Peripheral arterial vasodilation hypothesis: a new insight into the pathogenesis of ovarian hyperstimulation syndrome

Juan Balasch1,2, Francisco Fábregues3 and Vicente Arroyo2

1Department of Obstetrics and Gynecology and 2Liver Unit, Institut Clinic of Digestive Disease, Department of Medicine, Faculty of Medicine-University of Barcelona, Hospital Clinic i Provincial-Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

Ovarian hyperstimulation syndrome (OHSS) is a serious complication of ovulation induction which, at present, is being studied increasingly because of its frequent occurrence as a result of the growing number of in-vitro fertilization (IVF) programmes. The anatomical changes involving enlargement of the ovaries and increased capillary permeability leading to acute fluid shift have been traditionally proposed to explain the different clinical features observed in OHSS. Recent work from our group, however, has shown that the pathogenesis of severe OHSS is more complex than currently understood and that marked peripheral arteriolar vasodilation is a major event in the development of the syndrome. Peripheral vasodilation may, in its turn, alter microvascular haemodynamics and permeability. This leads to a circulatory dysfunction with marked homeostatic activation of endogenous vasoactive systems having vasoconstrictor and sodium- and water-retaining activities. In this way, sodium and water retention would be a cause rather than a consequence of ascites formation in severe OHSS. This report analyses current concepts on body fluid regulation as well as neurohormonal and haemodynamic studies both in patients with severe OHSS and asymptomatic IVF women, integrating their findings into the present knowledge of the pathogenesis of the syndrome. Therapeutic implications are discussed.

Key words: IVF/ovarian hyperstimulation syndrome/peripheral vasodilation/renin/sodium retention

Introduction

Severe ovarian hyperstimulation syndrome (OHSS) is an iatrogenic complication of ovulation induction mainly with human menopausal gonadotrophins and human chorionic gonadotrophin, which may cause severe morbidity and even mortality (Schenker and Weinstein, 1978). At present, the syndrome is being increasingly recognized because of the high number of women undergoing assisted reproductive techniques (Navot et al., 1992; Schenker, 1993). This has led to a renewed interest in the subject.

Clinical manifestations of severe OHSS include ovarian enlargement, ascites, pleural effusion, electrolyte abnormalities, hypovolaemia, oliguria, haemoconcentration, hypercoagulability and liver dysfunction. Exceptionally, respiratory distress syndrome, hypovolaemic shock, renal failure and even death may ensue (Schenker and Weinstein, 1978; Pride et al., 1990; Rizk and Aboulghar, 1991; Schenker, 1993). This clinical picture has been traditionally explained on the basis of marked ovarian enlargement and a sudden increase in capillary permeability, mainly of the ovarian vessels, which results in a rapid fluid shift from the intravascular space into the abdominal cavity (Schenker and Weinstein, 1978; Schenker, 1993; Elchalal and Schenker, 1997). It could be the rapid formation of ascites at the expense of the intravascular volume and the associated systemic vascular changes that contribute most to the morbidity and mortality associated with OHSS (Elchalal and Schenker, 1997).

Rapid body fluid shift in cases of OHSS would lead to hypovolaemia and haemoconcentration, as indicated by increased haematocrit values. When not corrected, hypovolaemia leads to decreased renal perfusion, subsequently stimulating the renal tubules to resorb salt and water, resulting in clinical manifestations of oliguria and sodium retention. The loss of fluid and protein into the peritoneal cavity can account for the hypovolaemia and haemoconcentration which, in turn, result in low blood pressure and decreased central venous pressure (Elchalal and Schenker, 1997). Since the abdominal cavity is linked to the pleural cavity by anatomic holes, ascitic fluid can pass into the pleural cavity giving rise to pleural effusion. This feature is promoted by the negative inspiratory intrathoracic pressure and the increase in intra-abdominal pressure due to the formation of ascites. In very extreme cases, the haemodynamic derangement caused by the vascular leakage of fluid can be so intense that hypovolaemic shock, acute renal failure and respiratory distress syndrome may develop. Finally, the rapid leakage of fluid from the intravascular space into the peritoneum causes haemoconcentration, increased blood viscosity and thromboembolic phenomena (Schenker and Weinstein, 1978; Elchalal and Schenker, 1997).

On the basis of the increased capillary permeability as the sole pathogenic mechanism in OHSS, there is a continuous effort to find the factors responsible for the increased vascular permeability and most recent publications on the syndrome deal with this topic (Elchalal and Schenker, 1997; Rizk et al., 1997). It should be noted that experimental studies suggest that ascites in OHSS may originate from extra-ovarian sites (Yarali et al., 1993) and, despite the fact that several substances...
of ovarian origin, mainly vascular endothelial growth factor and interleukins, have been proposed as mediators of increased vascular permeability (Elchalal and Schenker, 1997; Mathur et al., 1997; Rizk et al., 1997), their definite role in the pathogenesis of severe OHSS awaits further clarification (Elchalal and Schenker, 1997; Licht et al., 1997; Ludwig et al., 1998).

In fact, as recently stressed by Elchalal and Schenker (1997), ‘the puzzle is not resolved and many questions are still unanswered. Awareness of possible mechanisms and factors in the pathophysiology of OHSS will hopefully provide opportunities to design specific treatment regimens effective for both prevention and treatment of this potentially fatal iatrogenic condition’. In this regard, it is of note that recent work from our group has shown that the pathogenesis of severe OHSS is more complex than currently understood and that marked peripheral arteriolar vasodilatation is a major event in the development of the syndrome (Balasch et al., 1991, 1994, 1995, 1996a,b). This new pathogenetic concept in severe OHSS has important implications with respect to body fluid volume regulation, homeostasis of renal function, and pathogenesis of oedema as has been shown in other oedema-forming states such as liver cirrhosis, high-output heart failure and pregnancy (Schrier, 1988a,b; Schrier et al., 1988; Schrier and Briner, 1991). Also, this new concept may have important implications both from a therapeutic point of view (Balasch et al., 1996b) and for the investigation of factors potentially involved in the pathogenesis of the impaired circulatory function in patients with OHSS and even in asymptomatic women undergoing ovulation induction for in-vitro fertilization (IVF) (Manau et al., 1998).

The purpose of this report is twofold. First, to present current concepts providing a common pathophysiologic explanation of various diseases in which, as in severe OHSS, marked disturbances of systemic haemodynamics and renal function occur in association with oedema formation. Second, to summarize haemodynamic and neurohormonal studies both in patients with severe OHSS and asymptomatic IVF women, integrating their findings into the present knowledge of the pathogenesis of the syndrome.

Pathogenesis of sodium and water retention in oedema-forming states

Current concepts on body fluid volume regulation: the ‘effective arterial blood volume’

Body fluid volume regulation is critically important in maintaining life, and the regulation of the excretion of sodium and water in health and disease has been intensely studied for years. Yet there remain many perplexing dilemmas and apparent paradoxes about body fluid volume regulation in humans. Thus, in normal humans, expansion of the extracellular fluid volume, including expansion of the interstitial fluid and intravascular volumes, is associated with an increase in renal sodium and water excretion with resultant restoration of normal extracellular fluid volume (Schrier, 1990). Therefore, it seems extremely surprising that there are many pathological circum-
stances in which, despite expansion of total extracellular, interstitial and intravascular fluid volumes, avid renal sodium and water retention persists.

It is well known that sodium and water retention may expand the total extracellular fluid and blood volumes in patients with high- and low-output cardiac failure and cirrhosis, as well as in pregnant women, by as much as 50% (Schrier, 1988a,b, 1990; Schrier and Briner, 1991). If total extracellular fluid and blood volumes were expanded to this degree in a normal subject, the kidney would be excreting, not retaining, sodium and water. Moreover, the renin–angiotensin–aldosterone and sympathetic nervous systems, and the secretion of antidiuretic hormone (ADH), would be suppressed rather than increased as occurs in the sodium- and water-retaining states mentioned above (Schrier, 1988a,b; Schrier and Briner, 1991). It is clear that an extrarenal reflex initiates renal sodium and water retention in these varied oedematous states where there is no evidence of primary renal disease. For example, the kidneys from cirrhotic patients have been shown to function normally when transplanted into a subject with normal liver function (Koppel et al., 1969), and liver transplantsations into cirrhotic patients have been shown to reverse the renal and sodium retention (Iwatsuki et al., 1973). This suggests that the kidney is responding to signals from a volume-regulatory system; in other words, some ultimately important body-fluid volume compartment is reduced (underfilled) which triggers a volume-regulatory reflex leading to renal sodium and water retention (Schrier, 1988a).

On the basis of a series of investigations in experimental animals and humans, a unifying hypothesis of fluid volume regulation has been proposed recently by Schrier (1988a,b, 1990) whereby neither total extracellular fluid nor total blood volume determines renal sodium and water excretion. Rather, the integrity of the arterial circulation (that is, the dynamic interaction between cardiac output and peripheral arterial resistance) is proposed as the primary determinant of body fluid regulation. Thus, the ‘effective blood arterial volume’ (irrespective of the extracellular fluid and total intravascular volumes) is the ultimate factor responsible for activating extrarenal reflexes that enhance tubular sodium and water reabsorption by the otherwise normal kidney.

In considering the arterial circulatory integrity as the determinant of body fluid regulation, it is important to emphasize that approximately 85% of the total blood volume resides in the venous portion of the circulation. Thus, expansion of the venous blood volume may increase total blood volume even in the presence of arterial underfilling, as only 15% of the total blood volume circulates in the arterial vascular tree. Moreover, relative arterial underfilling may also occur secondary to peripheral arterial vasodilatation in the absence of an absolute decrease in arterial blood volume (Schrier and Briner, 1991).

On the other hand, when considering the arterial circulation as the primary body fluid compartment modulating renal sodium and water excretion, it is important to note that, in a 70-kg subject, total body water approximates 42 litres, of which only 0.7 litres or 1.7% resides in the arterial circulation. Thus, from a teleologic point of view, it is very attractive to

Pathogenesis of ovarian hyperstimulation syndrome
propose that the primacy for regulation of renal sodium and water excretion (and, thus, body fluid volume homeostasis) is modulated by a very small body fluid compartment, such as the arterial circulation. This endows the volume regulatory system with exquisite sensitivity to relatively small changes in body fluid volume, and locates it in the fluid compartment that is responsible for arterial perfusion of the body’s vital organs and tissues (Schrier, 1990). In this context, it is easy to understand that renal sodium- and water-retaining states that occur in the absence of intrinsic renal disease are initiated by either decreased cardiac output or peripheral arterial vasodilation leading to arterial underfilling. In other words, when kidneys are healthy, either a fall in cardiac output or peripheral arterial vasodilation may diminish arterial vascular filling and thereby initiate a series of haemodynamic and hormonal compensatory events that result in sodium and water retention (Schrier, 1988b, 1990). These compensatory mechanisms are discussed below.

Importance of peripheral arterial vasodilation on capillary leak of fluid

Results of experimental studies suggest that peripheral arterial vasodilation is associated with events at the capillary level that predispose patients to interstitial oedema and thus perpetuate vasodilation is associated with events at the capillary level that predispose patients to interstitial oedema and thus perpetuate vasodilation leading to arterial underfilling. In other words, when kidneys are healthy, either a fall in cardiac output or peripheral arterial vasodilation may diminish arterial vascular filling and thereby initiate a series of haemodynamic and hormonal compensatory events that result in sodium and water retention (Schrier, 1988b, 1990). These compensatory mechanisms are discussed below.

The homeostatic response to arterial underfilling

The neurohormonal compensatory response that defends against arterial underfilling involves rapid activation of the renin–angiotensin–aldosterone and sympathetic nervous systems and non-osmotic release of ADH, three neurohormonal vasoactive systems which are closely interrelated and operate simultaneously to regulate arterial pressure and intravascular volume (Schrier, 1988a; Laragh and Sealey, 1992; Robertson, 1992) (Figure 1).

Baroreceptor activation of the sympathetic nervous system appears to be the primary integrator of hormonal vasoconstrictor mechanisms involved in the volume control system. When diminished arterial pressure is sensed initially by the high-pressure baroreceptors located in the aortic arch and carotid sinus, and by the low-pressure baroreceptors (volume receptors) present in the cardiac atria and pulmonary veins, an increase in sympathetic efferent adrenergic tone is initiated. The haemodynamic effects of activation of the sympathetic nervous system result from the direct action of catecholamines, mainly norepinephrine released from the terminal ends of the postsynaptic sympathetic neurons. Norepinephrine release causes both increased cardiac rate and contractility and vasoconstriction in peripheral arterioles. The sympathetic nervous system also influences systemic haemodynamics indirectly by modifying renin release and ADH secretion (Mancia et al., 1995).

The renin–angiotensin–aldosterone axis is a major long-term regulator of blood pressure and electrolyte balance (Laragh and Sealey, 1992). By changing the plasma concentration of its two effector hormones, angiotensin II and aldosterone, the system simultaneously regulates body sodium and water content, arterial blood pressure, and potassium homeostasis. In this system the kidneys, responding to various stimuli perceived as a fall in renal arterial pressure or in distal tubular sodium supply, release renin. The juxtaglomerular apparatus, the site of renin synthesis and release, is richly innervated by sympathetic nerves. Activation of the sympathetic nervous system, via beta-adrenergic receptors, stimulates renin release and, therefore, aldosterone secretion. The renin release depends on local stimuli (renal perfusion pressure and distal delivery of sodium) and on the sympathetic nervous activity. These stimuli normally operate in the same direction influencing renin release. Renin liberates angiotensin I from a specific circulating plasma globulin. Angiotensin I is quickly transformed into angiotensin II by converting enzymes mainly in the lung. Angiotensin II raises pressure and stimulates the secretion of aldosterone by the adrenal cortex. Angiotensin and aldosterone together act to restore sodium balance and arterial pressure, thereby shutting off the initial signal for renin release.

More specifically, angiotensin II acts directly to support blood pressure by causing arteriolar vasoconstriction. This vasoconstriction is amplified by the sodium-retaining actions of angiotensin II, mediated via aldosterone-induced renal sodium retention and also by the direct renal sodium-retaining actions of angiotensin II. The increased body sodium content helps to maintain blood pressure by enhancing the vasoconstrictor action of angiotensin II and by increasing the filling volume of the vascular bed. Thus, the renin–angiotensin–aldosterone system maintains blood pressure both by reducing the capacity of the system (vasoconstriction) and by increasing the volume filling of the vascular tree through increased sodium and thus water retention (volume). As arteriolar constriction and sodium-volume retention work to raise or restore blood pressure and
flow, they concurrently operate to turn off renal renin secretion, thereby returning the system to the null point (Laragh and Sealey, 1992).

Sympathetic stimulation is also important in causing the non-osmotic release of ADH (Schrier, 1988a). As occurs with renin, the secretion of ADH is affected by changes in systemic haemodynamics through changes in the sympathetic nervous activity (Robertson, 1992). Small decreases (<10%) in blood volume or arterial pressure have little effect on plasma ADH. However, beyond this point, plasma ADH rises at a rapidly increasing rate. The ADH response to haemodynamic changes is mediated by neurogenic stimuli that arise from high- and low-pressure baroreceptors. The two major biological effects of ADH are to increase water reabsorption from the tubular lumen (hydro-osmotic effect) and to produce contraction of the vascular smooth muscle cell (vasoconstrictor effect) (Robertson, 1992; Skirecki et al., 1992).

Therefore, diminished circulatory perfusion of arterial baroreceptors activates simultaneously the three major vasoconstrictor systems: the sympathetic nervous system, the renin–angiotensin–aldosterone system, and the non-osmotic release of ADH. The extent of the activation of this integrative system has been shown to correlate with the severity of the disease in oedematous disorders (Schrier, 1988a). Although the more rapid response of this integrative system to circulatory dysfunction most likely involves the vascular effects of these three hormones, it is important to stress that maintenance of this integrated response to circulatory instability also involves ADH-mediated water retention and aldosterone-mediated sodium retention.

Figure 1 shows how this integrated system may modulate the retention of sodium and water whenever that cardiac output or peripheral vascular resistance are diminished. With peripheral arterial vasodilation, an increase in cardiac output secondary to afterload reduction constitutes another compensatory response to underfilling of the arterial circulation (Schrier, 1988a, 1990). According to this scheme, ‘underfilling’ of the arterial vascular tree provides the afferent stimulus for renal sodium and water retention. Other vasoactive substances, however, should be considered at present when analysing the homeostatic response to arterial underfilling in order to maintain arterial pressure. These are prostaglandins, natriuretic peptides and endothelins.

The kidneys are able to synthesize substances such as prostaglandins which act locally to regulate renal function. Prostaglandins are rapidly metabolized to products with no biological activity. Because of their rapid degradation, their biological actions are exerted at the site of synthesis. Therefore, prostaglandins synthesized by the arterioles and glomeruli are thought to regulate renal perfusion and glomerular filtration rate (Arroyo et al., 1991). Prostaglandins E₂ and I₂ have powerful vasorelaxant effects on the renal arterioles and the glomerular mesangium whereas thromboxane A₂ causes renal vasoconstriction (Conrad and Dunn, 1992). Interestingly, nor-epinephrine, angiotensin II and ADH stimulate the renal synthesis of vasodilator prostaglandins which antagonize the renal vasoconstrictor effect of these endogenous vasoactive compounds; that is, renal prostaglandins E₂ and I₂ regulate renal haemodynamics by modulating the renal vascular effects of endogenous vasoconstrictors (Clive and Stoff, 1984; Arroyo et al., 1991).

Natriuretic peptides are a family of closely related peptides which have similar amino acid composition and natriuretic and/or vasoactive properties (Brenner et al., 1990; Cogan, 1991; Lewicki and Proter, 1995). Among them, the most extensively studied is atrial natriuretic peptide (ANP). It is a 28-amino-acid peptide synthesized by atrial myocytes having potent vasodilator and natriuretic effects. It induces diuresis, natriuresis, and vasodilation; inhibits renin, aldosterone and ADH release; and antagonizes the antinatriuretic effects of angiotensin II (Brenner et al., 1990; Cogan, 1991). This cardiac hormone is released into the circulation in response to atrial distension. The plasma levels of ANP are therefore an index of the fullness of the intrathoracic vascular compartment. In this respect, any manoeuvre or disease that produces central volume expansion (e.g. i.v. saline administration, high sodium intake, congestive heart failure) is associated with an increased synthesis and release of ANP, and with high plasma levels of this hormone. Conversely, the decrease in central blood volume and in atrial distension produced by water or sodium restriction, diuretic administration, or adequate treatment in patients with congestive heart failure, is accompanied by reductions in the plasma concentration of ANP (Arroyo et al., 1991).

Therefore, ANP appears to play an important physiological role in sodium-repleted states, or when the effective plasma volume is increased. On the contrary, when the effective plasma volume is decreased or in sodium-depleted states, the natriuretic effect of ANP is severely blunted. Although the blockade by ANP of the main endocrine system involved in the conservation of sodium and water may contribute to the natriuretic effect of ANP, it should be stressed that, in conditions dominated by a marked activation of the renin–angiotensin–aldosterone system, a resistance to the natriuretic effect of ANP is frequently encountered. This may explain the lack of significant natriuretic effect of ANP in some pathological conditions such as heart failure or liver cirrhosis (Cogan, 1991).

Over the past few years, different investigations have shown that arterial pressure homeostasis is also regulated by vasoactive substances synthesized in the vascular endothelium, namely the vasodilator nitric oxide and the vasoconstrictor endothelins (Battistini et al., 1993; Levin, 1995). Endothelins are the most potent naturally occurring vasoconstrictor substances presently known, with a potency 10 times that of angiotensin II. Analysis of endothelin genes revealed the existence of three distinct genes that encode different mature sequences, designated endothelin-1, 2 and 3. Endothelin-1 is the only endothelin made by human endothelial cells, endothelin-2 is produced in the kidney and endothelin-3 is mainly associated with neural tissues (Masaki, 1993; Levin, 1995). Endothelins appear to function mainly as paracrine hormones acting on adjacent smooth muscle cells. They have homeostatic and compensatory actions in the circulatory and endocrine systems, presenting close interactions with other endogenous vasoactive substances (Haynes and Webb, 1993; Masaki, 1993; Remuzzi and Benigni, 1993). Thus, endothelins may increase the secretion of renin, aldosterone, catecholamines, ADH, and ANP
and potentiate the vasoconstrictor effect of norepinephrine and angiotensin II (Haynes and Webb, 1993; Remuzzi and Benigni, 1993; Levin, 1995).

Although endothelins are more likely to act as local autacoids rather than as systemic regulating hormones, with the development of specific and sensitive radioimmunoassays for endothelins, it is possible to measure the concentration of these peptides in biological fluids (Battistini et al., 1993; Masaki, 1993; Levin, 1995). Using these techniques, it has been shown that endothelins are present in the plasma of normal subjects, indicating that significant amounts of endothelins reach the circulation. Recent studies have shown that raised circulating levels of immunoreactive endothelins in pathological conditions are due to an increase in the plasma concentration of endothelin-1 and endothelin-3 (endothelin-2 is not detected in human plasma) (Moore et al., 1992). Endothelin-1 is not stored in the endothelial cells but rather is released constitutively in response to various stimuli, including shear stress, hypoxia, endotoxin, several vasoactive substances (e.g., angiotensin II, ADH, epinephrine) and some cytokines (Battistini et al., 1993; Masaki, 1993; Levin, 1995). Interestingly, plasma endothelin levels are increased in conditions associated with oedema formation such as high-output heart failure, cirrhosis, and pregnancy (Iwata et al., 1991; Stewart et al., 1992; Asbert et al., 1993).

The unifying hypothesis of fluid volume regulation and the pathogenesis of oedema

According to the above depicted scheme, ‘underfilling’ of the arterial vascular tree provides the afferent stimulus for renal sodium and water retention through the integrated system shown in Figure 1 which can modulate the retention of sodium and water in several pathological circumstances such as cirrhosis and congestive heart failure. If there is no evidence of intrinsic renal disease, renal sodium and water retention virtually always occurs as a compensatory response to arterial underfilling in association with the well-defined neurohumoral, vasoconstrictor response; these mechanisms combine in an effort to restore normal arterial circulatory integrity. The magnitude of the neurohumoral response and the avidity of renal sodium and water retention is an index of the initial degree of arterial underfilling (Schrier, 1990).

For example, as cirrhosis progresses from the compensated state without ascites to the decompensated state with ascites and then to the hepatorenal syndrome, the degree of peripheral (splanchnic) arterial vasodilation increases; blood pressure diminishes; the renin–angiotensin–aldosterone and adrenergic systems, and ADH are progressively stimulated; renal vasoconstriction worsens; and the avidity of sodium and water retention becomes more severe (Schrier et al., 1988). Similarly, the predominant mechanism of oedema in congestive heart failure could be an impairment in effective arterial blood volume secondary to the decrease in cardiac output. The high-pressure baroreceptors located in the aortic arch, carotid sinuses and juxtaglomerular apparatus could sense the underfilling of the arterial vascular compartment stimulating the renin–aldosterone and sympathetic nervous systems and ADH, thus inducing an increased renal tubular reabsorption of sodium and water. The retained fluid could extravasate in those areas with increased venous pressure. Additionally, the increased activity of these endogenous vasoconstrictor systems could produce systemic vasoconstriction and further decrease the cardiac output, thus closing a vicious circle.

These new concepts on oedema formation have had important clinical implications. It is thus pathogenically sound and not by chance that, in the absence of diuretic treatment, the hyponatraemic, high-renin patient with cirrhosis or cardiac failure has the worst prognosis (Arroyo et al., 1991, 1996; Bichet et al., 1986). This theory has also been important to improve the management of those oedematous conditions. Thus, in congestive heart failure, the administration of vasodilators decreases cardiac afterload, increases cardiac output, deactivates the endogenous vasoconstrictor systems, improves renal function and increases the response to diuretics. In the cirrhotic patient with ascites, the aim of the medical treatment is to mobilize the intra-abdominal fluid by creating a net negative balance of sodium. In approximately 10 to 20% of cases, those who spontaneously excrete relatively high amounts of sodium in the urine, this can be obtained simply by reducing the sodium content in the diet to 40 to 60 mEq/day. In the remaining cases with marked sodium retention, a negative sodium balance cannot be obtained without the aid of diuretics to increase urinary sodium excretion over the sodium intake. However, even in these patients, dietary sodium restriction is very important since it reduces the diuretic requirements. Otherwise, a frequent cause of diuretic-resistant ascites is inadequate sodium restriction (Arroyo et al., 1991). Finally, it is of note that a very recent study suggests the potential usefulness of ornipressin, a potent vasoconstrictor agent, for treatment of hepatorenal syndrome in advanced cirrhosis, a condition pathophysiologically characterized by a marked arterial vasodilation (Guevara et al., 1998).

The OHSS in the context of the unifying hypothesis of fluid volume regulation

In recent years we have performed pathophysiological studies in more than 50 patients with severe OHSS. The aim of these studies was to assess whether the pathogenesis of oedema in OHSS could also be explained on the basis of the unifying hypothesis of fluid volume regulation. Our investigations included circulatory function, neurohumoral measurements, renal function, and haemostasis parameters. Pertinent findings have been previously reported (Balasch et al., 1991, 1994, 1995, 1996a,b; Fábregues et al., 1998).

The specific background for our investigations was as follows. (i) Pregnancy is associated with arteriolar vasodilation and relative underfilling of the arterial vascular compartment, which lead to circulatory dysfunction characterized by arteri hypotension, high cardiac output, and stimulation of the renin–angiotensin system (Schrier 1988a,b; Schrier and Briner, 1991; August et al., 1995). (ii) These haemodynamic changes in pregnancy have been reproduced by systemic oestadiol administration in the animal model (Magnes and Rosenfeld, 1989). This suggests that arteriolar vasodilation during pregnancy may be related to hyperoestrogenaemia occurring with this
Pathogenesis of ovarian hyperstimulation syndrome

Table I. Summary of systemic haemodynamic, neurohormonal, and renal function changes during severe ovarian hyperstimulation syndrome

<table>
<thead>
<tr>
<th>Haemodynamic features</th>
<th>Neurohormonal measurements</th>
<th>Renal function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypotension</td>
<td>Increased plasma renin activity</td>
<td>Oliguria</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Increased plasma aldosterone</td>
<td>Reduced sodium excretion</td>
</tr>
<tr>
<td>High cardiac output</td>
<td>Increased plasma norepinephrine</td>
<td>Dilutional hyponatremia</td>
</tr>
<tr>
<td>Low estimated peripheral vascular resistance</td>
<td>Increased plasma antidiuretic hormone</td>
<td>Reduced serum osmolality</td>
</tr>
<tr>
<td>Haemocoagulation in ~50% of patients</td>
<td>Increased plasma atrial natriuretic peptide</td>
<td>Increased urine osmolality</td>
</tr>
<tr>
<td>Increased plasma endothelin</td>
<td>Increased plasma renin activity</td>
<td>Increased serum creatinine</td>
</tr>
<tr>
<td>Retained sodium</td>
<td>Increased plasma aldosterone</td>
<td>Increased urinary excretion of vasodilators prostaglandins E₂ and I₂</td>
</tr>
<tr>
<td>Dilutional hyponatremia</td>
<td>Increased plasma antidiuretic hormone</td>
<td>arterial hypertension is found, the hyper-reninism is</td>
</tr>
<tr>
<td>Increased urine osmolality</td>
<td>Increased plasma atrial natriuretic peptide</td>
<td>associated with arteriovenous vasodilation, haemoconcentration was observed in only half of patients having the syndrome. Furthermore, as expected, percentage changes in peripheral vascular resistance during the syndrome relative to baseline recovery values were associated with percentage changes in cardiac output and mean arterial pressure in our studies.</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>Increased plasma renin activity</td>
<td>arterial hypertension is found, the hyper-reninism is</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Increased plasma aldosterone</td>
<td>associated with arteriovenous vasodilation, haemoconcentration was observed in only half of patients having the syndrome. Furthermore, as expected, percentage changes in peripheral vascular resistance during the syndrome relative to baseline recovery values were associated with percentage changes in cardiac output and mean arterial pressure in our studies.</td>
</tr>
<tr>
<td>Reduced sodium excretion</td>
<td>Increased plasma antidiuretic hormone</td>
<td>arterial hypertension is found, the hyper-reninism is</td>
</tr>
<tr>
<td>Dilutional hyponatremia</td>
<td>Increased plasma atrial natriuretic peptide</td>
<td>associated with arteriovenous vasodilation, haemoconcentration was observed in only half of patients having the syndrome. Furthermore, as expected, percentage changes in peripheral vascular resistance during the syndrome relative to baseline recovery values were associated with percentage changes in cardiac output and mean arterial pressure in our studies.</td>
</tr>
<tr>
<td>Reduced serum osmolality</td>
<td>Increased plasma renin activity</td>
<td>arterial hypertension is found, the hyper-reninism is</td>
</tr>
<tr>
<td>Increased urine osmolality</td>
<td>Increased plasma antidiuretic hormone</td>
<td>associated with arteriovenous vasodilation, haemoconcentration was observed in only half of patients having the syndrome. Furthermore, as expected, percentage changes in peripheral vascular resistance during the syndrome relative to baseline recovery values were associated with percentage changes in cardiac output and mean arterial pressure in our studies.</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>Increased plasma renin activity</td>
<td>arterial hypertension is found, the hyper-reninism is</td>
</tr>
<tr>
<td>Increased urinary excretion of vasodilators prostaglandins E₂ and I₂</td>
<td>Increased plasma antidiuretic hormone</td>
<td>associated with arteriovenous vasodilation, haemoconcentration was observed in only half of patients having the syndrome. Furthermore, as expected, percentage changes in peripheral vascular resistance during the syndrome relative to baseline recovery values were associated with percentage changes in cardiac output and mean arterial pressure in our studies.</td>
</tr>
</tbody>
</table>

Our findings, therefore, indicate that severe OHSS is related to marked peripheral arteriolar vasodilation and suggest that this abnormality also may play an important role in the pathogenesis of the circulatory and renal dysfunction that characterizes the syndrome. In fact, while severe OHSS was consistently associated with arteriovenous vasodilation, haemoconcentration was observed in only half of patients having the syndrome. Furthermore, as expected, percentage changes in peripheral vascular resistance during the syndrome relative to baseline recovery values were associated with percentage changes in cardiac output and mean arterial pressure in our studies.

**Neurohormonal measurements**

Our studies confirmed that the renin–angiotensin–aldosterone system is markedly activated in severe OHSS. However, while hyperstimulated ovaries have been considered as the main source of hyper-reninism in OHSS (Navot et al., 1987; Golan et al., 1989; Ong et al., 1991; Bergh and Navot, 1992), our studies suggest that this is a homeostatic (secondary) rather than a primary event. Several lines of evidence support this contention:

(i) If hyper-reninism in OHSS was because of an autonomous production of renin by the ovaries, arterial pressure should be increased rather than reduced. This is understood considering the three basic tenets concerning plasma renin measurements (Laragh and Sealey, 1992). First, active plasma renin comes solely from the kidneys. Renin or renin-like substances as well as other components of the renin system exist inside certain endocrine gland cells, in the brain, and perhaps in the heart and blood vessels. These intracellular substances may be true renin or just a very similar molecule. However, they are not secreted into the bloodstream, and they do not contribute in a meaningful way to the circulating angiotensin II level. It is especially relevant that sizeable amounts of prorenin, the inactive precursor of renin, persist in the plasma of nephrectomized humans.

The organ sources of this prorenin are not known, but there is no evidence that it ever serves in vivo as a source for circulating active plasma renin. Indeed, if this large reservoir (prorenin is present in 10 times the amount of active renin) were an available source for circulating active plasma renin, cardiovascular chaos might result. In this context, there are studies demonstrating that prorenin in plasma derives partially from the ovaries and testes and perhaps from the adrenal cortex (Sealey et al., 1986, 1988). The likelihood that prorenin in these tissues may have a specific reproductive function is supported by the strong association of its very high levels in ovarian follicular fluid and in the increases that occur in plasma during ovulation (Sealey et al., 1985; Glorioso et al., 1986).

Accepting that active plasma renin is solely of renal origin, a second tenet states that plasma renin activity values have explicit physiological meaning because they closely reflect the concurrent degree of active renin-mediated (angiotensin II) vasoconstriction (Laragh and Sealey, 1992). A third tenet follows from the first two: the plasma renin activity values are a direct measure of the rate of renal secretion of renin (Laragh and Sealey, 1992).

Overall, the three tenets indicate that whenever plasma renin activity is increased over normal range and no associated arterial hypertension is found, the hyper-reninism is
undoubtedly a homeostatic response to a haemodynamic abnormality. This is the case in severe OHSS patients.

(ii) In our studies, we found a close, direct relation between increased plasma renin activity and aldosterone but, most important, plasma renin activity was closely correlated with the plasma levels of other volume-dependent endogenous vasoactive substances, such as norepinephrine and ADH, which were also markedly increased.

As discussed above, a highly specific hormonal interplay exists between the kidneys and the adrenals but also between the renin–angiotensin–aldosterone system and the sympathetic nervous system and non-osmotic release of ADH where the sympathetic stimulation plays a central integrator role to regulate arterial pressure and intravascular volume (Schrier, 1988a; Laragh and Sealey, 1992; Robertson, 1992). Plasma norepinephrine concentration is a sensitive index of baroreceptor activity and sympathetic discharge (Grossman et al., 1982). On the other hand, both renal renin release and ADH secretion are greatly stimulated by the sympathetic nervous system (Robertson, 1992).

There is considerable evidence that this rapid neurohumoral compensatory response is essential for maintaining the integrity of the arterial circulation in sodium- and water-retaining states (Schrier, 1990). Therefore, the most plausible explanation for increased plasma levels of renin and ADH in severe OHSS is a baroreceptor-mediated stimulation of the sympathetic nervous system secondary to circulatory dysfunction.

(iii) The plasma concentration of ANP was markedly elevated during severe OHSS in our patients. This observation is another argument indicating that circulatory dysfunction in OHSS cannot be satisfactorily explained only on the basis of hypovolaemia. Right atrial pressure (or atrial distension), which is the main stimulus of atrial natriuretic peptide release (Brenner et al., 1990), is decreased in conditions of intravascular volume depletion. Therefore, if circulatory dysfunction in severe OHSS was solely due to a shift of intravascular fluid to the abdominal cavity, the plasma concentration of ANP should not be increased. The pathophysiological significance of these increased levels of ANP is unknown but they may counteract the increased activity of antinatriuretic factors (Cogan, 1991).

(iv) We showed that circulating plasma levels of immuno-reactive endothelins are elevated in patients with severe OHSS. As discussed above, it is now well established that the role of the endothelium in modulating cardiovascular homeostasis is via regulation of the vascular smooth muscle tone. Wall shear stress, which is a powerful stimulus for endothelial production and release from the endothelium, is increased in conditions of hyperdynamic circulation such as that observed in OHSS (Battistini et al., 1993; Masaki, 1993; Levin, 1995). Therefore, increased immuno-reactive endothelin levels in OHSS, in parallel with other neurohumoral vasoconstrictor systems, may represent a paracrine compensatory effect for haemodynamic stress associated with the syndrome. In other words, it may represent a homeostatic response to reduce arteriolar vaso-dilation.

Renal function studies

When renal function was analysed during severe OHSS, we found that, at admission, patients had oliguria, sodium retention (low urinary sodium excretion) and hyponatremia. On average, the amount of fluid retained, estimated by loss of body weight during hospitalization, was 4–5 kg. According to data analysed above, the pathogenesis of sodium retention in severe OHSS would be the intense activation of the renin–angiotensin–aldosterone and sympathetic nervous systems which strongly enhance sodium reabsorption in the renal tubules.

The occurrence of hyponatremia in the setting of an increased extracellular fluid volume and sodium retention suggests a dilutional origin (i.e. the retention of water exceeds the retention of sodium). This may be explained by the increased plasma concentration of ADH which impairs the renal ability to excrete water by increasing its reabsorption in the renal collecting tubules. Accordingly, we found that plasma osmolality was reduced and urine osmolality was increased during severe OHSS. The increased plasma levels of ADH occurred in the setting of a reduced plasma osmolality, which in normal conditions would have suppressed the release of the hormone from the hypophysis (Robertson, 1992). This further supports the concept that the high plasma levels of ADH in severe OHSS are due to a non-osmotic release, namely the decreased effective arterial blood volume.

Although serum creatinine concentration was normal in all our patients, this parameter was about 40% higher during the syndrome than after recovery, suggesting a small decrease of glomerular filtration rate. Interestingly, however, despite arterial hypotension and intense stimulation of the renin–angiotensin and sympathetic nervous systems, which are powerful renal vasoconstrictors, no patient in our series developed spontaneous renal failure during OHSS. This finding is probably related to the markedly increased renal production of prostaglandin E₂ and prostacyclin observed in all cases. It is well known that, as discussed above, both prostaglandins are renal vasodilators and antagonize the renal vasoconstrictor effect of angiotensin II and norepinephrine (Clive and Stoff, 1984).

Haematocrit, and leukocyte and platelet counts and the severity of OHSS

On the basis of the intravascular depletion concept of OHSS, mainly the haematocrit concentration but also white blood cell count (as an additional measure of haemoconcentration) have been proposed as markers of severity in the clinical assessment of OHSS (Bergh and Navot, 1992; Navot et al., 1996). However, no objective data have been reported to support this contention.

We have investigated the correlation between changes in haematocrit concentration, and the white blood cell and platelet counts and the severity of OHSS as assessed by the sensitive neurohumoral markers of effective intra-arterial blood volume (Fàbregues et al., 1998). We confirmed that haematocrit is a marker of severity in OHSS. Firstly, a direct correlation was found between haematocrit and neurohumoral measurements during OHSS. Secondly, patients with increased haematocrit concentration had the highest plasma levels of renin, aldosterone, norepinephrine, and ADH.

Neither leukocyte nor platelet counts were correlated with the severity of the OHSS, despite the fact that both were significantly increased during the syndrome (Fàbregues et al.,...
These increases may be attributed to a generalized stress reaction and/or elevated cytokine production by the stimulated ovaries (Hollen et al., 1991; Abramov et al., 1996; Dhabhar et al., 1996; Loret de Mola et al., 1996a; Hock et al., 1997).

Increased platelets has been traditionally considered as a feature of severe OHSS which, together with other altered coagulation factors, and in combination with the hyperviscosity (haemoconcentration) could lead to intravascular thrombosis, an extreme clinical manifestation of the syndrome (Schenker and Weinstein, 1978; Pride et al., 1990). However, changes in coagulation parameters have been correlated neither with oestrogen nor with the haematocrit (Pride et al., 1990) and a recent report (Kodama et al., 1995) indicated that platelet count is not a blood haemostatic marker of thromboembolism in OHSS patients. This is in agreement with our findings showing that platelet count is not a marker of severity in the syndrome (Fábregues et al., 1998). Elevated levels of interleukins such as interleukin-6, interleukin-1 and tumour necrosis factor, as have been reported during OHSS and/or ovarian stimulation (Loret de Mola et al., 1996a, 1996b; Hock et al., 1997; Mathur et al., 1997; Rizk et al., 1997), are associated with reactive thrombocytosis (Hollen et al., 1991; Dan et al., 1995). Therefore, this may explain increased platelet counts found in patients with severe OHSS.

In fact, severe thrombotic events after ovulation induction have been reported recently in women without any concomitant clinical sign of OHSS (Aurousseau et al., 1995) and the occurrence of thromboembolic events in patients with severe OHSS may involve some specific factors, such as monocyte tissue factor, having procoagulant activity (Balasch et al., 1996a). Tissue factor is now considered to be the primary and most potent activator of the blood system coagulation (Carson and Brozna, 1993). Tissue factor forms a complex with plasma factor VII forming a potent procoagulant which can rapidly activate factors IX and X. Activated factor X results in thrombin generation which potentiates further factor IXa generation by feedback activation of factor XI. Accordingly, increased markers of thrombin (thrombin–antithrombin complex and prothrombin fragment 1 + 2) and fibrin (D-dimer) generation were found in patients with severe OHSS, thus reflecting a pro-thrombotic state (Balasch et al., 1996a).

Tissue factor is normally not in contact with blood but is present in the subendothelial layers to form a ‘haemostatic envelope’ ready to activate coagulation when vascular integrity is disrupted. Normal blood cells or endothelial cells do not express tissue factor under normal conditions, consistent with the hypothesis that expression of tissue factor is physically separated from the blood (Francis et al., 1995; Osterud, 1995). However, there is considerable evidence in the literature that tissue factor expression is elevated in a variety of clinical conditions and in a test model using lipopolysaccharides as a stimulant (Francis et al., 1995; Osterud, 1995).

It is accepted that, in the absence of vessel wall injury or severe permeability changes of the endothelium, circulating monocytes or monocytes adhering to the vessel wall are the only cells of the vascular system that may trigger blood coagulation through the tissue factor-dependent pathway (Osterud, 1995). Interestingly, however, even with minor injury to the vessel wall, tissue factor may be exposed to blood and thus trigger blood coagulation (Aune et al., 1993). Considering that wall shear stress is strongly increased in conditions of hyperdynamic circulation, and arteriolar vasodilatation may induce the formation of interstitial oedema by increasing capillary permeability, surface area for filtration and hydrostatic pressure (Grega and Svensjö, 1984; Sparks et al., 1984; Korthuis et al., 1988; Schrier, 1990), it is possible that changes in the vessel wall during the OHSS make the blood monocytes more sensitive to tissue factor activity. This increased procoagulant activity of blood monocytes may be important in thrombotic events associated with severe OHSS.

Summary: peripheral vasodilation hypothesis in the OHSS; therapeutic implications

A traditional view on the pathophysiology of OHSS considers that the syndrome is due to intravascular volume depletion secondary to massive extravascular protein-rich fluid shift from the intravascular to interstitial space and the peritoneal cavity. The mechanism of this could be an increase in capillary permeability, mainly of the ovarian vessels. Accordingly, renal sodium and water retention also could be a secondary phenomenon; hypovolaemia leads to decreased renal perfusion, subsequently stimulating the proximal renal tubules to resorb salt and water (Schenker and Weinstein, 1978; Elchalal and Schenker, 1997).

According to haemodynamic and neurohormonal studies during severe OHSS (Balasch et al., 1991, 1994, 1995), an alternative explanation exists. As reported above, marked arteriolar vasodilation is a constant finding in patients with severe forms of the syndrome and arteriolar vasodilation is the primary event of the stimulation of the renin–aldosterone and sympathetic nervous systems and ADH. These vasoactive systems, in turn, will strongly promote renal sodium and water retention which contribute to oedema formation. Therefore, sodium and water retention could precede and contribute to ascites in severe OHSS rather than to be its consequence.

The peripheral arteriolar vasodilation hypothesis in OHSS (Figure 2) proposes that a universal event initially occurring in all patients is an enlargement of the intravascular compartment rather than a decrease in the intravascular blood volume. This causes underfilling of the arterial vascular compartment (i.e. decreased ‘effective arterial blood volume’) and thus arterial hypotension which leads to high-pressure baroreceptor-mediated stimulation of endogenous vasoactive systems (renin–angiotensin–aldosterone and sympathetic nervous systems and ADH). Renal sodium and water retention ensues and plasma volume increases. The simultaneous occurrence of this compensatory hypervolaemia and tachycardia (caused by norepinephrine increase release which also promotes vasoconstriction in peripheral arterioles), low peripheral vascular resistance, high cardiac output (because of afterload reduction secondary to the enlarged arterial bed), and arterial hypotension compose the so-called ‘hyperdynamic circulation’ that characterizes conditions associated with oedema formation (Schrier, 1988a,b; Schrier et al., 1988).
In patients with moderate ovarian hyperstimulation the degree of arteriolar vasodilation is not intense, there is no capillary leak because of a moderate increase in capillary hydrostatic pressure and permeability, the fluid retained by the kidneys remains in the intravascular compartment and the arterial underfilling is corrected by the increased endogenous vasoconstrictor activity and plasma volume and cardiac output. Circulatory homeostasis is normalized, arterial pressure remains within normal ranges, and there is neither oedema formation nor haemoconcentration.

Severe OHSS patients with ascites represent a more advanced stage of the continuum in the pathophysiological process secondary to arteriolar vasodilation. As discussed above, peripheral arterial vasodilation is associated with events at the capillary level, events that if severe enough predispose patients to interstitial oedema and thus aggravate arterial underfilling. A link between arteriolar vasodilation and fluid leakage in OHSS thus exists. At this stage of the syndrome, an escape of fluid to extravascular spaces occurs and a critical point is reached in which the consequences of arteriolar vasodilation cannot longer be compensated. Compensatory endogenous vasoconstrictor activity and the increase in cardiac output and blood volume secondary to sodium and water retention are insufficient to maintain circulatory homeostasis. Arterial hypotension ensues which maintains a persistent activation of the renin–aldosterone and sympathetic nervous systems and ADH. This promotes continuous water and sodium retention. The retained fluid, however, leaks into the peritoneal cavity as ascites, renal sodium and water retention being therefore ineffective to refill the dilated arterial vascular bed.

In patients having severe OHSS with ascites but no haemoconcentration, the capillary escape of fluid could be buffered by renal sodium and water retention and the lymphatic return. This subgroup of patients would have a lesser degree of arterial vasodilation than patients having ascites and haemoconcentration. In this latter subgroup of patients, the more intense peripheral arterial vasodilation with the associated markedly increased capillary leak (see above) would have insufficient fluid retained by the kidney and that returned by lymphatic mechanisms to compensate capillary leakage. Thus, in these patients representing the most severe forms of the syndrome, a true reduction of circulating blood volume secondary to a marked extravasation of fluid will be present in addition to peripheral arteriolar vasodilation.

**Therapeutic implications**

Considering that the initial event of body fluid disturbance in OHSS will be a peripheral arteriolar vasodilation causing underfilling of the arterial vascular compartment, with marked stimulation of endogenous vasoconstrictor systems being the intermediate step, and renal sodium and water retention the final consequence which will contribute to ascites formation (i.e. sodium and water retention is a cause and not a consequence of ascites formation) (Figure 2), different therapeutic implications ensue.

(i) The use of salt solutions to treat patients having severe OHSS, as proposed by some authors to correct intravascular volume depletion and hyponatraemia (Rizk and Aboulghar, 1991; Navot et al., 1992), seems inappropriate not only because saline loading does not correct arterial underfilling (see above) but also because it may contribute to ascites formation.

(ii) The overactivity of renin–angiotensin–aldosterone system in severe OHSS patients is clearly a homeostatic compensatory mechanism for maintaining arterial pressure. Therefore, the use of angiotensin antagonists or angiotensin-converting enzyme inhibitors, as proposed by some researchers on the basis of a supposedly major role of the renin–aldosterone system in the pathogenesis of the syndrome (Navot et al., 1992), may induce severe arterial hypotension. In fact, the administration of these kinds of drugs has been shown to diminish arterial blood pressure in states of arterial underfilling.

---

**Figure 2.** Peripheral arteriolar vasodilation hypothesis in the pathogenesis of the ovarian hyperstimulation syndrome.
whether initiated by either decreased cardiac output or peripheral arterial vasodilation (Schrier, 1988a,b, 1990).

(iii) Non-steroidal anti-inflammatory drugs are one of the most widely prescribed drugs when grouped by generic categories (even excluding aspirin), but unfortunately they can cause various renal side-effects (Clive and Stoff, 1984). The anti-inflammatory properties of these agents appear to reside in their common ability to inhibit cyclo-oxygenase, a major enzyme in the biosynthesis of all prostaglandins. Prostaglandins are ubiquitous in their distribution throughout the body, and they function for the most part as ‘local hormones’. Their biological activity is exerted primarily at the site of their synthesis, since they have a short half-life in the circulation.

The kidney is extremely active in the synthesis and metabolism of prostaglandins. These compounds participate in several processes in renal physiology, including autoregulation of renal blood flow and glomerular filtration, modulation of renin release, tubular ion transport and water metabolism (Clive and Stoff, 1984). As discussed above, in high-renin states (e.g. cardiac decompensation, liver cirrhosis and OHSS), the renal vasoconstrictive influence of the vasoactive systems is mitigated by a simultaneous stimulation of vasodilatory renal prostaglandins. Renal blood flow and glomerular filtration rate are thus maintained by prostaglandins, averting prerenal azotaemia or even ischaemia damage to the renal parenchyma. When the protective modulating intrarenal actions of prostaglandins are suppressed by drugs which inhibit cyclooxygenase, impairment of renal haemodynamics may result (Clive and Stoff, 1984).

Therefore, the use of indomethacin in severe OHSS (supposedly to reduce vascular permeability), as has been proposed for years (Schenker and Weinstein, 1978; Katz et al., 1984), not only is inefficient (Borenstein et al., 1989; Elchalal and Schenker, 1997) but also is dangerous because it may induce acute renal failure (Balasch et al., 1990).

(iv) Although the determinants of ascites formation in severe OHSS remain to be elucidated, the therapeutic goal is more clear-cut. Medical treatment of severe OHSS should be directed to maintain circulatory function and to mobilize the intra-abdominal fluid by creating a net negative balance of sodium and water. This can be fulfilled (Balasch et al., 1996b) by a conservative medical therapeutic approach based on bed rest, dietary sodium restriction, plasma volume expansion and natriuretic agents as similarly done in other oedematous states with ascites (Arroyo et al., 1991).

The assumption of an upright posture by patients with cirrhosis and ascites is associated with a striking activation of the renin–angiotensin–aldosterone and sympathetic nervous systems, a reduction of glomerular filtration rate and sodium excretion, and a decreased response to loop diuretics (Bernardi et al., 1985; Ring-Larsen et al., 1986). For this reason bed rest is advised in patients with cirrhosis and ascites, particularly in those with intense activation of the endogenous neurohormonal systems (Arroyo et al., 1991). These kinds of studies are lacking in severe OHSS but endogenous vasoactive systems are markedly activated in these patients. Therefore, there is a rational basis for strict bed rest in severe OHSS treatment.

As in other oedema-forming states, the second important therapeutic measure in severe OHSS is dietary sodium restriction and the administration of furosemide. The major goal of diuretic therapy is to block the various renal sodium-retaining mechanisms and thereby increase urine volume and sodium excretion. This is an essential part in the treatment of other oedematous states such as congestive heart failure, nephrotic syndrome and cirrhosis with ascites (Suki and Eknoyan, 1992). Intravenous furosemide is the diuretic selected because it is rapidly effective, has a short pharmacological effect and is one of the most powerful natriuretic agents presently available (Borenstein et al., 1989). It is to be noted that the administration of diuretics in oedema-forming states is obviously not directed to correct the underlying circulatory abnormality but to treat its main consequence, that is, sodium and water retention and oedema formation. In fact, the main prospect of the treatment should be aimed at maintaining the intravascular volume thus preserving renal function. Therefore, diuretics should be used just to recover a spontaneous diuresis which heralds the resolution of the condition, and their administration should always be immediately preceded by plasma volume expansion as discussed below (Golan et al., 1989; Pride et al., 1990; Navot et al., 1992; Balasch et al., 1996b).

All oedema-forming states are characterized by a low effective intra-arterial blood volume. In severe OHSS, effective hypovolaemia is the consequence of both arteriolar vasodilatation and extravasation of intravascular fluid secondary to increased vascular permeability (Balasch et al., 1991, 1994). Therefore, the third component of the therapeutic approach should be the administration of a plasma volume expander to increase effective arterial blood volume. Low-salt human albumin is selected because it is considered the volume expander of choice in OHSS (Navot et al., 1992). Albumin is the protein that is lost in this syndrome; it is non-toxic, is safe from viral contamination and has a longer half-life than the various plasma volume expanders currently available.

Using this therapeutic approach (Balasch et al., 1996b), we showed a rapid improvement in clinical symptoms, standard laboratory parameters, diuresis, urinary sodium excretion and degree of activity of endogenous neurohormonal vasoactive systems after 2 days of therapy in severe OHSS patients. The length of treatment correlated directly with the severity of the syndrome. Patients responding rapidly (within 2 days) to bed rest, dietary sodium restriction, i.v. furosemide and plasma volume expansion had significantly lower baseline haematocrit and plasma renin activity and norepinephrine concentrations than those requiring a longer period of treatment.

Unanswered questions and future perspectives

While current evidence indicates that severe OHSS is characterized from a pathophysiological point of view by the simultaneous occurrence of marked arteriolar vasodilation and increased capillary permeability, the site and mechanism of arterial vasodilation and capillary leakage, the possible link between both phenomena, and the reason why the peritoneal cavity is the predominant site where the fluid-shifting occurs in OHSS remain to be clarified. Also, the temporal relationship between the decrease in peripheral vascular resistance and renal sodium
and water retention in OHSS is unknown. Future investigations on these subjects may contribute to a better understanding of the syndrome.

Factors predisposing to the development of the circulatory dysfunction associated with severe OHSS (only 1–2% of women undergoing gonadotrophin ovarian stimulation for IVF develop the syndrome) are not well established. Two possible explanations have been raised. Since severe OHSS is usually associated with enlarged multifollicular ovaries and very high plasma levels of oestradiol, it has been proposed that it develops in those patients having a more intense ovarian response to gonadotrophin treatment (Navot et al., 1992). According to this postulate, in the remaining cases, the ovarian response would be insufficient to alter circulatory function. However, a second possibility exists, which is that circulatory dysfunction would be a universal event during IVF cycles, with symptoms developing only in those very few patients with a profound impairment in circulatory function.

A recent study from our group (Manau et al., 1998) supports the latter contention. We have shown that the circulatory dysfunction that characterizes severe OHSS (namely decreased mean arterial pressure and peripheral vascular resistance, increased cardiac output and a marked increase in plasma renin activity and plasma norepinephrine concentration 7 days after the ovulatory injection of human chorionic gonadotrophin) is a universal event in asymptomatic women undergoing controlled ovarian hyperstimulation for IVF. The degree of activation of those endogenous vasoactive systems, however, although intense, was much lower than that observed in patients with severe OHSS studied by our group using identical laboratory techniques (Balasch et al., 1991, 1994). This suggests that severe OHSS would be the extreme expression of a circulatory dysfunction occurring in all women undergoing IVF.

Since severe OHSS is associated with dramatically increased circulating plasma oestradiol concentration, and accumulating clinical and experimental evidence exists indicating that oestradiol has marked systemic vasodilator effects both in pregnant and non-pregnant states which may be mediated by endothelial vasodilators (Magness and Rosenfeld, 1989; Schrier and Briner, 1991; Herrington et al., 1994; Gura, 1995), it may be postulated that circulatory dysfunction is related to hyperoestrogenaemia (Golan et al., 1989; Magness and Rosenfeld, 1989; Rizk and Aboughar, 1991; Sealey et al., 1994; Delbaere et al., 1997). However, in that study (Manau et al., 1988), we showed that despite the increase in oestradiol levels during IVF cycles being associated with significant circulatory changes, the circulatory dysfunction that characterizes severe OHSS is clearly unrelated to the onset of hyperoestrogenaemia. Also, arteriolar vasodilatation during IVF cycles was not associated with an increased activity of the nitric oxide supposedly related to the vasodilator effects of oestradiol (Manau et al., 1998).

The low prevalence of severe OHSS is a major limiting factor for investigating the syndrome. The recent demonstration by us (Manau et al., 1998) that circulatory dysfunction, as manifested by the development of hyperdynamic circulation and marked increase in plasma renin activity and norepinephrine concentration, consistently develops in asymptomatic patients undergoing ovarian stimulation for IVF is important in this respect. Investigations in these patients may throw light on the pathogenesis of severe OHSS, which would represent the extreme expression of the circulatory dysfunction associated with ovarian hyperstimulation treatment. In this regard, molecular biology studies involving cytokines, mainly vascular endothelial growth factor but also interleukins (Eichalal and Schenker, 1997; Rizk et al., 1997; Mathur et al., 1997), may allow a better understanding of this still enigmatic disorder.

Acknowledgements

This work was supported in part by grants from the Fondo de Investigaciones Sanitarias de la Seguridad Social (FIS 96/0355) and the Comissionat per a la Universitat i Recerca-Generaltat de Catalunya (1995SGR 00153, 1995PIRA 00026, and 1997SGR 00213) to J.B.

References


J.Balasch, F.Fàbregues and V.Arroyo


Received on March 12, 1998; accepted on July 15, 1998

2730