Impact of BMI on IVF outcome in females - A Prospective study

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Abstract- Background-Various prognostic factors in assisted reproduction procedures have been described and analysed, including woman's age, the cause of infertility, the ovarian response and uterine receptivity, the semen quality, and the BMI. Optimal BMI is required for an optimal response.There is controversy among various reports, which is partly caused by the varying focus of investigators and differences in study designs, led us to examine the relationship between BMI and IVF/ICS1 outcome in our unit.

OBJECTIVE: To study impact of BMI on IVF outcome prospectively.

MATERIAL/METHODS: It Prospective study over a period of 1 year in the age group 25-35 years attending the IVF clinic was conducted at a tertiary infertility centre in Bangalore, India between November 2010-October 2011.

RESULTS: There was close association of increased BMl in particular when BMl is > 30 kg/m2 and the reduced outcomes of IVF/ICSI treatment in the form of less clinical pregnancy and higher early pregnancy loss. Furthermore, increased BMl was related to an increased FSH requirement, longer days of stimulation, higher dosage of gonadotropins, increased risk of cancellation and fewer collected oocytes.

CONCLUSIONS: Obesity is associated with an increased risk of early pregnancy loss.

Also need of high dose of gonadotropin ,less number of collected oocytes is observed. Implantation rate ,pregnancy rate and miscarriage rate was comparable but live births are high in normal weight and overweight as compared to extremes of BMI due to high number of miscarriages in extremes of BMI though not statistically significant.So will be appropriate to recommend weight loss prior to IVF.

Index Terms- BMI/gonadotropin/IVF/pregnancy

I. INTRODUCTION

Initiation and maintenance of reproductive functions are related to an optimal body weight in women. Underweight [body mass index (BMI) <18.5 kg/m2], as well as overweight (BMI ≥25 kg/m2) and obesity (BMI ≥30 kg/m2) are associated with an increased risk of anovulatory infertility[1,2,3]

Reduced fecundity of underweight and overweight women is probably related to multiple endocrine and metabolic alterations, which include—but are not limited to—effects on steroid metabolism and altered secretion and action of insulin and other hormones, such as leptin, resistin, ghrelin or adiponectin.

These alterations can affect follicle growth, embryo development and implantation[4,5,6] , and it is therefore of concern that being underweight or overweight may interfere with treatment of infertility with IVF and ICSI. . Recently, a debate is started in literature whether or not restricting the access to fertility treatment on the ground of female body mass index[7,8,9,10].

In assisted reproduction, however, there are conflicting reports on the effect of obesity on oocyte quality, embryo development, lower number of mature oocytes, lower implantation and pregnancy rates .Endometrium also seems to have a negative impact on reproductive outcome in studies based on oocyte donation model.

Clinical observations on the effects of body weight during IVF and ICSI are conflicting Changes in body mass index (BMI) has serious impact on the various aspects of health in particular the reproductive function of women. There is controversy among various reports, which is partly caused by the varying focus of investigators and differences in study designs, led us to examine the relationship between BMI and IVF/ICS1 outcome in our unit.

II. MATERIAL AND METHODS

Study design –

It is a Prospective study over a period of 1 year in the age group 25-35 years(with 500 females subjects) attending the IVF clinic was conducted at a tertiary infertility centre in Bangalore, India between November 2010-October 2011.Approval was obtained from the Institutional Ethics Committee(IEC) .An informed consent was taken from all patients.

Various inclusion and exclusion criterias were taken so as to avoid confounding variables as much as possible so as to get comparable results.

The patients had their BMI recorded at the initial consultation before starting the treatment cycle. Patients were divided into four groups: Group A (BMI <19 kg/m2); Group B (BMI between 19 and 24.9 kg/m2); Group C (BMI 25 to 29.9 kg/m2) and Group D (BMI> 30 kg/m2).

Group A is underweight which comprised of 2%(10) patients, 41.6% (208) in group B
(Normal BMI), 42.6%(213) in group C (overweight) and 13.8%(69) in group D (obese).

The **primary** end-point assessed was- clinical pregnancy rate.

The **secondary** end-points included- cycle cancellation rate, the number of oocytes retrieved, mature oocytes, implantation rate and live birth rate.

INCLUSION CRITERIA: Fresh IVF/ICSI cycles,Non donor cycles,,Age group 25-35 years

EXCLUSION CRITERIA: >35 years age,Frozen embryo transfer,Donor oocyte,Gestational surrogacy,Patients with an accompanying medical problem which may lead to abnormal BMI such as diabetes mellitus, hyper or hypothyroidism

Variables taken are -Clinical and Embryological parameters

Stimulation protocol was decided based upon baseline endocrine profile, age and response in previous cycle if any, baseline hormonal levels , baseline vaginal ultrasound scan (for antral follicle count using 6.5 MHz vaginal probe and Prosound 4, Medison India Ltd. Ultrasound Machine) on Day 3, Anti Mullerian Hormone (AMH) values using DSL-ELISA kit and response in previous IUI/IVF cycles. Patients with good ovarian reserves were stimulated by long agonist down-regulation protocol for ovarian stimulation while women with poor ovarian reserves were stimulated by antagonist protocol. (Details of both the protocols is given vide infra).

Ovarian stimulation was achieved by human menopausal gonadotropin (Menopur, Ferring). As a rule, the starting daily FSH dose was 150 IU, Gonal F (Serono, Italy) or Recagon (Organon) with exception of women older than 35 years who received 225 IU and women with polycystic ovaries who received 75-150 IU.

The history and investigation reports were entered in a specially prepared performa. All patients undergoing conventional IVF-ET or Intra-cytoplasmic Sperm Injection (ICSI) were stimulated in accordance with the appropriate protocol decided for them and the treatment cycle was monitored using transvaginal ultrasound scans (TVS) and serum Estradiol (E2), progesterone (P) & Luteinising Hormone (LH) levels, wherever required. Inj uhCG, 5000IU IM (Ovutrig HP, VHB Life Sciences, Mumbai, India, Profasi, Serono or Pregnyl, Organon) or recombinant hCG 250 mcg (Ovidrel, Serono, Inc.) used in some cases(poor responders ,those at high risk of OHSS) was administered when the average diameter of lead follicle becomes more than 18mm and at least 2 follicles become more than 16mm in diameter. Oocytes were retrieved 34 to 36 hours after u hCG injection, by trans-vaginal ultrasound guided aspiration

Standard laboratory protocols were followed, including intracytoplasmic sperm injection(ICSI) , Laser assisted hatching(LAH) for cleavage stage embryos and extended culture for blastocyst transfer, as clinically appropriate

III. RESULTS

Figure 1 - BMI distribution

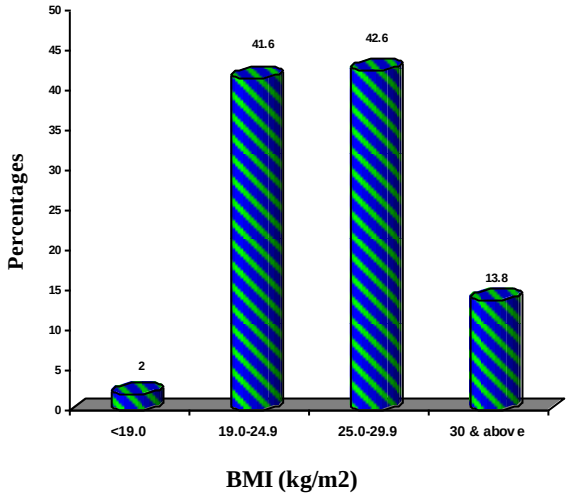

Table 1: Clinical characteristics of women according to BMI (kg/m^2)

Clinical variables	BMI (kg/m^2)				P value
	<19.0 (n=10)	19.0-24.9 (n=208)	25.0-29.9 (n=213)	30& above (n=69)	
Age in years	29.80±2.20	29.98±3.39	30.92±3.19	32.36±2.74	<0.001**
Duration of infertility	5.40±2.67	5.27±2.49	5.63±2.54	6.21±2.73	0.073+
Main causes of infertility					

• Mixed causes	0(0%)	1(0.5%)	1(0.5%)	0(0%)	0.946
• Tubal factor	1(10%)	49(23.6%)	47(22.1%)	16(23.2%)	0.786
• Anovulatory	1(10%)	3(1.4%)	2(0.9%)	0(0%)	0.055+
• Unexplained	2(20%)	33(15.9%)	29(13.6%)	8(11.6%)	0.762
• Male factor	6(60%)	122(58.7%)	134(62.9%)	45(65.2%)	0.676
Type of Infertility					
• Primary	5(50%)	148(71.2%)	152(71.4%)	42(60.9%)	0.205
• Secondary	5(50%)	60(28.8%)	61(28.6%)	27(39.1%)	

Table 2: Clinical characteristics of women according to BMI (kg/m^2)

Clinical variables	**BMI (kg/m^2)**				**P value**
	<19.0 (n=10)	**19.0-24.9 (n=208)**	**25.0-29.9 (n=213)**	**30& above (n=69)**	
Baseline FSH(Day2/3)mIU/ml					
• <10	8(80%)	184(88.5%)	197(92.5%)	67(97.1%)	0.180
• 10-20	2(20%)	21(10.1%)	15(7%)	1(1.4%)	
• >20	0(0%)	3(1.4%)	1(0.5%)	1(1.4%)	
• Mean ±SD	7.52±2.95	7.52±3.66	6.94±2.75	7.08±4.37	
Number of frozen embryos					
• Nil	8(80%)	172(82.7%)	175(82.2%)	56(81.2%)	0.849
• 1-5	1(10%)	27(13%)	28(13.1%)	10(14.5%)	
• >5	1(10%)	5(2.4%)	6(2.8%)	1(1.4%)	
• Mean ±SD	7.00±2.82	4.39±2.16	4.16±1.92	3.46±2.02	
Endometrial thickness(mm)					
• 6-8	1(10%)	18(8.7%)	17(8%)	5(7.2%)	0.988
• 8-10	4(40%)	98(47.1%)	106(49.8%)	32(46.4%)	
• >10	2(20%)	82(39.4%)	81(38%)	23(33.3%)	
• Mean ±SD	9.61±1.33	10.28±1.48	10.22±1.32	10.09±1.52	
Day of Embryo transfer					
• Day 2	0(0%)	21(10.1%)	34(16%)	19(27.5%)	0.008**
• Day 3	5(50%)	109(52.4%)	94(44.1%)	28(40.6%)	
• Day 5	3(30%)	71(34.1%)	75(35.2%)	16(23.2%)	
Protocol followed					
• Long	2(20%)	44(21.2%)	44(20.7%)	14(20.3%)	0.786
• Antagonist	7(70%)	142(68.3%)	152(71.4%)	46(66.7%)	
• Others	1(10%)	21(10.1%)	14(6.6%)	9(13%)	
Complications					
• No	10(100%)	208(100%)	213(100%)	69(100%)	1.000
• Yes	0	0	0	0	
Age in years					
• <25 years	1(10%)	17(8.2%)	8(3.8%)	0(0%)	0.005**
• 25-30 years	5(50%)	95(45.7%)	84(39.4%)	17(24.6%)	

• 30-35 years	4(40%)	93(44.7%)	116(54.5%)	50(72.5%)	
• 35-40 years	0(0%)	3(1.4%)	5(2.3%)	2(2.9%)	
no of ampules of Gns					
• <20	0(0%)	27(13%)	17(8%)	6(8.7%)	
• 21-40	8(80%)	147(70.7%)	143(67.1%)	43(62.3%)	
• 41-60	1(10%)	31(14.9%)	49(23%)	14(20.3%)	0.012*
• >60	1(10%)	3(1.4%)	4(1.9%)	6(8.7%)	

Table 3: Outcome of IVF/ICSI of women according to BMI (kg/m^2)

Outcome	**BMI (kg/m^2)**				**P value**
	<19.0 (n=10)	**19.0-24.9 (n=208)**	**25.0-29.9 (n=213)**	**30& above (n=69)**	
Days of stimulation	10.30±0.67	11.32±1.35	11.43±1.49	11.67±1.79	0.037*
Number of ampules of Gn	28.20±13.92	30.75±10.94	33.63±11.37	43.97±14.89	0.003**
Follicles>14mm	12.30±6.15	11.32±7.17	10.79±6.73	10.24±6.94	0.626
No of M2 oocytes	5.10±5.63	8.98±4.81	7.62±4.34	6.53±4.96	0.654
Grade of embryo					
• A	6(60%)	188(90.4%)	201(94.4%)	60(87%)	0.593
• B	0(0%)	12(5.8%)	7(3.3%)	3(4.3%)	
No of embryos transferred	2.37±0.52	2.46±0.68	2.49±0.68	2.30±0.66	0.284
ET(Embryo transfer)					
• Easy	8(80%)	198(95.2%)	187(94.4%)	56(81%)	0.045*
• Difficult	0(0%)	3(1.4%)	17(8%)	9(13%)	
• ET cancelled	0(0%)	5(2.3%)	9(4.2%)	4(5.8%)	
CYCLE OUTCOME					
• Cancelled	2(20%)	10(4.8%)	6(2.8%)	6(8.7%)	0.027*
• Negative	5(50%)	123(59.1%)	127(59.6%)	41(59.4%)	0.947
• Positive	3(30%)	75(36.1%)	80(37.6%)	22(31.9%)	0.828
Oocyte retrieval rate	89.29±43.52	91.57±17.55	106.29±17.89	86.19±17.02	0.012*
Fertilization rate	91.11±26.67	91.67±15.82	91.44±15.61	93.41±14.02	0.854
Cleavage rate	88.88±33.33	97.22±9.36	96.41±10.42	98.90±5.08	0.040*
Implantation rate	15.00±33.74	13.26±24.36	16.35±27.35	16.87±28.17	0.621
Outcome					
• Biochemical pregnancy	0(0%)	16(7.7%)	15(7%)	2(2.9%)	0.438
• Ectopic	0(0%)	2(1%)	1(0.5%)	0(0%)	0.817
• Missed abortion	0(0%)	6(2.9%)	9(4.2%)	4(5.8%)	0.630
• Single	1(10%)	42(20.2%)	44(20.7%)	14(20.3%)	0.879

• Twins	1(10%)	7(3.4%)	8(3.8%)	3(4.3%)	0.749
• Triplets	0(0%)	1(0.5%)	4(1.9%)	0(0%)	0.388
• Quadruplets	0(0%)	0(0%)	0(0%)	1(1.4%)	0.100

Figure 2-

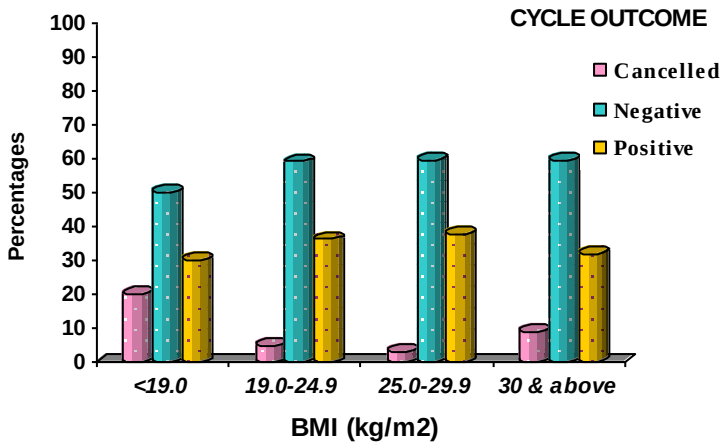

Figure 3-

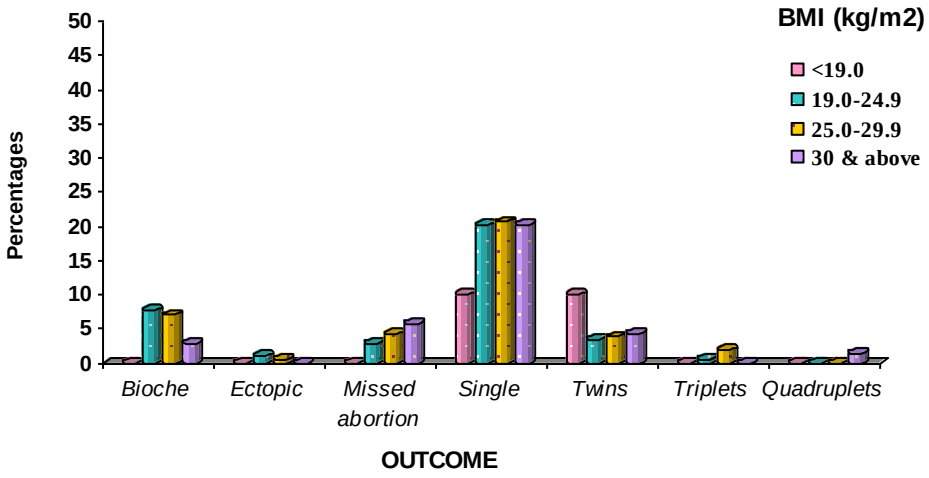

Table 4: Outcome of IVF/ICSI of women according to BMI (kg/m^2)

Outcome	BMI (kg/m^2)				P value
	<19.0 (n=10)	19.0-24.9 (n=208)	25.0-29.9 (n=213)	30& above (n=69)	
CPR	2(20.0%)	58(27.9%)	66(30.9%)	12(17.4%)	0.163
LBR	2(20.0%)	50(24.1%)	56(26.3%)	18(26.1%)	0.929

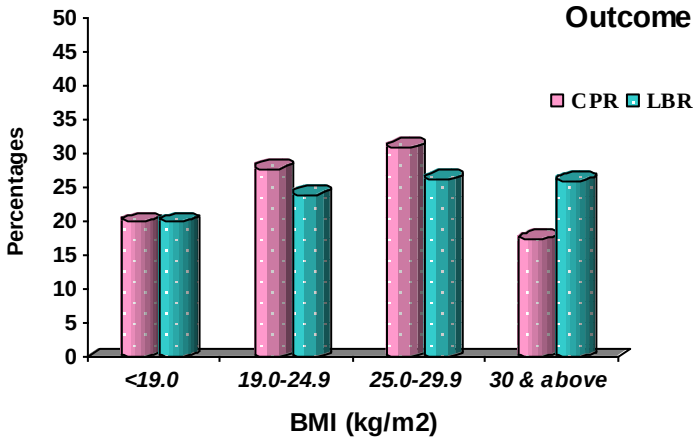

Figure 5

IV. DISCUSSION

In our study, as per age distribution, 54.6%(273/500) were in age group>30years and 45.4%(227/500) were <30years age. Group A is underweight which comprised of 2%(10) patients, 41.6% (208) in group B (Normal BMI), 42.6%(213) in group C (overweight) and 13.8%(69) in group D (obese).Mean duration of infertility was 5.27±2.49 years in group B and in group C it was 5.63±2.54 years .Among the causes of infertility in all patients, most common was male factor in form of oligospermia, severe oligoasthenozoospermia, necrospermia, asthenozoospermia, azoospermia or sexual dysfunction in 60%(6) in group A,58.7%(122) in group B,62.9%(134) in group C and 65.2%(45) in group D followed by the tubal factor(20%),unexplained infertility(15%),ovulatory dysfunction and mixed causes in remaining patients(**Table 1**).

Number of frozen embryos were more in group B and C as compared to A and D though not statistically significant(p=0.849).Endometrial thickness was 8-10mm in 98(47.1%) in group B,106(49.8%) in group C as compared to 4(40%) and 32(46.4%) in groups A and D with p=0.988(statistically non significant). Day 2/3 embryo transfer was done in 62% of patients and in remaining blastocysts were transferred in our clinic(p=0.008).

Dosage of gonadotropins was high in overweight and obese group such that 41-60 ampules were used in 23% in group C compared to 14% in group B(**Table 2**).

The primary and secondary outcomes of our study are depicted in **Table 3**.

Days of stimulation were more in group C(11.43±1.49 and group D(11.67±1.79) with p=0.037.

Dosage of gonadotropins was more in overweight and obese patients(p=0.003) compared to normal BMI and underweight groups.

Number of dominant follicles, number of mature (M2,Metaphase 2) oocytes,number of grade A(good quality) embryos formed and frozen were more in normal weight and overweight patients(groups B and C) as compared to extremes of BMI variations(underweight and obese) though not statistically significant.Mean number(2.46±0.68)of embryos transferred were comparable in four groups with p=0.289.

90% of embryo transfers done were easy. Difficult embryos transfers were more in group C(8%) and group D(13%) compared to group A(none,0%) and group B(1.4%).

Embryo transfer was cancelled in 9(4.2%) patients in group and 4(5.8%) in group D as compared to 2.3% in group B and none in group A(p=0.045)(**Figure 2**).

Ooocyte retrieval rate was high in group B(91.57±17.55) and group C(106.29±17.89) as compared to group A and D. Fertilization rate was comparable. Cleavage rate was high in groups B,C and D as compared to group A (p=0.040).Implantation rate was almost similar in all four groups(16-17%) with p=0.621.Pregnancy rate was 38% in group C(maximum) followed by 36% in group B,31% in group Dand 30% in group A(p=0.828) so it was comparable statistically(non significant).

Number of miscarriages were maximum in overweight and obese patients but comparable to normal BMI group with p=0.630(**Figure 3**).

In our study out of 500 patients recruited, 171 were pregnant so overall pregnancy rate was 34%(171/500) with clinical pregnancy rate of 31% and 28% in overweight and normal BMI patients as compared to 17% and 20% in obese and underweight patients in comparable age group(p=0.163)(**Table 4,Figure 4**).

While live birth rate was upto 26% in group C and D as compared to 20% and 24% in groups A and B(p=0.929).

So concluding that in terms of primary outcomes, pregnancy rate was comparable with comparable rates of biochemical pregnancies, missed abortions, ectopic pregnancies, singletons and multiple pregnancies but on further analysis we found that there was difference in clinical pregnancy rate and live birth rate in all four groups such that these rates fall drastically on either side of extremes of variation in BMI though not statistically significant(p>0.05).

In summary, this study suggests that obesity is associated with lower clinical pregnancy and live birth rate and the need for higher and longer period of FSH stimulation due to impaired

ovarian response but underweight was not related to an impaired outcome.

The study has some significant strength. First of all, the major strength was its prospective nature. In the literature, most of the data about this topic has been based on retrospective studies or pooled data, thus allowing potential for observer bias.

Another advantage was, this study included only first ART cycle. There are many studies including more than one cycle of the same participants. In this situation, undiagnosed bad prognostic factors of an individual may cumulatively effect on results.

Lastly, we calculated BMI of the participants at the beginning of ovarian stimulation. In the Literature, some studies encompassed patients with BMI assessed within the last one year or last six months. However, there is no doubt that significant weight changes may have occurred in this time interval.

In conclusion, our results indicate that obesity and overweight is associated with reduced pregnancy rates and increased requirement gonadotropin for ovulation induction. This information is valuable for counselling couples before initiation of ART. Obese and overweight patients should be strongly encouraged to loose weight before starting ART. Actually optimal BMI should be a pre-requisite before recruiting the patients for the controlled ovarian stimulation(COS).

V. CONCLUSIONS

Clinical observations on the effects of body weight during IVF and ICSI are conflicting. In overweight/obese compared with normal weight women, increased FSH requirement during ovarian stimulation, fewer collected oocytes, decreased serum estradiol concentrations, frequent cycle cancellations and low pregnancy rate have been observed

Obesity is associated with an increased risk of early pregnancy loss occurring before 6 weeks gestation. Positive correlation between BMI and gonadotropin requirement during stimulation and negative correlation between BMI and number of collected oocytes is observed.

Dosage of gonadotropins is high with more days of stimulation in overweight and obese group.

Number of dominant follicles,number of mature (M2,Metaphase 2) oocytes,number of grade A(good quality) embryos formed and frozen are more in normal weight and overweight patients as compared to extremes of BMI variations(underweight and obese) though not statistically significant.

Difficult embryos transfers with more of embryo transfers cancelled in obese and overweight such that the visibility on ultrasound guided embryo transfer is poor in case of overweight and obese patients as compared to normal weight and underweight patients.

Implantation rate ,pregnancy rate and miscarriage rate was comparable but live births are high in normal weight and overweight as compared to extremes of BMI due to high number of miscarriages in extremes of BMI though not statistically significant.

It appears that it may be appropriate to recommend weight loss prior to IVF in patients especially in young patients whereas in older patients, a more immediate and aggressive approach to ART may be warranted.

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