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IMPACT OF BODY MASS INDEX ON SOME REPRODUCTIVE HORMONES LEVELS AND INTRA-CYTOPLASMIC SPERM INJECTION OUTCOMES OF FEMALE PATIENTS.

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ABSTRACT

Background: Assisted reproduction is a complicated process involving multiple stage of ovarian stimulation, ovum pick-up, fertilization, embryo cleavage and implantation. The goal of all these procedures is achievement of viable intrauterine pregnancy as a step of achievement of healthy baby. **Aim**: The aim of the current study was to find out possible effect of body mass index on serum inhibin levels, and at the end on the fade of intracytoplasmic sperm injection outcome in women. In addition, the present study evaluate the rate of pregnancy in association with BMI either obese, overweight and normal. **Methods:** This prospective study was performed in the fertility center and urology center at AL-Sader medical city in AL-Najaf governorate involving(150) female participate in this study between November 2015 and June 2016. **Results:** Present study demonstrated that obese women who are subfertile were undergoing ICSI procedure are prone to have lower pregnancy rate in comparison to normal one. While, there is no significant correlation between categorized groups of women regarding BMI and inhibin B in serum measure at second day of cycle and follicular inhibin B at ovum pickup. Inhibin B is less sensitive to BMI. **Conclusion**: Finally, present study concluded that age of women is important factor affecting the outcomes of ICSI, in women age >35 years old had

lower retrivedoocyte, 2pn and total number of embryos that signicantly differ in compare with younger women < 35 years.

KEYWORDS: Inhibin, BMI, Infertility.

INTRODUCTION

Infertility is defined by WHO and ASRM.[1,2] as a disorder of the system of reproduction in which there is unsuccessful clinical child bearing following 12 months or more of regular unprotected sex intercourse. On the other hand the duration is extended up two years by NICE guidelines.[3] Female age is the major determinant of infertility. Natural female fertility falls gradually after age 30 years, with a rapid decline after age 35 years to cessation at menopause. Other factors associated with female infertility are obesity (body mass index greater than 29), low body weight (body mass index less than 19 and irregular or absent menstruation), and smoking.[4] (NCCWCH, 2004).Regarding obesity, it has been associated with reduced fecundity as well as impaired pregnancy success for women who undergo assistant reproductive technique (ART) procedures.[5,6] One postulated mechanism is that obesity affects the hypothalamic-pituitary-ovary axis, resulting in irregular menstrual cycles.[7] Although some evidence indicates that the effect of obesity on fecundity persists for women with regular menstrual cycles.[8] Obesity has also been associated with poor pregnancy outcomes, such as unexplained intrauterine death.[9]

The mechanisms by which obesity causes or exacerbates subfertility are manifold. High BMI is associated with an increase in serum and follicular fluid leptin concentration.[10] and decrease in serum adiponectin levels. Lower adiponectin levels are associated with increased circulating insulin.[11] which can cause hyperandrogenaemia partly by inhibiting the hepatic SHBG (sex hormone binding globulin) production. In addition, insulin acting via IGF1(insulin like growth factor 1) enhances LH mediated steroidogenesis in the theca cell system of the ovary and thus increases ovarian androgens.[12] Hyperandrogenaemia results in granulosa cell apoptosis. Obesity is also associated with polycystic ovary syndrome (PCOS) which is a heterogeneous condition characterized by oligo or anovulation, hyperandrogenism, menstrual irregularities and subfertility.[13] (Pasquali and Gambineri.2006). Obesity which occurs in 30-75% of women with PCOS, increases the magnitude of hormonal and metabolic dysfunction in these women.[14]

The association of overweight and obesity with invitrofertilisation (IVF) results is still controversial. Lashen *et al.*,[15] published a case–control study with 333 women undertaking IVF and concluded that extremes of body mass (BMI_30 and_18 kg/m2, respectively) do not adversely affect the outcome of hyperovulation and IVF. Lewis *et al.*[16] conducted a systematic review of observational studies on overweight and obesity in assisted reproductive technology and concluded that women with BMI_25kg/m2 showed decreased pregnancy rates, required higher doses of gonadotrophins for ovulation induction in IVF and had high miscarriage rates.[17]

Moreover, one of such mediators that could effect on female fertility is Inhibin which is produced mainly by granulosa cells of ovarian follicles in mammalian females and corpus luteum across the menstrual cycles.[18] It production has been to vary with the maturation of follicles.[19] While in males, the source of inhibinisthesertoli cells.[20] Infusion of recombinant human inhibin A into the circulation in castrated rams resulted in a specific suppression of FSH secretion commencing approximately 6 h after the start of the infusion and continuing for a period of approximately 12 h following its cessation.[21] The responsiveness of pituitary FSH to inhibin feedback is set up early in postnatal life, with the maximum sensitivity occurring by the age of puberty.[22] Both inhibin A and B are secreted into follicular fluid, where their concentration seem to increase during the process of follicle development. Among its negative feedback activity on anterior pituitary FSH synthesis and secretion, few other biological roles have been discovered for inhibin.[23] reported that inhibin could increase luteinizing hormone (LH)-stimulated steroidogenesis in cultured, immature leydig cells. Free inhibin α-subunit is also has a potentially significant role is that of gonadal tumor suppression.

MATERIALS AND METHODS

Study Design

This study was designed as a prospective study, participants were enrolled(n=150) who are referred from many Iraqi govemorates to the fertility center in A1 —Sader Medical City in Al-Najaf Al- Ashraf seeking treatment for infertility problems and they were treated by Intra-cytoplasmic sperm injection.

Patients selection (subjects)

The participants (n=150) was selected from patients attends the fertility center between November 2015 and june 2016. All couples were surveyed for their etiology of infertility

by the female were asked about their medical, surgical and gynecological history. They underwent complete medical examination with measurement of weight, height and body mass index (BMI). Gynecological examination was performed, cycle day 2(CD2) ultrasound (U/S) and blood tests for inhibin B Once the couple have been screened and found to be fit for selection criteria. Exclusioncriteriainclude**;** ICSI cycles without follicle aspiration and embryo transfer.

Preparation of female for ICSI

Transvaginal U/S: TransvaginalU/S on CD2 was done by the gynecologist in the fertility center to count antral follicle count (AFC) using real time ultrasound device (Philips 11*E), using vaginal probe (5-7 MHZ). Follicles measuring 2-10 mm were counted to assess the antralfollicles, also to rolled out the presence of ovarian cyst and to measure the endometrial thickness.

Human Inhibin B (INHB) assay

The measurement has been done by using ELISA technique and the steps of procedure precisely done according to manufacturer instructions in the leflet of ELISA kit (Elabscience, USA).

RESULTS

The mean body mass index of the entire sample was 27.88 ±4.2 kg/m^2 and the range was from 18.73 to 39.04. Patients were categorized into three groups according to BMI: 36 women with normal BMI of less than 25 kg/m2, 65 women with overweight (25 to <30 kg/m^2) and 49 infertile women who were obese (≥ 30 kg/m^2). There was no significant difference in mean follicular fluid (FF) inhibin, serum inhibin, serum FSH, serum estradiol and serum LH with respect to body mass index (P>0.05), **table (1)**. The pregnancy rate was highest in patients with normal BMI and lowest in obese women; however, no statistical significance was obtained following overall chi-Square test, **table (2).** None of the outcomes of ICSI were significantly affected by BMI (P>0.05), **table (3).** Nevertheless, pregnancy rate was significantly lower in obese women when compared to that of normal women and women with overweigh. Pregnancy rates were 30.6%, 24.6% and 14.3% in normal, overweight and obese infertile women, respectively, **figure (1).** No significant correlation was obtained between FF inhibin and serum inhibin (r=0.025;P=0.759), **figure (2).** In addition, FF inhibin showed significant correlation neither with hormonal parameters nor with variables of ICSI outcome, **table (4).**

Table (1): Comparison of hormonal levels according to BMI

Variable	Normal (n = 36)		Over weight (n = 65)		Obese (n = 49)		P
	Median	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	
FF inhibin (pg/ml)	58	63.25 ±36.62	67	65.24 ±26.80	67	72.00 ±40.64	0.066
Serum inhibin (pg/ml)	106	95.80 ±25.69	106	108.78 ±38.92	106	120.43 ±80.26	0.276
FSH (IU/ml)	6.22	5.87 ±1.97	5.53	5.40 ±2.42	5.37	5.17 ±2.39	0.104
E2 (pg/ml)	1651	1844.35 ±772.04	1651	1666.90 ±596.32	1449	1474.00 ±577.54	0.099
LH (IU/ml)	3.50	3.63 ±2.06	3.20	3.15 ±1.54	2.70	2.77 ±1.22	0.151

Table (2): Clinical pregnancy outcome following ICSI in relation to BMI

Pregnancy	Normal	Over weight	Obese	Total	χ^2	P
Positive n (%)	14 (30.6)	22 (24.6)	9 (14.3)	45 (22.7)	3.382	0.184
Negative n (%)	22 (69.4)	43 (75.4)	40 (85.7)	105 (77.3)		
Total	36 (100.0)	65 (100.0)	49 (100.0)	150 (100.0)		

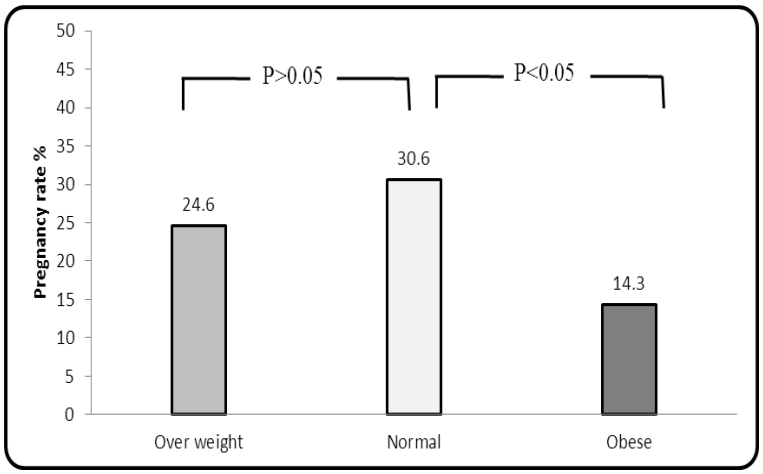

Figure (1): Clinical pregnancy outcome following ICSI in relation to BMI

Table (3): Outcome of ICSI according to body mass index

Characteristic	Normal			Over weight			Obese			P
	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	
mature follicles count	12.00	11.77	5.06	10.00	11.14	5.21	10.00	10.87	5.05	0.660
no.of oocytes retrived	9.00	10.26	5.35	8.00	9.32	5.55	7.00	8.70	5.01	0.361
M2	7.00	8.00	4.83	6.00	6.91	4.74	6.00	6.91	4.50	0.431
good injected oocytes	6.00	7.94	4.84	6.00	7.02	4.70	6.00	7.09	4.45	0.575
fertilized oocytes (2PN)	4.00	4.37	2.97	3.00	3.70	2.99	4.00	4.15	3.27	0.424
fertilization rate	53.00	52.97	27.91	55.00	56.82	30.04	63.00	59.22	29.15	0.476
no.of embryos	4.00	4.00	2.66	3.00	3.45	2.80	4.00	3.96	3.13	0.355
no.of embryos transferred	3.00	2.66	1.19	3.00	2.41	1.12	3.00	2.52	1.22	0.403
Endometrial thickness(mm)	9.00	9.23	1.61	10.00	9.96	1.84	10.00	9.74	1.90	0.164
Cleavage rate	100.00	85.44	29.72	100.00	85.09	35.34	100.00	80.53	39.58	0.677

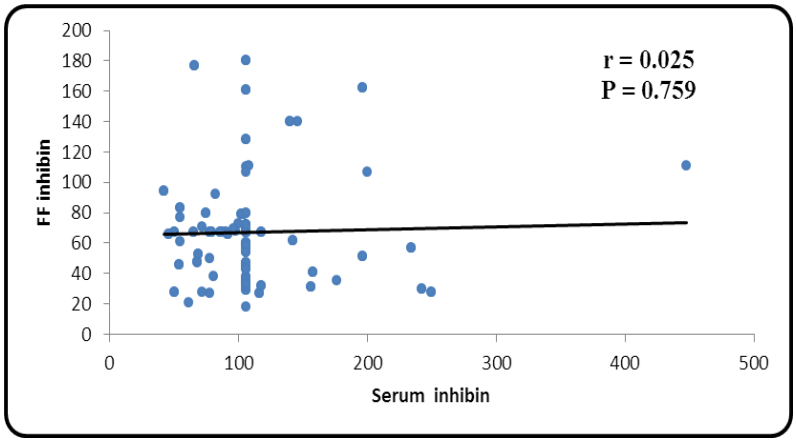

Figure (2): Correlation between serum and follicular fluid inhibin

Table (4): Correlation between serum and FF inhibin and ICSI outcome variables

Variable		Serum (pg/ml)	FF (pg/ml)
mature follicles count	r	0.126	-0.093
	P	0.137	0.276
no.of oocytes retrived	r	0.094	-0.033
	P	0.269	0.700
M2	r	0.095	-0.030
	P	0.268	0.728
good injected oocytes	r	0.120	-0.048
	P	0.166	0.580
fertilized oocytes(2PN)	r	0.140	-0.021
	P	0.104	0.806
fertilization rate	r	0.058	-0.043
	P	0.502	0.617
no.of embryos	r	0.169	-0.049
	P	0.049	0.568
no.of embryos transferred	r	0.025	-0.130
	P	0.771	0.131

DISCUSSION

Body mass index show no significant correlation with serum and follicular inhibin in the present study. One of the studies showed no relation between BMI and serum inhibin.[24] On the other hand BMI has been shown to be negatively correlated with serum inhibin.[25] The pregnancy rate in Sudan was approximately 21%.[26] In 21 countries where all clinics reported to the ART register, a total of 399 020 ART cycles were performed in a population of 373.8 million, corresponding to 1067 cycles per million inhabitants. For IVF, the clinical pregnancy rates per aspiration and per transfer were 28.9 and 32.9%, respectively and for ICSI, the corresponding rates were 28.7 and 32.0%.[27] Other adverse outcomes of ovarian stimulation in obese women are reduced oocyte retrieval, poor quality of oocyte and embryo, decreased

intrafollicular human chorionic gonadotrophins concentration, decreased peak estradiol levels, decreased number of mature oocytes, decreased incidence of embryo transfer and decreased number of transferred embryos.[28]

However, obese women, had lower peak estradiol levels and required higher doses and longer duration of gonadotrophins injections compared to overweight and normal weight women.[29] Overweight women showed lower inhibin B ($p < 0.05$) levels compared with normal-weight women, whereas follicle count were not significantly different between the two groups. In another study, overweight women showed lower inhibin B ($p < 0.05$) levels compared with normal-weight women.[30] Obesity was associated with fewer normally fertilized oocytes, lower estradiol levels, and lower pregnancy and live birth rates.[31]

CONCLUSION

In conclusion current study demonstrated that obese women who are subfertile were undergoing ICSI procedure whose(BMI >30kg/m^2) are prone to have lower pregnancy rate in comparison to normal (BMI <25kg /m^2),while the comparison of the three categories normal (BMI < 25 kg/m2), overweight (25< BMI <30 KG / M2),obese >30) regarding pregnancy rate there is no significant between. Moreover, there is no significant correlation between categorised groups of women regarding BMI and inhibin B in serum measure at second day of cycle and follicular inhibin B at ovum pickup. inhibin B is less sensitive to BMI. Finally, this study demonstrated that age of women is important factor affecting the outcomes of ICSI, in women age >35 years old had lower (retrived oocyte, 2pn and total number of embryos that signicantly differ in compare with younger women < 35 years.

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