CHAPTER 10

Clinical aspects of polycystic ovary syndrome

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HISTORICAL PERSPECTIVE

Sclerocystic disease of the ovaries was first described by Chereau[1]. He observed a thickened, pearly white, sclerotic capsule in those patients who had their ovaries removed that were thought to be diseased or damaged. In 1872, Robert Battey of Georgia described an operation for the removal of the ovaries through the vagina with the patient positioned on their side[2]. Battey suggested that ovarian extirpation of the ovary or 'ovarian ovariotomy' through the vagina be performed for severe dysmenorrhea, excessive menorrhagia, hysteroneurosis, a tendency toward epilepsy with menstruation, and pelvic pain due to pelvic engorgement where all other treatment options had failed. This became known as the Battey operation. In 1876, Battey published his first 10 cases. Six women had improved or complete resolution of their symptoms, whereas two had no relief. Two deaths occurred postoperatively from the procedure[2]. This became the widely accepted surgical procedure until it was challenged by a less radical, ovarian sparing approach recommended by Pozzi in 1884 and Waldo in 1895[3]. Their approach was to remove only the diseased portion of the ovary, which was later to be known as 'ovarian wedge resection'. Postoperatively, those patients who underwent partial ovarian resection were noted to initiate their menses.

In 1935, at the Michael Reese Hospital in Chicago, Irving Stein and Michael Leventhal correlated the symptoms of amenorrhea, hirsutism, infertility, and obesity with the large sclerotic ovaries in seven patients[4]. Expecting to find abnormal cells within the ovaries due to the severity of the clinical symptoms, they sent sections of the ovaries to pathology. The histologic appearance was the same as the previously reported 'polycystic' appearance of the ovary. They removed around 50–75% of the ovary. Their belief was that the thickened capsule inhibited ovulation. This became the only treatment for these patients to induce ovulation[5].

Many years later it would be shown that the effect of the ovarian wedge resection was to reduce the intraovarian testosterone level[6]. Resumption of menses was an unexpected finding following the surgery. Stein and Leventhal[4] then described a subgroup of patients with polycystic ovarian syndrome (PCOS) with symptoms of obesity, amenorrhea, hirsutism, the inability to conceive with bilateral ovarian engorgement as having Stein–Leventhal syndrome. Follow-up studies reported a reversal of amenorrhea to cyclic menses in 95% of patients and conception

in 85% of patients in those treated with ovarian wedge resection[7].

HISTOLOGIC APPEARANCE

An early report of the histologic appearance of the ovary revealed numerous microfollicular cysts occupying the cortex of the ovaries[8]. These follicles were in various stages of maturation and atresia. The cyst walls were lined with a thin layer of granulosa cells and a thickened layer of theca interna. This was a clear difference from the histologic appearance of the normal ovary. The bilateral engorged ovaries observed on the histologic sections initiated the terminology 'polycystic ovaries'. The common feature that seems to bind the wide spectrum of the presenting disease is the multi-follicular histologic appearance found in the pathologic cross-section. Thus, the terminology of PCOS encompasses multiple clinical symptoms of menstrual dysfunction from oligo-ovulation to amenorrhea. Based on the microscopic appearance, the condition should actually be termed polyfollicular rather than polycystic.

DIAGNOSIS

It is estimated that 3 to 7% of women have PCOS. The varieties of clinical presenting symptoms are numerous. In a review of clinical symptoms, Goldzieher and Axelrod[9] documented that of patients who were surgically proven to have PCOS, 20% had no menstrual irregularity, 59% were not obese, and 31% were not hirsute. This report recognized the phenotypic heterogeneity of the disease.

The cardinal clinical feature of PCOS is the disruption of normal cyclic ovarian function. PCOS is associated with tonic or inappropriate luteinizing hormone (LH) secretion which independently increases androgen levels[10]. The common physiologic feature is the elevation in androgens and their precursors, resulting in menstrual irregularities, oligo-ovulation, signs of estrogen excess, and obesity[11,12]. The androgen excess contributes to the elevated level of the total estrogens from the peripheral conversion of androstendione to estrone. As a syndrome, PCOS does not have a single diagnostic criterion sufficient for the clinical diagnosis. Thus, PCOS remains a diagnosis of exclusion from other known menstrual dysfunction problems causing chronic anovulation disorders. Late onset congenital adrenal hyperplasia (LOCAH), premature ovarian failure, hyperandrogenism, ovarian hyperthecosis, Cushing's syndrome, pituitary tumors, and hypothalamic amenorrhea should be ruled out before the patient is given the diagnosis of PCOS. Unfortunately, many menstrual disorders routinely get categorized into the PCOS basket before these other conditions are ruled out.

WORKUP

The initial workup of women presenting with menstrual dysfunction or oligo-ovulation should include early follicular serum LH, follicle stimulating hormone (FSH), and estradiol (E_2) levels to exclude hypogonadotropic hypogonadism or premature ovarian failure. Patients with PCOS are part of a large spectrum where normal to slightly elevated gonadotropins and estrogenic environments are noted. Serum LH levels are frequently elevated in these patients. Serum 17OH- progesterone and a complete androgen profile will aid in the diagnosis of LOCAH and rule out the other disorders of androgen and chronic anovulation. In patients with centripetal obesity, fasting cortisol or 24 h urinary cortisol will eliminate inappropriate adrenocorticotropic hormone (ACTH) secretion. Routine measurements of serum prolactin levels are mildly elevated in hyperandrogenic patients. The free androgen level must be calculated secondary to the measurement of sex steroid binding globulin or total testosterone

levels with the assistance of ammonia sulfate precipitation[13].

INAPPROPRIATE LH SECRETION

Due to the inappropriate secretion of LH, the serum levels were the mainstay of the laboratory diagnosis of PCOS. The relationship of circulating LH to FSH was found to be elevated or inverted in PCOS patients compared with controls[14]. Elevated LH serum concentrations appear to be secondary to increased amplitude and frequency of LH pulses from the hypothalamic–pituitary axis. The abnormal levels of LH have been shown to have detrimental effects on oocyte maturity and fertilization, as well as causing lower pregnancy and higher miscarriage rates[15]. Although this is controversial, the absolute LH value in relation to the FSH value may be clinically more important in assessing oocyte quality than the LH level alone.

ANDROGEN EXCESS

Patients with PCOS have excess androgens. Some patients manifest unwanted clinical features of these excess androgens with the appearance of hirsutism or male pattern hair growth[16,17]. It has been clearly shown that the hirsutism is caused by the local androgen stimulation by the conversion of testosterone to 5α-dihydrotestosterone (DHT) at the hair follicle by the enzyme 5α-reductase[18]. The wide disparity between those patients displaying androgen excess appears to be related to the local 5α-reductase activity. Studies have shown that increased levels of the metabolite 3α-androstanediol glucuronide (3α-diol G) have been associated with clitoromegaly, temporal balding, voice changes, and a full facial beard[19]. Overt clinical symptoms such as clitoromegaly, temporal balding, and voice changes should alert the clinician to rule out a virilizing tumor before concluding the symptoms are from long-standing androgen excess[20].

Hyperandrogenism seems to be the most common clinical marker for PCOS patients. Patients with PCOS may still have the characteristic ultrasonographic appearance of the ovaries, but do not demonstrate an abnormality in any of the circulating androgen levels[21]. The limitations of this chemical marker of hyperandrogenism have come under considerable criticism due to the fact that:

(1) Age and body mass index (BMI) were not considered when normal values were established. There is also a wide variability of hair growth and patterns in the general population between different ethnic groups.

(2) Not all androgens may have been assessed in the patient's initial work-up.

(3) Normal ranges may not have been established in well characterized controlled populations from various geographic and ethnic backgrounds.

(4) The free testosterone or free androgens index (FAI) seem to be more sensitive in the assessment of hyperandrogenism. The level of free thyroid hormone must also be assessed, since improvement in insulin resistance seems to ameliorate a portion of these menstrual abnormalities[22].

OBESITY

Adipose tissue has long been known as the largest endocrine organ in the body as it provides the storage and metabolism of sex steroid hormones. Adipose tissue plays a critical role as it constitutes a dynamic portion of the endocrine–metabolic compartment. Obesity has long been associated as a clinical symptom for patients with PCOS. However, it is now known that obesity is not a universal clinical feature of PCOS, as a significant

number of PCOS patients have a normal BMI[23]. There is also controversy about whether PCOS produces obesity or whether the high peripheral circulating estrogen level contributes to the etiology of obesity in this complex disorder.

The two types of obesity, upper vs. lower body, appear to have opposite endocrine environments. The upper body is associated with higher androgen production rates and elevated free testosterone levels, whereas lower body obesity is linked to increased levels of estrone from aromatization of androstenedione[24–26].

INSULIN RESISTANCE

Patients with PCOS have been clearly identified with insulin resistance[27–30]. PCOS is associated with peripheral insulin resistance, glucose intolerance, and hyperinsulinemia, regardless of the BMI. However, studies have shown that there appears to be a higher prevalence of insulin resistance in obese compared to non-obese PCOS patients. The endocrinologic biophysical profile of obese patients should be evaluated as they are at increased risk of developing type II diabetes[31,32]. Patients with several symptoms such as obesity, elevated blood pressure (BP) or hypertension, and cholesterolemia should be evaluated with an oral glucose tolerance test (OGTT) and further medical evaluation for the likelihood of developing full-blown type II diabetes as well as other significant medical problems[33]. Those patients with mild PCOS, by clinical assessment, may be evaluated with a fasting and a 2 h glucose tolerance test (GTT), along with fasting insulin level and biochemical indexes for hyperandrogenemia. In patients with severe insulin resistance, HAIR-AN (Hyper Androgenic Insulin Resistant Acanthosis Nigricans) syndrome must be ruled out[34,35].

The relationship between insulin resistance and PCOS appears to be directly correlated with a tissue defect impairing the insulin action sequence. Studies reveal that IGF-I and IGF-II in fat cells inhibit glycerol release and stimulate glucose transport and oxidation as effectively as insulin. IGF levels are found to be decreased in PCOS patients[36–38]. This may provide a key to the insulin hypersensitivity. A positive correlation has been reported between the degree of hyperinsulinemia and hyperandrogenemia[39]. Reduction of the hyperinsulinemia lowers hyperandrogenemia. However the converse does not apply and a reduction in the androgen levels does not correlate with a reduction in the insulin levels.

First degree relatives of PCOS patients with type II diabetes are known to be more insulin resistant than age and body matched indexed controls[40,41]. Insulin resistance was also seen even when compared to young and non-obese controls. The familial basis for this disorder was clearly demonstrated when the sisters of women with PCOS were found to be more insulin resistant than age and BMI matched controls[42]. The familial clustering has been confirmed, as well as the genetic association, with the identification of a single gene causing PCOS and male pattern baldness[43,44]. Other studies have also shown a genetic susceptibility to this disorder[45,46].

IMAGING

The introduction of ultrasound (u/s) has enabled the imaging of the ovaries to aid in the diagnosis of PCOS. The 'pearl-like' appearance of the ovary on u/s appears to be synonymous with PCOS. This clinical sign is a common feature in PCOS patients and is a common finding[45–47]. The ultrasound criteria used to define PCOS are as follows:

(1) The presence of 12 or more follicles in each ovary, measuring 2–9 mm in diameter;

(2) Ovarian volume greater than 10 mm;

(3) The ultrasound evaluation should be performed when there is no dominant follicle (> 12 mm) or a corpus luteum, present by u/s, or elevated progesterone (P_4) level[48].

Ovarian volume appears to be an even more quantitative measurement than stromal volume in the clinical practice setting[49]. Patients should not undergo u/s diagnostic information to confirm or exclude the u/s appearance of the polycystic ovary when an oral contraception or central access suppression has been initiated. The calculation of ovarian volume can be made from a simplified formula that multiplies together 0.5 times the length by the width by the thickness[50]. Ideally, ovarian measurements should be taken between cycle days 3 to 6. A progesterone withdrawal bleed should be considered in those patients without menses for three months before assessing both clinical and ultrasonographic information.

It is estimated that between 6 and 35% of women have the u/s appearance of PCOS, but of these women with u/s findings, not all have PCOS[51]. Women having the ultrasonographic appearance of polycystic ovaries on cursory u/s evaluation in the absence of the clinical symptoms of an anovulatory disorder with regular menstrual cycles or the identification of any elevated androgen levels, should not be considered as having the diagnosis of PCOS. These patients are at risk for developing ovarian hyperstimulation syndrome (OHSS) with gonadotropins for controlled ovulation induction (OI). There are no long-term studies concerning the transition from the u/s appearance of the ovaries and the development of PCOS. However, these patients should be counseled and monitored at yearly intervals for any changes in the endocrine androgenic profile.

Several studies have looked at ovarian stromal blood flow, with high resolution two-dimensional (2D), three-dimensional (3D) u/s, Doppler imaging, and quantization of the Doppler signal, using the 3D power as a critical marker for the appearance of the ovary to further evaluate and assess the degree of PCOS[52]. The vascularized blood flow index (VFI) and vascularization index (VI) are all significantly higher in patients with PCOS than in those with normal ovaries[53].

TREATMENT

The treatment focus for patients with PCOS is to establish normal cyclic ovulatory function in those patients desiring to conceive. In those patients not desiring to conceive, treatment should be aimed at restoring menstrual cyclicity and suppression of hyperandrogenism. New oral contraceptive medications combine the suppression of hyperandrogenism and increase sex steroid binding globulins.

Ovulation induction

Patients seeking fertility who are anovulatory, oligo-anovulatory, or amenorrheic are treated with ovulation medications. Traditionally, OI can be initiated with clomiphine citrate and/or human menopausal gonadotropins (HMGs). Patients with elevated levels of androgens can be treated with a low dose of dexamethasone. Dexamethasone at bedtime reduces testosterone, androstenedione, and dehydroepiandrosterone sulfate in 21–46% of PCOS patients through the blunting of the ACTH peak[54]. Dexamethasone can reduce free testosterone by 50%.

Metformin, an insulin-sensitizing agent commonly used for type II diabetes, reduces the insulin response, decreasing hepatic gluconeogenesis and reducing androgens, and was found to restore normal menstrual cycles in chronic anovulatory patients[55].

Letrozole, a third generation aromatase inhibitor, is an agent which suppresses the biosynthesis of estrogen and reduces the negative feedback effect on the hypothalamic–pituitary system. This increases the secretion of FSH. Letrozole has been recently used for OI in anovulatory PCOS women resistant to clomiphene or with inadequate endometrial thickness during clomiphene treatment[56]. At a daily dose of 2.5 mg from days 3 to 7 of the menstrual cycle, ovulation was seen in 9 of 12 cycles (75%) treated with letrozole and only in 8 of 18 cycles (44.4%) treated with clomiphene, while the endometrium

on the day of hCG administration was thicker in the letrozole group[56].

Insulin-sensitizing agents

Several insulin-sensitizing agents have been studied in the treatment of PCOS. They include metformin, thiazolidinediones, troglitazone, rofiglitazone, pioglitazone, and D-chiro-inositol[57]. The most extensively used insulin-sensitizing drug in the treatment of PCOS is metformin. Hyperinsulinemia is critical in the development of hyperandrogenemia and disrupts follicular genesis. Metformin is an orally administered agent used to lower the blood glucose level in non-insulin-dependent diabetics. It is antihyperglycemic in its action, but does not cause hypoglycemia, increased glucose uptake, or utilization in the muscle tissue.

Metformin enhances insulin sensitivity in the liver, where the peripheral tissue inhibits hepatic glucose production. Metformin has been studied and has been mostly shown to restore menstrual cycles and confirm ovulation in anywhere between 25 and 90% of cases[57]. A recent analysis of 13 randomized controlled trials showed that metformin increased the ovulation rate almost four times compared to placebo when it was administered in combination with clomiphene citrate[58]. In clomiphene resistant women, a significantly higher ovulation rate from metformin plus clomiphene citrate was seen when compared to clomiphene citrate plus placebo[59].

The benefits of metformin for OI are important as it does not confer the same risks of ovarian hyperstimulation or multiple pregnancies compared with clomiphene citrate or HMG. Although metformin has not yet been listed as one of the treatments for ovulation, several randomized controlled trials revealed that metformin plus clomiphene citrate is superior when compared to clomiphene citrate alone or with placebo[59].

Metformin has also been studied in women who continued the treatment during pregnancy. One study has shown the clear benefit of reducing gestational diabetes in those women with PCOS who took metformin throughout their pregnancies[60]. The safety of metformin as a category B medication allows its use in patients who do conceive. One study has shown a reduction in first trimester spontaneous abortions.

In an excellent systematic review of metformin in patients with PCOS, Costello and Eden[58] did an analysis of the literature on metformin used as a single agent or in combination with other ovulatory inducing medications in restoring menses or establishing a pregnancy.

Their review indicated that for 3 to 6 months PCOS patients have a 60% chance of regular menses and ovulation. The addition of clomiphene citrate to metformin shows that for up to 9 months patients have approximately a 66% chance of regular menses and ovulation and 34% have a chance of pregnancy.

Surgical treatment

In 1984, an attempt to introduce a minimally invasive surgical treatment for PCOS and move away from the classical wedge resection, using laparoscopic surgical treatment of the polycystic ovary, was reported[61]. Gjonnaess studied 62 women with PCOS who were treated surgically with serial systematic electrocautery of the ovarian capsule. He reported that ovulation occurred within 3 months in 92% of the patients who underwent the surgical procedure, with regular menses established in 51 (86%) of the patients proven by an elevated progesterone level. Seven of nine women with a diagnosis of PCOS who had been previously treated with clomiphene citrate up to 150 mg for OI showed signs of ovulation with elevated progesterone levels after ovarian drilling. The remaining two patients, who did not spontaneously ovulate, did become responsive with use of clomiphene citrate. Gjonnaess reported a pregnancy rate of up to 80% of those treated with ovulation inducing medications. The proposed theory was that there were local

factors within the ovary which were responsible for triggering ovulation.

Laparoscopic ovarian drilling (LOD) is a surgical treatment used to debulk the ovarian tissue either with monopolar, bipolar electrocautery, or with laser energy (Figures 10.1 and 10.2). There are different techniques to accomplish the task of volume reduction of the ovaries, all of which seem to have a beneficial effect in reducing the excess androgen levels, the hallmark of this condition. LOD was studied in preventing cancellation in patients undergoing controlled ovulation induction for IVF due to their risk of severe OHSS. Rimington et al.[62] studied 25 women who underwent ovarian electrocautery followed by gonadotropin therapy. This study found that, when compared to a control, the patients who underwent laparoscopic ovarian electrocautery after pituitary desensitization followed by gonadotropin therapy had a reduced risk of cancellation of their cycle due to impending or actual OHSS.

Parsanezhad et al.[63] studied ovarian stromal blood flow following LOD in 52 women and found serum concentrations of LH and testosterone were significantly decreased. Systolic velocity blood flow decreased significantly as well as pulsatile index and resistance index. The study showed a total of 73% of the women ovulated. This finding was inversely related to the pulsatile index and testosterone level. Those patients who did not have ovulatory cycles showed less of a change in their Doppler pulsatile index than those who ovulated. In an attempt to identify predictors of success for LOD Amer et al. looked at markers[64].

Obesity, hyperandrogenism, and long duration of infertility seemed to be the most profound clinical predictors of success from LOD. In addition, higher levels of LH often seemed to be a high predictor of success in those patients undergoing LOD.

Because of the invasive process of the surgical procedure, the risk of a general anesthetic does not justify LOD as a first line treatment in those patients with severe PCOS. The introduction of the insulin-sensitizing agents should be tried with or without clomiphene citrate as a first line treatment, depending on the results of the initial physiologic presentation. In those clomiphene citrate resistant patients, LOD is an excellent option. LOD may also help with patients who are at high risk for severe OHSS or who have been unable to achieve controlled ovarian stimulation without the significant risks associated with OHSS.

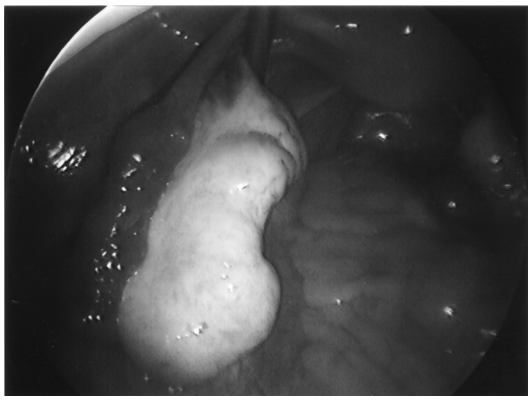

Figure 10.1 Engorged polycystic ovary before LOD

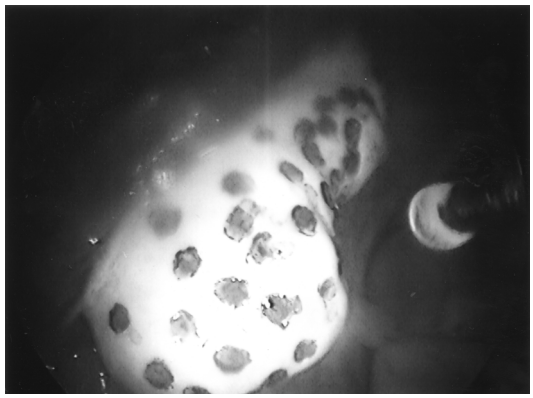

Figure 10.2 Engorged polycystic ovary after LOD with a Nd:YAG laser at 20 watts

Unstimulated IVF cycles

Immature oocyte retrieval is another treatment option recently presented for PCOS patients. Edwards[65], in 1965, leading up to the first in-vitro fertilization (IVF), studied in-vitro maturation (IVM) in mammalian species including human oocytes[65]. It was not until 1991, when Cha et al.[66] reported the use of immature oocytes excised from ovarian tissue, that the full clinical potential was actually realized. Cha established a triplet pregnancy with immature oocytes after they were matured, fertilized, and then transferred as frozen-thawed embryos to a recipient during a donor oocyte cycle. In 1994, Trounson et al.[67] brought the clinical feasibility of IVM with immature oocytes to PCOS patients when they were able to retrieve immature oocytes with u/s guidance transvaginally. They matured the immature oocytes, fertilized them, and then transferred embryos to the intrauterine cavity during the same cycle from which the oocytes were retrieved. This was a tremendous breakthrough for patients who had had a very difficult time with the use of gonadotropins and the high risk of ovarian hyperstimulation and the associated complications. Since that time, several other groups have reported successful transvaginal u/s guided oocyte retrieval, maturation, fertilization, transfer, and implantation[68–70]. IVM is now being used throughout the world in a select group of patients.

Due to the abundance of follicles in the ovary, PCOS patients present an excellent clinical opportunity for the retrieval of unstimulated immature eggs. Although Cha started the process of IVM through oophorectomized patients, it was really brought to clinical practise by Trounson. To enhance the success rate of IVM after retrieval of unstimulated oocytes, Chian et al.[71] reported utilizing human chorionic gonadotropin (hCG) priming, which seems to improve the maturation rate and 2PN fertilization rate for those patients undergoing immature oocyte retrieval (IOR).

OVARIAN HYPERSTIMULATION SYNDROME

One of the complications associated with the clinical treatment of PCOS with gonadotropins is the OHSS. OHSS is a serious, potentially life-threatening, iatrogenic complication of controlled ovarian stimulation. An excellent comprehensive review by Whelan and Vlahos[72] evaluated the risk factors, staging, pathophysiology, prevention, management, and treatment of OHSS. The triggering factor for OHSS is the exogenous hCG injection given to mimic the LH surge. The pathophysiology of the disease process appears to be related to the increased capillary permeability resulting in an intravascular fluid shift in the third space.

Risk factors include young age, low body weight, high estradiol levels, number of oocytes retrieved, and PCOS. The baseline antral follicle count appears to correlate well with the risk of developing OHSS. The risks vary widely and the only consistent clinical presentation appears to be the patient's androgen profile in the development of OHSS. Surgical puncture, for those patients undergoing in-vitro follicular aspiration with IVF, has been reported to interfere with corpus luteum progesterone production, increasing the severity of OHSS. At the time of oocyte retrieval, several investigators have suggested the use of IV albumin along with the oocyte retrieval to decrease the risk of developing OHSS. Although this has been reported to be successful, several conflicting studies have shown no benefit to the use of IV albumin.

OHSS has been determined to be a time limited phenomenon. The typical course with full recovery, even for severe cases, will run anywhere from 10 to 28 days from the onset of symptoms. A declining level of serum hCG is responsible for the self-limiting resolution of the disease. Conversely, patients who conceive with a rising hCG level will have a prolonged course with ascites, shortness of breath, pulmonary effusion, and possible deep vein thrombosis (DVT) due to

loss of vascular capillary permeability. Mild to moderate ovarian hyperstimulation can be managed on an outpatient basis. Abdominal bloating, mild shortness of breath (SOB), and weight gain should be re-evaluated by the clinician to decide between hospital vs. outpatient management. Limited physical activity is essential as the disease progresses, with the worst symptoms occurring around early evening. Rapid weight gain with intravascular depletion, decreased urine output of <1000 ml/day, or fluid discrepancies between intake and output should alert the clinician to worsening conditions. Baseline electrolytes, hemodynamic concentration, ovarian u/s measurements, fluid volume, abdominal girth, and daily weight are critical to the ongoing assessment and should be evaluated.

Patients with severe OHSS should be admitted to hospital for close monitoring of vital signs, strict intake and output measurements, white blood cell count (WBC), hemoglobin and hematocrit, electrolyte panel, and liver function tests. The clinician should also run a full coagulopathy panel, and an X-ray to rule out pulmonary infiltrates with SOB. In addition, baseline pulse oximeter studies are essential to assess pulmonary reserve and function. Patients with severe OHSS are hypovolemic with an increase in third space fluid retention. Patients are typically hypernatremic with low urinary output and do not respond well to fluid restriction. On admission, patients should start protein supplementation or albumin infusions.

Paracentesis has become an integral part of the management of third spacing in these patients and the procedure can be performed with a transvaginal approach with a paracervical block using an oocyte retrieval needle[73]. The needle is connected through an adapter to a 1000 ml vacuum suction bottle. The patient should be monitored for hemodynamic stability during the procedure. Between 2 and 3 liters should be drawn off during this time. Less than 2 liters may put the patient at undue risk for such a small volume to be retrieved and more than 3 liters may put too much of a shift on the patient's intravascular space. The procedure can be repeated typically every 48 to 72 h, or as the symptoms and clinical signs of worsening conditions avail themselves. If pulmonary ascites is present, the paracentesis may actually reduce the pulmonary ascites if the fluid is primarily located in the lower pleural space. Consideration of a thoracocentesis may be an option by a pulmonologist in those severe cases with a compromised pulmonary function.

Patients with PCOS have a major risk of OHSS with the controlled ovarian stimulation protocols. The side-effects include weight gain, bloating, nausea, vomiting, mood swings, and possible hospitalization. Numerous protocols have been suggested, including albumin treatments, paracenteses, and cryopreserving all embryos along with bed rest in an attempt to reduce the disadvantages of controlled OHSS in these patients.

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