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Success of IUI in Women with Unexplained Infertility: Evaluation of Predictive Factors

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Abstract

***Objective:** To evaluate the predictive factors associated with successful intrauterine insemination (IUI)*

***Methods:** A prospective observational study included 130 women with unexplained infertility and planned to IUI after controlled ovarian stimulation. The semen was prepared by swim up technique and IUI was done 24 hours after hCG injection using 0.3 -0.5 ml of sperm suspension using sperm transcervical catheter attached to a 1 ml tuberculin syringe*

***Results:** There was a significant difference between the 2 study groups regarding BMI (30.59±4.93 vs. 28.75±2.75, P value 0.05) and paternal age (27.2±5.24 vs. 31.3±5.9, P value 0.05).*

There was a highly significant difference between the 2 study groups regarding maternal age (24.84±3.64 vs. 27.7±4.36, P value <0.001).

There was a highly significant difference between pregnant and non pregnant women regarding sperm count before (78.06±24.21 vs. 54.87±34.04) and after processing (63.87±23.047 vs. 40.93± 19.377), sperms with progressive motility after processing and total motile sperms after processing (30.00± 7.303 vs. 23.74± 8.93) (P value <0.001).

Pregnant women showed a significantly higher number of follicles (3.03 ± 1.18 vs. 2.18 ± 0.95), larger follicles (21.84±2.38 vs. 19.9±1.89)and thicker endometrium (11.29±1.49 vs. 8.42±1.73)than non pregnant ones (P value <0.001).

***Conclusion:** Maternal age, Body mass index, paternal age, the sperm count before and after processing, sperms with progressive motility evaluated after processing and the number of total motile sperms evaluated after processing, the number of follicles, size of largest follicle and endometrial thickness are highly predictive of success of IUI*

Key Message Points

- *IUI is one of the lines of treatment of couples with unexplained infertility.*
- *Many maternal, paternal factors affect IUI success.*
- *Maternal age, BMI, the number of follicles , size of largest follicle and endometrial thickness are highly predictive of success of IUI*
- *Paternal age, the sperm count , progressive motility and the number of total motile sperms are highly predictive of success of IUI.*

Keywords: *Intrauterine insemination; unexplained infertility; sperm count; maternal age; follicular count; endometrial thickness.*

Introduction

Unexplained infertility refers to the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception despite a thorough evaluation, or after six months in women 35 and older [1].

It accounts for nearly 40% of female infertility[2] and 8% to 28% of infertility in couples[3].The reported incidence of unexplained infertility varies according to the age and selection criteria in the study population[4]

Controlled ovarian hyperstimulation (COH) combined with intrauterine insemination (IUI) is widely used in first line treatment of unexplained and male factor infertility before In Vitro Fertilization (IVF) treatment[5].

The rationale for the use of intrauterine insemination (IUI) in the management of unexplained infertility is to benefit from the deposition of a bolus of concentrated, motile, morphologically normal sperm as close as possible to the oocyte[6].

IUI has been shown to be a much less expensive and less invasive procedure in comparison with the in vitro fertilization-embryo transfer (IVF-ET) [7].

The success rates for IUI vary between 5 and 155 per cycle attempt depending on a number of factors including maternal age.

In the latest statistics from Australian Institute of Health and Welfare (AIHW), 2390 cycles of IUI resulted in a pregnancy rate of 14.5% and live delivery rate of 11.1%[8].

Following IUI, pregnancy rates vary widely due to multiple factors including heterogeneity and variability of studied patients and parameters [9].

There are numerous factors that might influence the success rates in COH–IUI cycles as women's age, etiology and duration of infertility, semen parameters, sperm preparation methods, IUI timing, ovarian hyperstimulation protocol, number of pre-ovulatory follicles and premature LH surge [10,11].

Semen quality and several seminal parameters such as sperm motility and their normal morphology might be strong predictors of IUI success [12,13].

The objective of our study is to evaluate the predictive factors associated with successful IUI.

Material and Methods

The present two center prospective observational study included women who attended the infertility clinic at Kasr El-Aini Hospital and Beni-Suef hospital, Egypt, between May 1, 2015, and June 31, 2016. The study was approved by the local Ethics Committee (kasr AlAiny ethical committee approval number 234529) and informed written consent was obtained from all participants.

Patient and Public Involvement

The development of the research question and outcome measures were informed by the patient by a professional health care providers with more than 10 years' experience in the field of infertility. All approving women attending the infertilityclinic at Kasr Alainy hospital with unexplained infertility were involved. The participants were not involved in the design of this study. The results will be disseminated to study participants through direct personal contact. In our study burden of the intervention was assessed by both the patients and the investigators

The number of cases 130 had a power of at least 75% to discriminate an IUI success difference of 20%; as well as differences between successful and unsuccessful groups of 5000/ cu mm (10-15) in sperm counts, of 0.25 (1.75-2) in mean mature follicles, of 2 mm (8-10) in ET, assuming standard deviations of 8, 0.5 and 3 respectively.

Our study included 130 women with unexplained infertility and planned to IUI after controlled ovarian stimulation (COH). The diagnosis of unexplained infertility was done through the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception despite a thorough evaluation [14]. Inclusion criteria was normal semen analysis according to World Health Organization criteria [15], patent tubes confirmed by HSG or laparoscopy, normal hormonal profile including day 3 FSH , LH and AMH and Day 21 progesterone, age less than 40 years old, regular menstrual cycle.

Exclusion criteria were the presence of any ovarian cyst detected by ultrasound , uterine lesions as submucus polyp. Women with hormonal disorders as PCOS/anovulatory patients, thyroid or pituitary disorders , those with stage III and IV endometriosis

and women with sensitivity to stimulation drugs were also excluded from our study.

COH was conducted with 100 – 150 mg of oral clomiphene citrate (Clomid GNP, 6th October, Egypt) for 5 days starting on day 3 of the menstrual cycle dose selected according to BMI, patients were monitored by transvaginal ultrasound starting from cycle day 8 every two days for follicular size and numbers and endometrial thickness and pattern. If no adequate response daily injection of 150 IU of human menopausal gonadotropin (hMG;Menogon; Ferring Pharamceutical Co, Germany)(only 2 women needed 3 ampoules) When one or more leading follicle or more reached a mean diameter of 18 mm, trigerring of ovulation using 5000 IU of hCG (Chriomon IBSA, Switzerland) intramuscularly. IUI was done 24 hours after hCG injection[16].

Semen was obtained by masturbation in a sterile container after 4 days of abstinence within 2 hours of insemination time. It was left at room temperature for 30 minutes to liquefy and subsequently assessed. The semen was prepared by swim up technique in which an equal volume of sperm washing medium (Earle´s Balanced salt solution, sigma- Aldrich Chemie company, UK) was used then centrifugation at 400Xg for 10 minutes was done. The resultant supernatant was discarded and the pellets were broken and overlayered with 0.5 ml of Earle´s solution with HEPS buffer then incubated at 37 in 5% CO2 for 30-45 minutes to allow the most active motile sperms to swim up into the solution which was then carefully removed.

IUI was done using 0.3 -0.5 ml of sperm suspension using sperm transcervical catheter (sperm processor, Aurangabad, India) attached to a 1 ml tuberculin syringe. Slow injection of the suspension into uterine cavity after cervical exposure with Graves speculum after cleaning the cervix with saline. Patients remained in the supine position for 30 minutes after insemination. Patients are instructed to have intercourse 24 hours after IUI and every 2 days for 1 week. All patients received luteal phase support in the form of natural progesterone 100 mg three times daily (Utrogestan , October pharm, Egypt) for 2 weeks till serum β HCG was done and continued for 1st 12 weeks if positive.

The primary end point was clinical pregnancy rate defined as the presence of gestational sac using transvaginal ultrasound done 5 weeks after IUI.

Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Wilcoxon; ranked test for unrelated data (Z-test) and Chi-square test (X^2 test) for variability between groups. Statistical analysis was conducted using the

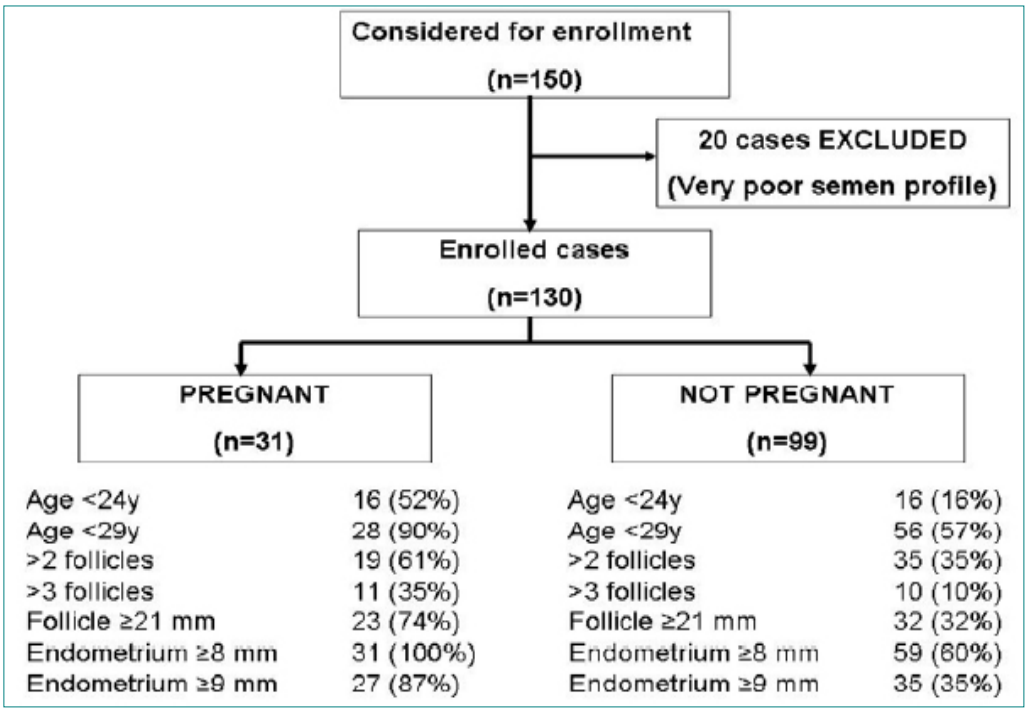


Figure 1. *Flow chart of the studied population*

There was no significant difference between the 2 study groups regarding type of infertility, duration of infertility or the number of previous IUI cycles (Table 1).

There was a significant difference between the 2 study groups regarding BMI and paternal age (Table 1).

There was a highly significant difference between the 2 study groups regarding maternal age (Table 1).

Table 1. *Baseline characteristics among the study population*

		Pregnant (31)	Nonpregnant (99)	P value
Age (years)		24.84±3.64	27.7±4.36	<0.001
BMI (Kg/m^2)#		30.59±4.93	28.75±2.75	0.05
Duration of infertility (years)		4.29±1.77	5.24±2.58	0.058
Type of infertility *	1ry	19 (61.3%)	64 (64.6%)	0.08
	2ry	12 (38.7%)	35 (35.4%)	
Previous IUI		0.52±0.72	0.48±0.71	0.831
Male age		27.2±5.24	31.3±5.9	0.05

Data are presented as mean ± SD * Data are presented as number (percent) # BMI Body Mass Index

There was a highly significant difference between pregnant and non pregnant women regarding sperm count before and after processing, sperms with progressive motility after processing and total motile sperms after processing, while there was no significant difference between the two groups regarding motility before and after processing, progressive motility before processing or TMS before processing (Table 2).

There was no significant difference between the 2 study groups regarding hormonal profile named FSH, LH, FSH/LH ratio , E2 level or Progesterone level (Table 2).

Regarding the stimulation cycle characteristics, pregnant women showed a significantly higher number of follicles, larger follicles and thicker endometrium than non pregnant ones (Table 2).

Table 2. *Semen parameters, hormonal levels and stimulation cycle characteristics among the study population*

			Pregnant	Nonpregnant	P value	OR (95% CI)
Semen	Count	Before	78.06±24.21	54.87±34.04	0.001	10.06 - 36.13
		After	63.87±23.047	40.93± 19.377	<0.001	14.68 – 31.21
	Motility	Before	30.97±12.61	27.39±13.93	0.21	-1.979 - 9.126
		After	58.06± 16.617	51.52± 18.119	0.076	-0.69 – 13.79
	PR	Before	10.65±4.78	8.97±5.37	0.12	-0.459 - 3.810
		After	30.00± 7.303	23.74± 8.93	0.001	2.77 – 9.76
	TMS	Before	25.03±13.99	17.33±22.91	0.79	- 0.92 - 16.32
		After	37.68± 17.018	20.90± 12.440	<0.001	11.22 – 22.34
Hormonal	Day 3 FSH (IU/L)		6.06±1.38	6.40± 2.069	0.390	-0.443-1.129
	Day 3 LH(IU/L)		7.78±4.42	6.48±3.57	0.097	-2.847- 0.238
	FSH/LH ratio		1.03±0.54	1.19±0.71	0.233	-0.108-0.44
	E2(pg/ml)		46.19±19.69	41.09±22.24	0.255	-13.93- 3.729
	P4		13.03±6.21	10.27±6.44	0.038	-5.366 - -0.161
Cycle characteristics	Number of follicles		3.03 ± 1.18	2.18 ± 0.95	<0.001	0.483-1.212
	Largest follicle (mm)		21.84±2.38	19.9±1.89	<0.001	-2.761- -1.118
	Endometrial thickness (mm)		11.29±1.49	8.42±1.73	<0.001	-3.556- -2.189

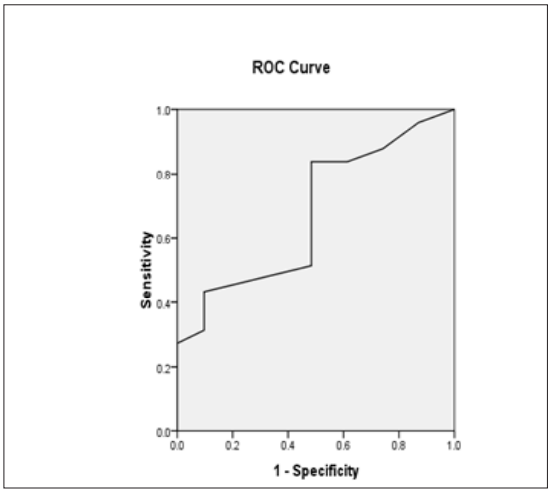
Data are presented as mean ± SD

PR Progressive motility; TMS Total motile sperm; FSH Follicle stimulating hormone; LH Luteinizing hormone; E2 Estradiol; P4 Progesterone

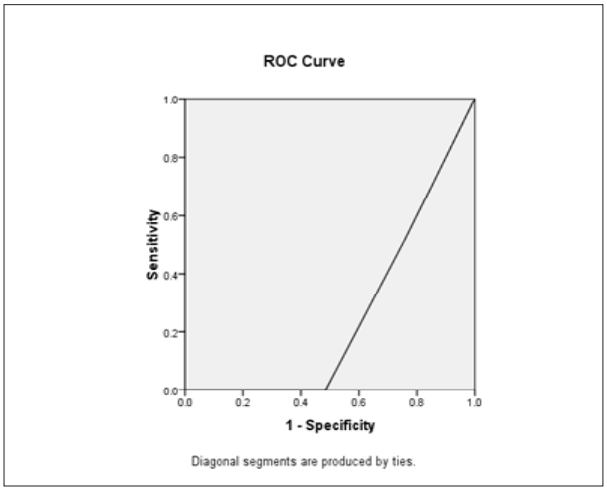
Table 3 and figure 2 shows the cut-off value, sensitivity, specificity, PPV, NPV and accuracy of different factors with 100 % sensitivity of endometrial thickness more than 8 mm. The highest specificity and accuracy was found with maternal age less than 24 years old.

Table 3. *Cut-off, sensitivity, specificity, PPV, NPV and accuracy of effective factors*

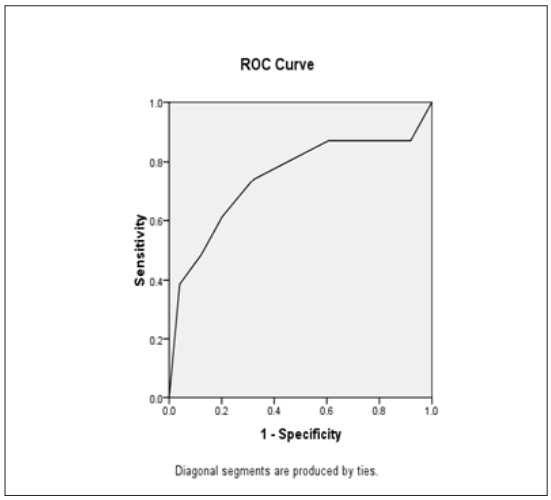
	Cut-off	Sensitivity	Specificity	PPV	NPV	accuracy	OR	AUC
Maternal age (years)	< 24	51.61	83.84	50	84.69	76.15	3.194	0.676 (0.57-0.78)
	< 29	90.32	43.43	33.33	93.48	54.62	1.597	
Duration of infertility (years)	<4.75	74.19	48.48	31.08	85.71	54.62	1.44	0.571 (0.47-0.68)
	<6	87.1	36.36	30	90	48.46	1.369	
Number of follicles	>2	**61.3**	**64.6**	**35.2**	**84.2**	**63.8**	**1.73**	0.746 (0.59-0.82)
	>3	**55.5**	**89.9**	**52.4**	**81.7**	**76.9**	**3.51**	
largest follicle	≥21	74.19	67.68	41.82	89.33	69.23	2.295	0.746 (0.63-0.86)
Endometrial thickness (mm)	≥8	100	40.4	34.44	100	54.62	1.678	0.879 (0.82-0.94)
	≥9	87.1	64.65	43.55	94.12	70	2.464	



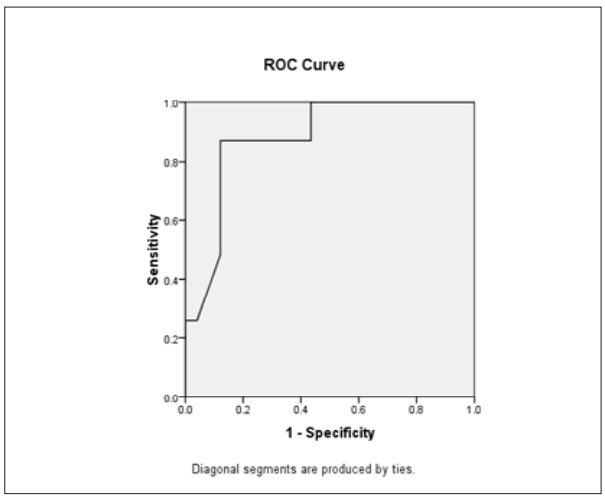
A (AUC 0.676)



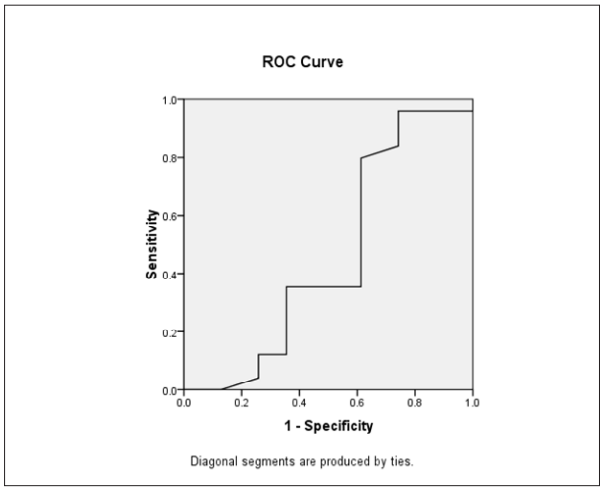
B (AUC 0.254)



C (AUC 0.746)



D (AUC 0.879)



E (AUC .459)

Figure 2. *ROC curves for different factors*

A Age; B Follicular number; C LARGEST FOLLICLE DIAMETER ; D Endometrial thickness; E Body mass index

SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Flow charts of the studied population is shown in figure 1

Discussion

Our study confirmed that the maternal age, Body mass index, paternal age, the sperm count before and after processing, sperms with progressive motility evaluated after processing and the number of total motile sperms evaluated after processing, the number of follicles , size of largest follicle and endometrial thickness are highly predictive of success of IUI.

The decrease fertility with advancing maternal age is well known and that eventually affects the success of IUI. Fertility begins to decline from age 25. This is due to a decline in oocyte quality such as aneuploidy rather than merely decreasing oocyte numbers [17].

Fertility is also affected by BMI. The insulin resistance and hyperinsulinemia in obese women leads to hyperandrogenemia. The sex hormone-binding globulin (SHBG), growth hormone (GH), and insulin-like growth factor binding proteins (IGFBP) are decreased and leptin levels are increased. Thus, the neuro-regulation of the hypothalamic-pituitary-gonadal (HPG) axis deteriorates[18]. These alterations may explain impaired ovulatory function and so reproductive health.

Increased male age is a risk factor for infertility. It is related to falling androgen levels, decreased sexual activity, alterations in sperm motility and morphology, and deterioration in sperm quality and DNA integrity. Time to pregnancy (TTP) increases with increasing male age [19].

Our study also found that the highest sensitivity of predictive value was achieved with number of follicles more than 3 and endometrial thickness more than 8 mm while the highest specificity was achieved with maternal age less than 24 years and number of follicles more than 2.

The highest accuracy of predictive value was found with maternal age less than 24 years.

Many variables may influence success rates after IUI. Normal morphology of the sperms and their progressive motility has higher sensitivity andspecificity for prediction of IUI success[20].

In 301 infertile Saudiwomen treated with IUI the pregnancy rate was approximately 10% for agegroups between 19 and 40. While after 40 it declinednoticeably, which means that direct IVFtreatment would be in their favor. There was apositive but not statistically significant correlationof pregnancy rates with BMI[21].

One study suggested thatfemale age, duration of infertility, cause of infertility, menstrual irregularities, ejaculatory volume and total dose of gonadotropin be the most importantprognostic factors in predicting successfuloutcome of IUI[22].

Woodward and colleagues suggestthat provision of stimulated IUI, in centres where asatisfactory live birth rate is achieved, represents a significantcost-saving to those commissioning fertilityservices with lower risks than IVF and an improvementon providing no treatment[23].

The main limitation of our study is the inability to follow up pregnant women to study the incidence of abnormal pregnancies with abortions to correlate it with the predictive value. Another limitation is the lack of data about abnormal forms and the type of sperm abnormality as a predictive factor of success of IUI.

The importance of this study is clear. It is to prevent unnecessarycycles and reduce the waiting time to pregnancy andchildbirth by shifting women with high risk for unsuccessful pregnancy after IUI to another ART procedure or at least not to repeat IUI trials in these patients to save timeand costs for the infertile couples and subsequently the unnecessary stress caused by repeated failures of IUI trials.

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