THE PATHOPHYSIOLOGY OF OVARIAN HYPERSTIMULATION SYNDROME (OHSS)

A Proposal Role of the Ovarian Derived Prorenin to Angiotensin Cascade (ODPAC)

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INTRODUCTION

Despite the fact that it was first described over thirty years ago, the factors responsible for OHSS have continued to elude investigators. During this time, several theories have been popularized but none have become widely accepted. Recently, it has been suggested that angiotensin II (Ang II) derived from the ovary plays an important role in the development of OHSS (1). This paper will briefly review previous theories and present the results of experiments performed at the University of Southern California School of Medicine that add weight to the notion that ODPAC is involved in OHSS.

BACKGROUND

OHSS is the name given to the complex of symptoms that occasionally arise in some women who receive gonadotropin stimulation for the treatment of infertility. These patients frequently have exaggerated responses to gonadotropins exhibiting high estradiol (E2) levels and developing numerous follicles (2). It seems to occur most commonly in women who have polycystic ovary syndrome (PCOS) (2). It also occurs more frequently in those patients who receive additional human chorionic gonadotropin (hCG) stimulation either endogenously through pregnancy or exogenously for luteal phase supplementation (3,4). The underlying physiologic derangement which is primarily responsible for the manifestations of OHSS is increased vascular permeability (5). Increased permeability results in fluid leakage and intravascular volume depletion (3). Ascites, edema, pleural, and pericardial
effusions are the result of fluid leakage into the peritoneal cavity, interstitium, thorax, and pericardium respectively (5). Clinically, weight gain, abdominal distension, and occasionally respiratory distress are seen (6). Low circulating blood volume can cause hemoconcentration and is evidenced by an elevated hematocrit (HCT) (7). This may result in electrolyte abnormalities, thrombosis, and oliguria leading to renal failure (7,8,9). Schenker and Weinstein classified OHSS into three levels of severity (mild, moderate, severe) based on these parameters (6).

Early studies with the gonadotropin stimulated New Zealand white rabbit demonstrated that OHSS results from a soluble factor which arises from the ovary (5). Much work has been performed in attempting to ascertain the identity of this factor.

Initially, the estrogens were suspected since both estrone (E1) and E2 are driven to high levels during ovarian stimulation. Additionally, E2 has been shown to increase vascular permeability in the uterus (10). However, Schenker and Polishuk were unable to induce OHSS in rabbits by administering high doses of E1 alone (5). In 1991, Miles et al., in our lab administered the aromatase inhibitor, testolactone, to hyperstimulated patients. Although E1 and E2 levels dropped significantly, no improvement was seen in several indices of OHSS (11).

Several inflammatory mediators have been investigated to determine a role in OHSS. Prostaglandins, specifically PGI2, are produced by the ovarian follicle (12). Prostaglandins may increase the permeability of the follicle wall allowing follicular fluid into the peritoneal cavity (12,13). However, when PGI2 metabolites were measured in stimulated cycles, the levels were not increased over the normal luteal phase (12). Further, indomethacin was ineffective in relieving several stigmata of OHSS in the New Zealand white rabbit (14).

Histamine is a vasoactive amine which can have marked effects on vascular permeability and edema formation (15). Mast cells have been identified in the ovary of humans and histamine released is stimulated by gonadotropins (16,17). Knox was able to prevent ovarian enlargement and ascites by administering histamine receptor antagonists to hyperstimulated rabbits (18). Subsequently, Elik et al. measured plasma histamine levels in patients with OHSS but failed to demonstrate any elevation (16). Additionally, the number of mast cells in the ovaries of OHSS patients were not increased over controls (16). Serotonin is another vasoactive amine which was studied in the rabbit model. However, two potent anti-serotonin drugs (methysergide and cyproheptadine) were ineffective in preventing OHSS (15).

Recently, interest has arisen in the cytokines as possible mediators of OHSS. White blood cells are residents of the ovary and various cytokines have been proposed to have roles in the reproductive process (19). Further, some cytokines have been shown to increase vascular permeability (20). Elevated levels of interleukin-6 have been noted in the serum of patients with OHSS (20).

Angiotensin II has also been proposed as a possible mediator of OHSS development. The evidence is several-fold. First, Ang II and other components of ODPAC such as prorenin (PR) and renin (AR) are stimulated to high levels by exogenous gonadotropins (21,22). The highest levels occur in early pregnancy (23). Angiotensin II has been demonstrated to increase vascular permeability in a number of different models. In 1962, Bisset and Lewis found that the injection of the subcutaneous tissue of guinea pigs with Ang II increased vascular permeability and tissue edema (24). Later, Robertson et al. discovered that rabbit aorta allowed leakage of Evan’s blue dye when the endothelium was injected with Ang II but not with Ringer’s lactate (25). Electron microscopy revealed endothelial cell contraction and widening of interendothelial junctions. Recently, Morel confirmed this observation (26). Bovine pulmonary microvessel endothelial cells were grown on a silicone substratum. In this model, cell contraction could be easily visualized by “wrinkling” of the silicone. Low doses of Ang II (5 X 10⁻⁵ M) resulted in cell contraction (26).