor renal function, pain and ascites. In patients with severe OHSS, an antithrombotic medication should be initiated [26,27]. Those women with neurologic complaints require an expeditious consultation. Neurologists need to be aware of the propensity of thrombotic complications both venous and arterial in this group of otherwise healthy women in order to rapidly assess, utilize appropriate imaging and treat.

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