OVARIAN HYPERSTIMULATION SYNDROME DURING INDUCTION OF OVULATION FOR INTRA UTERINE INSEMINATION

Lt Col SK RATH*, Lt Col RK SHARMA⁺,
Surg Capt (Mrs) P TARNEJA[#], Col AB CHATTOPADHYAY^{**},
Lt Col RD WADHWA^{vsm++}

Abstract

Ovarian Hyperstimulation Syndrome (OHSS) is a known iatrogenic complication of ovulation induction. Our experience of such complication while managing basic assisted conception cycles has been analysed in the present study. 12 such cases were identified in 976 cycles studied giving an overall incidence of 1.22%. All the cases were of mild to moderate variety and were managed conservatively. The duration of the complication ranged between 10 days to 6 weeks. Polycystic ovarian disease, LH : FSH ratio of more than 1, presence of four or more secondary follicles were found to be important predictive criteria. Identification of predictive factors of OHSS can be helpful in taking due care while using ovulation inducing drugs. Conception does worsen OHSS, but termination is usually not necessary.

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Introduction

With the availability of potent drugs for induction of ovulation, infertile women have been subjected to a variety of stimulation protocols. Any modality of treatment is associated with certain side effects and ovarian hyperstimulation syndrome (OHSS) is one such entity associated with ovulation induction [1].

Ovaries are stimulated with ovulation inducing drugs for treatment of anovulation as well as to achieve multiple ovulation in assisted conception cycles. Clinically the manifestation of ovarian hyperstimulation can vary from abdominal distension in mild cases to coagulation defects and compromised renal function in severe ones. Whereas the severe forms of OHSS with hemoconcentration and hypercoagulability is associated with GnRH agonist+ Gonadotrophin + HCG used for in vitro fertilisation (IVF) cycles, lesser degree of OHSS is possible with other regimes. These regimes include use of clomiphene citrate (CC) alone or in combination with human menopausal gonadotrophin (HMG) follicular stimulating hormone (FSH) human chorionic gonadotrophin (HCG) [2]. Reports on the experience with OHSS in IVF cycles have been coming up in last two decades but there are very few reported studies on the experience with OHSS in basic assisted conception

cycles involving intra uterine insemination (IUI). Since our centre is undertaking sizable number of these basic assisted conception cycles it was decided to study our experience of OHSS with the use of (CC) alone as well as in combination with gonadotrophin. The objectives were to find the incidence, assess the response to conservative management and identify predisposing factors.

Material and Methods

The study design is a retrospective analysis of all cases of OHSS amongst patients who underwent stimulation for intra uterine insemination (IUI) during last 2 years. All patients who had experienced OHSS had been managed conservatively with uniform protocol. They were graded as per Golan [3]. Gr 1: Abdominal distension and discomfort, Gr 2 : Accompanied by nausea, vomiting and ovarian enlargement > 5 cm, Gr 3 : Ultrasonic evidence of ascitis, Gr 4 : Clinical ascitis and hydrothorax and Gr 5 : Hemoconcentration and impaired renal function. Gr 1 & 2 are considered as mild, Gr 3 is moderate and Gr 4 & 5 are severe OHSS. All the cases had been admitted to the hospital for observation. They were monitored with abdominal girth, urine output, haematocrit, coagulation parameters, blood urea, serum creatinine and ultrasonographic study (USS) of pelvis. Emphasis was on maintenance of fluid and electrolyte balance. Administration of exogenous HCG was withheld if not already given. Treatment cycles had not been cancelled and IUI had been performed on ultrasonic demonstration of ovulation. However luteal phase support with HCG was not given which could have aggravated the existing OHSS. Time taken for relief of symptoms was noted.

Indication of ovulation induction, pre induction endocrinological profile and folliculometry records of the affected cycles were

*.+.++Reader, #Professor, Department of Obstetrics and Gynaecology, Armed Forces Medical College, Pune - 411 040. **Senior Advisor,(Obstetrics & Gynaecology), 151 BH, C/o 99 APO.

analysed to identify any predisposing factors. Incidence of such factors as well as the pregnancy rates were compared with that of all the cases of matching age group for statistical significance.

Results

The details of the treatment cycles undertaken and hyperstimulation encountered during the period of study is given in Table - 1.

TABLE 1

Number of patients	410
Number of cycles	976
Number of cycles with CC*	830
Number of cycles with CC+FSH#	146
Number of OHSS	12

*CC 100 mg OD from day 2 to day 6

#CC 100 mg OD for 5 days + FSH 75 IU OD from day 6 to day 9

The incidence of OHSS according to severity has been indicated in Table - 2. Though we recruited patients up to the age of 40 in treatment cycles, the oldest patient in the OHSS subset was aged 30 years. In order to have comparison with a matching age group, all cases aged above 30 were excluded and the total number of patients came down to 308 involving 734 cycles.

TABLE 2

Cases showing OHSS

Induction protocol	Mild		Moderate		Severe		Total	
	n	%	n	%	n	%	n	%
CC (n=830)	3	0.36	-	-	-	-	3	0.36
CC+FSH (n=146)	5	3.42	4	2.73	-	-	9	6.16
Total (n=976)	8	0.81	4	0.41	-	-	12	1.22

Out of the 12 cases who developed OHSS, 4 had developed manifestations before and 8 after administration of HCG. The time of onset of symptoms was between day 12 to day 18 of the cycle. None of our patients had progressed beyond grade 3. Average duration of persistence of symptoms was 10 days for those who did not conceive and 6 weeks for those who did conceive.

Clinical evidence of polycystic ovarian disease (PCOD) which is considered as a risk factor for development of OHSS, was present in 6 out of 12 patients. In addition to infertility, presence of oligomenorrhoea, hirsutism and typical USS picture of the ovaries had been taken as clinical criteria of PCOD. On study of the folliculometry records of the affected cycles it was observed that besides the dominant follicle at least 4 other follicles (size > 10mm) were present in 11 patients. On examining the endocrine picture of the pre induction workup, it was observed that in 7 of the affected patients the D3 LH was more than the FSH. The overall incidence of these 3 risk factors in matching age group has been compared with that of OHSS subset in Table-3.

5 out of the 12 cases of OHSS had conceived giving a pregnancy rate of 41.1% which was much above the overall pregnancy rate of 21.8%.

TABLE 3

Predictive criteria for OHSS

Criteria	All cases n=308		OHSS subset n=12		p value
	No.	%	No.	%	
Clinical PCOD	38	12.73	6	50	0.0002
D-3 LH : FSH > 1	55	17.85	7	58.3	0.002
Secondary follicles > 4	30	9.74	11	98.3	0.0002

Discussion

OHSS is a well recognised iatrogenic complication of ovulation induction [4]. The patho physiological hallmark is a massive extra vascular exudate and intra vascular volume depletion alongwith hemoconcentration. With the rapid popularisation of assisted reproduction technologies (ART), the use of ovulation inducing drugs have been on the increase. The incidence of OHSS when entire stimulation is done with exogenous gonadotrophin has been widely reported. It ranges between 8.4 to 23% for mild OHSS and 3.5 to 4.8% for severe ones [5]. OHSS of clinical significance with the use of clomiphene alone is rare. In our series we have encountered the same only in 3 cases. Combined CC and gonadotrophin cycles can result in OHSS [6]. We have found this incidence to be 6.16% whereas overall incidence has been 1.22%. Higher incidence has been reported in literature when biochemical criteria of hyperstimulation is included [7]. It has been felt now that since biochemical criteria of raised oestradiol levels is present in most assisted conception cycles, it should not be taken as a criteria of OHSS [8].

All the cases of OHSS in our series have been mild to moderate, the highest being that of Gr 3 with ultrasonic evidence of ascitis. Severe OHSS with clomiphene alone has been reported by only one worker [9] as a case report. It was following an extended stimulation protocol for 14 days which is no longer practised.

PCOD is considered a risk factor for development of OHSS, because of disturbed steroidogenesis. The percentage of OHSS cases having PCOD; when compared to general incidence has been found to be highly significant (p=0.0002).

A ratio of LH:FSH 2.1 is taken as an endocrinological marker of PCOD. However, even the ratio >1 has been suggested as a predictive criteria for development of OHSS [10]. This observation of significance in our study (p=0.002) confirms the validity of such a criteria.

The steroidogenic function of the ovary is under control of FSH & LH. High LH levels stimulate theca cells to produce androgens [11]. It has been suggested that LH dominance leads to disturbed androgen-estrogen conversion and a higher predilection for OHSS.

Association between ultrasound volumetric measurement of ovary at base line study and development of OHSS has been suggested [12]. In the study cycle however, a positive correlation between number of immature follicle and development of OHSS has been observed [13]. It has been found in our study that almost all (98.3%) of OHSS cycles had more than 4 secondary follicles. While the dominant follicle is engaged in preparing for terminal events of ovulation, secondary follicles possibly engage in additional estradiol production contributing to OHSS. An endocrine laboratory may not be within easy reach but USS is always available. Hence, demonstration of an ultrasonic predictive factor for OHSS [14] to be as good as endocrinological predictive factors (E2, FSH, LH, Androstendione) [15,16] is of high clinical utility.

Most assisted conception cycles have a modest pregnancy rate (PR). However when OHSS is encountered the PR is said to be high [17]. Hence we did not terminate any of our cycles because of OHSS and went ahead with planned insemination. However, administration of HCG either for ovulation or as luteal phase support has not been done for apprehension of aggravation of OHSS. PR has been demonstrably high. It can be concluded that, though OHSS can be encountered in CC or CC+FSH cycles, they are not severe and can be managed conservatively while going ahead with the planned IUI. Certain predictive criteria can be kept in mind to expect OHSS and remain watchful.

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