PREVALENCE AND PREDICTORS OF OVARIAN HYPER STIMULATION SYNDROME AMONG WOMEN WHO HAD UNDERGONE CONTROLLED OVARIAN STIMULATION: A RETROSPECTIVE STUDY AT THE CENTER FOR FERTILITY AND REPRODUCTIVE MEDICINE, PUBLIC INVITRO FERTILIZATION CENTER, ETHIOPIA

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ABSTRACT

BACKGROUND: Infertility affects fifteen percent of couples who wish to conceive. The mainstay of artificial re-productive technologies is in vitro fertilization and embryo transfer (IVF-ET), in which aspirated oocytes are fertilized, followed by the trans cervical replacement of an embryo(s) into the uterine cavity. However, the practice of assisted reproductive technology is loaded with short- and long-term complications. Complications may occur during the course of stimulation, ovum pickup, or embryo transfer. Ample studies are done on in vitro fertilization, but the frequency and im-portance of complications of IVF in low-resource settings where the treatment itself is not widely available are not well known.

OBJECTIVE: This study aimed to determine the rate of ovarian hyper stimulation syndrome (OHSS) and asso-ciated factors among women who underwent controlled ovarian stimulation and IVF in a public IVF center in Ethiopia.

METHODOLOGY: A retrospective cohort study was conducted to review the medical records of women who have undergone ovarian stimulation and IVF treatment at the Saint Paul's Hospital Center for Repro-ductive Medicine and IVF.

RESULTS: A total of 428 clients had controlled ovarian stimulation and IVF. The mean age of the partici-pants was 33 years. Among 428 couples who had IVF, majority 245 (57%) had IVF for female fac-tor infertility, followed by male factor infertility 89 (20%), and unexplained causes 53 (12%).

The incidence of OHSS in our IVF population was 19 (4.4%) out of 428 women. Out of the 19 patients with OHSS, 17 (89%) developed mild and moderate symptons,and 2 out of 19 (10 %) had severe OHSS. The odds of developing OHSS was 6 times higher among those with PCOS, OR 5.78 CI (1.19, 28.22), p value of 0.03.

CONCLUSIONS AND RECOMMENDATIONS: The overall rate of ovarian hyper stimulation syndrome is higher in our IVF population. Emphasis should be given on thorough counseling and risk minimizing measures when women with PCOS undergo controlled ovarian stimulation.

KEY WORDS: IVF complications, fertility, reproductive-medicine, ovarian hyperstimulation syn-drome

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INTRODUCTION

Infertility impacts 15% of couples aspiring to conceive, with in vitro fertilization and embryo transfer (IVF-ET) being the primary artificial reproductive technologies. IVF's history spans over 50 years, marked by the first non-human mammal birth through IVF in 1959 and the first IVF-conceived baby in 1978. Initially designed for tubal factor infertility, IVF is now recommended for various infertility conditions, with male factor infertility being the most common indication.[1-3]

The evolution of IVF treatments has seen the development of controlled ovarian stimulation (COS) as a crucial element for successful assisted reproductive technology (ART) outcomes. Ovarian reserve markers, such as antral follicle count (AFC) and anti-Müllerian hormone (AMH), guide individualized stimulation strategies. Ultrasound-guided transvaginal route (US-TV) has become the gold standard for oocyte collection during IVF cycles since its introduction in 1983.[4-8]

Despite IVF's promising success rates, it comes with short and long-term medical complications. Ovarian hyperstimulation syndrome (OHSS) stands out as a serious complication, linked to hormonal and surgical aspects of the procedure. OHSS is theorized to result from vasoactive media-tors released due to ovarian hyperstimulation, leading to increased capillary permeability and fluid extravasation, causing hemoconcentration and related complications.[9, 10]

Women at higher risk of OHSS include those who are young, have polycystic ovary syndrome (PCOS), undergo profound hyperstimulation protocols, and have a large number of preovulato-rygraafian follicles. Studies show that the incidence of severe OHSS increases significantly with the number of oocytes retrieved, particularly exceeding 18. Reported OHSS incidence varies, ranging from 3.1% to 8% of IVF cycles, potentially reaching 20% in high-risk women.[11-13]

Experienced IVF centers adopt strategies like antagonist protocols with agonist triggers and elective cryopreservation of embryos to mitigate OHSS risk. However, in settings lacking widespread access to agonist triggers and facing logistical challenges with cryopreservation, the risk of OHSS remains high. Our study aims to fill this gap by assessing the incidence and predictors of OHSS in our specific setting, providing valuable insights for reproductive health practitioners and research-ers.

METHOD AND MATERIALS

This study was conducted at the Center for Reproductive Medicine and IVF Center, St. Paul's Hospital Millennium Medical College, the first public IVF center in Ethiopia, inaugurated in February 2011. The research involved a retrospective review of medical records for couples undergo-ing IVF treatment. Inclusion criteria comprised women who underwent controlled ovarian stimu-lation and ovum pickup. The primary outcome was the development of ovarian hyperstimulation syndrome (OHSS), assessed clinically through symptoms such as abdominal pain, distension, nau-sea, and ultrasound evidence of peritoneal fluid collection. Severity levels (mild, moderate, or se-vere) were determined by physicians and documented in patient charts. Baseline characteristics, including age, antral follicle count (AFC), body mass index (BMI), anti-Mullerian hormone (AMH) level, day 3 follicle-stimulating hormone (FSH), ovarian stimulation protocol, and presence of ovulatory disorders, were also evaluated.

IVF Treatment Practice of the Center

The center employed three ovarian stimulation protocols: long, antagonist (flexible), and mild stimulation, based on patient ovarian reserve and age. The long protocol involved zoladex injection on the 21st day, followed by gonadotrophin injections. Monitoring was conducted via transvaginal ultrasound. Mild stimulation used oral ovulation induction drugs like letrozole, followed by low-dose gonadotrophin and the antagonist cetrotide. The antagonist protocol, reserved for low ovarian reserve or advanced age, initiated

gonadotrophin stimulation and GnRH antagonist when the leading follicle reached 14 mm. Common strategies to prevent OHSS included coasting, reducing HCG trigger dose, and freezing all embryos.

Treatment of OHSS

Patients with anticipated OHSS received cabergoline. Management for mild cases involved outpa-tient care with oral hydration and follow-up tests, while moderate-to-severe cases required IV hy-dration, peritoneal tapping, and thromboprophylaxis. Vital signs and laboratory tests were regu-larly monitored.

Dependent and Independent Variables

The dependent variable was the development of OHSS, dichotomized as "yes" or "no." Independent variables included age, AFC, BMI, AMH, Day 3 FSH, ovarian stimulation protocol and ovula-tory disorders (PCOS).

Inclusion criteria: Women who had undergone controlled ovarian stimulation, ovumpickp and embryo transfer

Exclusion criteria: Women with cancelled cycles due to poor response

Sample Size Determination

The sample size, determined using a single population proportion formula, by taking P= 50 %. (The anticipated rate of complications of IVF and controlled ovarian stimulation was 422, with a 95% confidence interval, 5% margin of error, and 10% non-response rate.

Sampling Technique and Data Collection

Simple random sampling was employed. Every 4th case((1600÷422) was selected from the registra-tion book. Data were collected using Open Data Kit (ODK) with structured questionnaires, re-trieving information from patient charts, electronic medical records (EMR), and registration logs. Ethical clearance was obtained from the Institutional Board Review of St. Paul's Hospital Millen-nium Medical College. In order to maintain patients' confidentiality, data from patients' charts was abstracted anonymously.

Data Analysis

Data were processed using Stata Statistical Software. Univariate analyses employed proportions and means or medians. The rate of major complications was computed, and associations between OHSS and variables were assessed using Fisher's exact test, independent t-test, or bivariate logistic regression. A significance level of 0.05 was applied.

RESULTS

A total of 428 women who had undergone controlled ovarian stimulation and IVF were included in the analysis. As outlined in Table 1, of the 428 cases, 327 (80%) had primary infertility, with a female factor being the cause in 245 (57%), a male factor in 89 (20%), and an unexplained factor in 53 (12%). Among the 245 cases with female factors infertility, 211 (87%) of them were diag-nosed with tubal factors, and 31 (13%) were diagnosed with ovulatory dysfunction.

Obstructive azoospermia was the leading cause among male factor infertility (62/89, 70%) fol-lowed by oligospermia and asthenospermia.PCOS was the most common underlying endocrino-logic abnormality, identified in 39 out of 428 women (9%).

Day 3 FSH was done for 55% (233 out of 428) of the cases, the mean being 7.3.Among those who had AMH, 89 out of 428 (20% of cases) the mean AMH level was 1.6 with ± SD 1.9. Antral folli-cle count was done for nearly 100% the cases. The mean AFC was found to be 10 with± SD of 7.

Table 1: Characteristics of women and fertility profiles of couples who have undergone COS and IVF, at CFRM, SPHMMC, Addis Ababa Ethiopia

Variables	No.	%
Age		
20–24 years	14	3.3
25–29 years	100	23.4
30–34 years	142	33.2
35–39 years	142	33.2
≥40 years	30	7
BMI category		
Underweight	5	6.9
Normal Weight	40	55.6
Overweight	21	29.2
Obesity	6	8.3
Type of infertility		
Primary	327	76.4
Secondary	101	23.6
Cause of Infertility		
Female factor	245	57.2
Male factor	89	20.8
Both	41	9.6
Unexplained	53	12.4
Female factor cause		
Tubal	211	86.1
Ovulatory	31	12.7
Uterine	3	1.2
Male factor cause		
Oligospermia	15	16.9
Asthenospermia	12	13.5
Obstructive Azoospermia	62	69.7
Endocrinology abnormality		
None	381	89.0
PCOS	39	9.1
Hypothyroidism	6	1.4

Table 2: Controlled ovarian hyperstimulation and IVF treatment outcomes of women who have undergone COS and IVF, at CFRM, SPHMMC, Addis Ababa Ethiopia

Variables	No.	%
Type of protocol		
Long agonist	148	34.6
Antagonist	17	4
Ministim	263	61.4
Embryo transfer done		
No58	13.6	
Yes	370	86.4
Stage of transferred embryo		
Day 3	296	80
Day 5	74	20
Level of Physician who have done ET		
2nd Year Fellow	43	11.6
Subspecialist	327	88.4
Pregnancy test		
Negative	306	72.5
Positive	116	27.5

Among the 428 cases, the majority (263, or 61%) of them had minimal stimulation, followed by long agonists (148, or 34%). Among those who had stimulation and ovum pickup, 370 (86%) of them had embryo transfers, with 80% (296/370) day 3 transfers and 20 % (74/370) day 5 transfers. The rest (3.5%) had no oocyte retrieved (15), 37 (8.6%) failed fertilization of retrieved oocytes, and 6 (1.5%) postponed embryo transfer (freeze all).

As noted in Table 3, of the total 428 women who have undergone COH, 4.4% (19) of them de-veloped ovarian hyperstimulation syndrome. The majority were mild or moderate (47% (9/19) and 8 out of 19 (42%), respectively), and the rest (10%) were severe. Most of them had early onset, detected before the OPU and embryo transfer (14 or74%); the rest (5 or 26%), detected pregnan-cy tests confirmed to be positive. Of those who developed OHSS, 11 (58%) of them were man-aged as outpatients, and 8 (42%) were managed as inpatients.

Table 3: Rate of ovarian hyperstimulation syndrome of women who have undergone COS and IVF, at CFRM, SPHMMC, Addis Ababa Ethiopia

Complications	No.	%
Ovarian Hyperstimulation Syndrome		
No	409	95.6
Yes	19	4.4
Severity of OHSS		
Mild	9	47.4
Moderate	8	42.1
Severe	2	10.5
Time of onset of OHSS		
Before OPU	1	5.3
Before ET	13	68.4
After positive pregnancy	5	26.3
Place of management of OHSS		
Outpatient	11	57.9
Inpatient	8	42.1
Presence of pleural effusion		
No	16	84.2
Yes	3	15.7

The median age of women with OHSS was 29 years, versus 33 for those without OHSS. Upon bivariate analysis, a statistically significant association was found between the age of the women and the rate of OHSS. The median AFC was 20 for those with OHSS and 8 for the group with no OHSS. The median number of mature follicles was 27 for the group with OHSS and 5 for the group with no OHSS. The median number of oocytes retrieved was 18 and 5 for the groups with OHSS and no OHSS, respectively. A higher dose of gonadotrophins was used in those with OHSS, the median being 225 IU versus 150 IU in those with no OHSS. As an outcome of bivari-ate analysis, there was also a statistically significant association between the baseline AFC, the numbers of mature follicles at the time of trigger, the number of oocytes retrieved, and the rate of OHSS. Women who had an underlying endocrinology abnormality of PCOS were found to have a statistically significant higher rate of OHSS. Long agonist stimulation protocols resulted in a higher rate of OHSS (95% of OHSS cases were stimulated with a long agonist protocol) (Tables 4 and 5)

Table 4: Bivarate analysis of factors determining the rate of OHSS at the CFRM, SPHMMC, Ad-dis Ababa, Ethiopia

Variables/ Factors	Ovarian Hyper stimulation		p-value*
	No (n=409)	Yes (n=19)	
Age in Years, median (IQR)**	33.0(29.0,36.0)	29.0 (27.0, 32.0)	<0.001
Day 3 FSH, median (IQR)	6.3 (4.2, 8.8)	5.4 (3.8, 7.2)	0.25
AFC, median (IQR)	8.0 (4.0, 12.0)	20.0 (16.0, 29.0)	<0.001
Dose of Gonadotropins per day(in IU/day), median (IQR)	150.0(150.0, 225.0)	225.0 (225.0,300.0)	0.002
Total No of mature follicles>13mm in diameter , median (IQR)	5.0 (3.0, 9.0)	27.0 (14.0, 37.0)	<0.001

P-values were calculated based on non-parametric test of difference of medians (Mann Whitney U test).**IQR=Inter quartile range

Table 5: Bivarate analysis of factors determining the rate of OHSS at CFRM, SPHMMC, Adddis Ababa, Ethiopia

Variables	Ovarian Hyper stimulation		p-value*
	No (n=409)	Yes (n=19)	
Age			
20–24 years	14 (3.4%)	0 (0.0%)	0.006
25–29 years	90 (22.0%)	10 (52.6%)	
30–34 years	134 (32.8%)	8 (42.1%)	
35–39 years	141 (34.5%)	1 (5.3%)	
≥40 years	30 (7.3%)	0 (0.0%)	
Day 3 FSH			
<=7 IU/L	137 (62.6%)	10 (71.4%)	0.58
>7 IU/L	82 (37.4%)	4 (28.6%)	
AFC			
<15	335 (82.1%)	3 (15.8%)	<0.001
>=15	73 (17.9%)	16 (84.2%)	
Total No of mature follicles>13mm			
<=18	384 (93.9%)	8 (42.1%)	<0.001
>18	25 (6.1%)	11 (57.9%)	
Serum Pregnancy test			
Negative	299 (73.3%)	7 (50.0%)	0.069
Positive	109 (26.7%)	7 (50.0%)	
Cause of Infertility			
Female factor	235 (57.5%)	10 (52.6%)	0.098
Male factor	87 (21.3%)	2 (10.5%)	
Both	36 (8.8%)	5 (26.3%)	
Unexplained	51 (12.5%)	2 (10.5%)	
Type of protocol			
Long agonist	130 (31.8%)	18 (94.7%)	<0.001
Antagonist	17 (4.2%)	0 (0.0%)	
Ministim	262 (64.1%)	1 (5.3%)	
PCOS			
No	383 (93.6%)	6 (31.6%)	<0.001
Yes	26 (6.4%)	13 (68.4%)	

Percentages are calculated from the column total, *P-values were calculated using Fisher's exact test

Table 6: Multivaratelogistic Regression: factors determining the rate ofOHSSat the CFRM, SPHMMC, Addis Ababa, Ethiopia

Factors	Ovarian Hyper Stimulation Syndrome		AOR	P-value	95%	CI
	No (n=409)	Yes (n=19)				
AFC						
<15	335 (82.1%)	3 (15.8%)				
>=15	73 (17.9%)	16 (84.2%)	6.30	0.06	0.93	42.82
Total no of mature follicles>13mm						
<=18	384 (93.9%)	8 (42.1%)				
>18	25 (6.1%)	11 (57.9%)	1.92	0.39	0.44	8.37
PCOS						
No	383 (93.6%)	6 (31.6%)				
Yes	26 (6.4%)	13 (68.4%)	5.78	0.03	1.19	28.22

On multivariate logistic regression analysis having PCOS was independent predictors of the rate of OHSS,the odds of developing OHSS was 6 times more like among those with PCOS, OR 5.78 CI(1.19,28.22), p value of 0.03.

DISCUSSION

The overall rate of OHSS in our study was found to be 4.4%., 9 (2.1%) cases were mild, 8 (1.8%) were moderate, and 2 (0.5%) were severe.

The reported prevalence of the severe form of OHSS varies widely. A rate ranging from 0.5 to 5% has been reported for severe OHSS[12]. A study done in 2005 using data from the Finnish registry reported an incidence of severe OHSS of 1.4% per cycle, with an individual risk per pa-tient of 2.3% over a mean number of 3.3 cycles[14].

In a study that assessed the incidence of OHSS among women undergoing fresh in vitro fertilization (IVF) cycles between 2000 and 2004, among high-risk women (with peak serum estradiol levels >2500 pg/mL and presumed to be at risk for OHSS), the overall incidence was 20.2% (38 out of 188) and the incidence in the whole IVF population was 38 out of 1002 (3.8%).[13]

The moderate and severe forms may occur in 3% to 10% of all ART cycles, and the incidence may reach 20% among high-risk women.[15]

The rate of OHSS in our study population is 4.4%, which is in the reported range of the general IVF populations of other studies, but lower than the high-risk population OHSS rate, which is ex-plained by the fact that our study population included all groups of patients with respect to the risk category.

Baseline ovarian reserve tests as a predictor of ovarian response and risk of OHSS have been studied. Prediction of in vitro fertilization outcome at different antral follicle count thresholds in a prospective cohort of 1,012 women revealed antral follicle count was predictive of ovarian re-sponse, with the risk of moderate or severe OHSS. 2.2% with an AFC of less than or equal to 24; the risk increased to 8.6% at an AFC of more than 24.[16]

In a study by Kwee et al., an antral follicle count (AFC) > 14 had the highest sensitivity (82%), specificity (89%), and positive predictive value for ovarian hyper-response.[17]

Basal anti-Müllerian hormone (AMH) levels prior to COS have also been shown to be predictive for OHSS. A systematic review and meta-analysis of the existing literature were performed. Nine studies reporting on AMH and five reporting on AFC were found, with the accuracy of AMH in excessive response prediction having a sensitivity of 82% and specificity of 76%. The clinical value of basal levels of FSH and AMH as well as antral follicle count (AFC) as a predictor of ovarian re-sponse for ovulation induction and IVF has been studied,

and it has been found that AMH has the ability to predict excessive response independent of age and PCOS. Basal AMH levels ~ ≥3.5 ng/mL were predictive of hyper-response or OHSS with high sensitivity and specificity.[18-20]

There is a significant and consistent relationship between PCO and OHSS. In a systematic review of ten studies done to assess and quantify the relationship between polycystic ovaries (PCOs) and ovarian hyperstimulation syndrome (OHSS), when PCOs were present, the combined odds ratio for OHSS was found to be 6.8 (95% confidence interval 4.9–96).[21]

In a study done to evaluate if gonadotropin-releasing hormone agonist (GnRHa) trigger is a better alternative to human chorionic gonadotropin (hCG) in polycystic ovary syndrome (PCOS) of Indian origin undergoing in vitro fertilization, (IVF) cycles with GnRH antagonist for the prevention of ovarian hyper stimulation syndrome (OHSS), the incidence of moderate to severe OHSS in the hCG group was found to be as high as 37.6%.[22]

Similarly, our study findings identified PCOS as an independent predictor of the rate of OHSS. The odds of developing OHSS were six times higher among those with PCOS, OR 5.78 CI (1.19, 28.22), p value of 0.03. The other baseline reserve tests, including age and AFC > 15, which were found to have significant associations upon bivariate analysis, were not found to be independent predictors upon logistic regression. The possible explanation for the loss of association is the smaller sample size (evidenced by a wider CI).

In a study that analyzed data from 256,381 IVF cycles using the 2008–2010 Society for Assisted Reproductive Technology national registry, retrieval of >15 oocytes significantly increased OHSS risk [23].

In another study, which was done to determine the incidence of ovarian hyper stimula-tion syndrome (OHSS) in a large series of GnRH antagonist-stimulated cycles and to assess the predictive value of E2 and the number of follicles on the day of hCG administration, 53 patients were hospitalized because of OHSS (2.1%; 95% confidence interval [CI]: 1.6–2.8). The combina-tion of a threshold of more than or equal to 18 follicles and/or an E2 of ≥5,000 ng/L yields an 83% sensitivity rate with a specificity as high as 84% for severe OHSS cases.[23].

Numerous study findings have shown the number of follicles at oocyte aspiration, the number of aspirated oocytes, and the total number of medium- or large-sized follicles before hCG as independent predictors of OHSS.

In a recent retrospective analysis of all consecutive IVF/intracytoplasmic injection cycles per-formed during a 5-year period (2009–2014) in a single university fertility center, the number of follicles ≥10 mm on the day of triggering final oocyte maturation represented the best predictor of severe OHSS in IVF cycles.[24-26]

The lack of association between the well-known risk factors, high doses of gonadotropins, high or large numbers of large and medium-sized follicles, and large numbers of eggs retrieved, in our logistic regression is again explained by the smaller sample size, as evidenced by the wide CI.

CONCLUSION AND RECOMMENDATION

The overall rate of ovarian hyperstimulation syndrome is higher in our IVF population. PCOS, an endocrinology disorder, has been found to be an independent predictor of the risk of OHSS. It is important to stick to OHSS risk-reducing strategies, including using antagonist protocols and possible agonist triggers, followed by freeze all, especially in patients with PCOS. In order to iden-tify the other important determinant factors for the complications of ovulation induction and IVF, studies with a larger sample size and a possible multicenter (including private) setup should be conducted.

LIMITATIONS OF THE STUDY

Some important baseline characteristics were omitted from analysis (BMI, cause of infertility) due to incomplete data from the electronic medical records. On the basis of logistic regression analysis, the finding of a wide range for the CI indicates that

a much larger sample size is needed to identi-fy the determinant factors of complications.

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