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The Impact of Female Pre-Cyclic and Cyclic Parameters and Semen Analysis Parameters on the Pregnancy Rate in IUI Cycles; a Prospective Study

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Abstract **Original Research Article**

Introduction: Intrauterine insemination (IUI) could be the first-line option in the treatment of infertile couples with different aetiologies before moving to the more sophisticated, expensive and time-consuming techniques. Therefore, this study was conducted to evaluate prognostic factors for IUI success. ***Material and method***: a prospective study conducted between August/2015 and January/ 2019, 188 IUI cycles were done during the study period for infertile couples attending Albayda Fertility Centre/Libya. The baseline clinical and biological characteristics were compared between the pregnant and non-pregnant groups. The pre- and post-preparation semen parameters for the husbands of both groups were also compared. Regression analyses were performed to identify the most explanatory factor for the occurrence of the clinical pregnancy after Controlled ovarian hyperstimulation (COH) and IUI. ***Results:*** the clinical pregnancy rate was 17% per cycle and 19.6% per couple. The clinical pregnancy rate was significantly and positively associated with the endometrial thickness (OR=1.4, p=0.023), and shows a significant inverse correlation with wives'age (OR=0.90, p=0.016). ***Conclusion:*** this study confirms the efficacy of IUI as an effective modality of infertility treatment. Wifes' age and endometrial thickness were the strongest predictors for IUI success.

Keywords: subfertility, wife's age, infertility duration, intrauterine insemination, endometrium, pre-ovulatory follicle, semen analysis.

INTRODUCTION

Subfertility is defined as the inability of the couples to conceive after trying for at least 12 months of regular unprotected intercourse [1, 2]. Intrauterine insemination (IUI) with controlled ovarian hyperstimulation as treatment of infertile couples afford a reasonable chance of conception for numerous infertility aetiologies [3]. As mentioned in the literature, IUI and COH result in pregnancy rates between 8 and 19.6% [4-6]. A study conducted in our center found that the clinical pregnancy rate and the live-birth rate after IUI and COH were 15.5%, and 8% respectively [7]. This wide range difference in the success rate between the studies could be due to the variations in the patients' criteria, stimulation protocol or difference in the reference criteria for semen analysis and in the preparation of semen sample.

COH-IUI was associated with higher ongoing pregnancy rates and live birth rates compared to expectant management [8,9]. Furthermore, a study conducted on couples with unexplained infertility found that the live birth rate was higher with stimulated IUI than those with Natural IUI cycle [10]. The same study [10] reported that, in stimulated cycles, the live birth rate was higher in the IUI group than those who were having timed intercourse. Moreover, in a multicentre randomized trial conducted in the Netherlands, the effectiveness of IUI-COH was found not to be inferior to IVF with a single embryo transfer or IVF in a modified natural cycle [11].

In addition to the acceptable pregnancy rate following COH and IUI, IUI has the advantage of being a simple and non-invasive technique, a cost-effective strategy, with minimal risk for complications such as ovarian hyperstimulation syndrome (OHSS), therefore IUI has good couple compliance [11]. However, IUI resulted in a reasonably higher rate of multiple gestations [11], which was not supported by the Cochrane review [10].

In view of these results, IUI could be the first-line option in the treatment of infertile couples with different aetiologies and an unfavourable prospect for natural pregnancy before moving to the more sophisticated, expensive and time-consuming techniques. In support of this, 96% of fertility clinics in the UK continued to offer IUI as a first-line fertility treatment strategy [12, 13].

The purpose of our study was to determine female and male prognostic factors for predicting COH and IUI success. This may offer the possibility of developing IUI guidelines which could help the physician to make a better clinical decision for the patient's selection, who is more likely to conceive with IUI.

MATERIALS AND METHOD

Design: a prospective study conducted at Albayda Fertility center (afc.med.ly), a Governmental Teaching Centre in Albayda/Libya. The study received ethical approval from the local ethics committee (Ethics Reference Number: AG 12/12/59& amendment date: 1 June 2015) and the couples were counselled before the commencement of the COH and IUI.

Participants: a total of 188 IUI cycles were performed on 157 couples with primary or secondary infertility between August 2015 and January 2019 with different infertility aetiologies.

All couples had been trying to conceive for at least 1 year before their enrolment in the study. However, those having menstrual or sexual problems likely to affect conception or when the wife was aged 35 years or more were included earlier. After the initial evaluation of detailed infertility-related history and basic examination, the infertile couples underwent standard evaluation for infertility. Including at least two seminograms, after abstinence of 3-5 days, were performed and semen parameters were interpreted by two well-trained technicians according to standardized methods using the WHO (2010) criteria [14]. On the second or third day of the menstrual cycle (baseline), a detailed transvaginal ultrasonography scan Transvaginal scan (TVS) with a high-resolution ultrasound scan machine (sonix ultrasound machines/BK ultrasound) was performed to exclude any possible pelvic pathology, to assess the endometrial cavity and the antral follicular count (AFC). The baseline hormones-related fertility profile was analyzed; follicular stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), thyroid stimulating hormone (TSH), prolactin. Anti-Mullerian hormone (AMH) was done for young patients with low AFC. Hysterosalpingogram (HSG) and/or laparoscopy were used to assess the tubal patency. Inclusion and exclusion criteria listed in Table 1.

Superovulation Protocol

On the second day of the menstrual cycle, the eligible wife received either oral clomiphene citrate (100 to 200 mg daily) or letrozole (2.5 mg or 5 mg daily) for five days. Letrozole mainly used for patients with polycystic ovarian syndrome (PCOS). On the third day, gonadotropin injections (GnH) were given intramuscularly daily. The initial dose of gonadotropin prescribed (75–150 IU/day) depended on the woman's age, hormonal profile, and infertility duration. The initial dose was maintained for six days. The patient's response to ovulation induction was assessed by serial TVS ± E_2 level. Ultrasonography was used to assess the follicular size and number and the endometrial thickness (EMT) and pattern. The gonadotropin dose was adjusted according to the patient response until at least two follicles reached ≥17 mm were obtained to give the trigger for ovulation. If EMT is less then 7mm, oral tablet progynova 2 mg and/or per-vaginal viagra 50 mg tablet was given daily and continued during the luteal phase. Once the above-mentioned criteria for ovulation trigger were met, intramuscular injection of 5000 or 10000 IU of human chorionic gonadotropin (hCG) (manufacturer Merck sharp& Dohme Limited) was given. For the cases at high risk for OHSS, serum estradiol concentration was measured on the day of the trigger. The cycles were canceled if there was a poor response to COH or for the wife was at high risk to develop OHSS (a large number of follicles ≥17 mm and the E_2 on day of trigger > 3500 ng/ml).

Semen preparation Protocol

Semen specimens were collected by masturbation near the lab inside the centre after 3-5 days of abstinence. After 30 minutes of liquefaction with a buffer solution (G-MOPsTM vitrolife) at room temperature, the freshly ejaculated semen samples were assessed according to the WHO (2010) laboratory manual for the examination and processing of human semen.

The standard swim-up technique was used for semen preparation; the media used was (G-GAMATETM vitrolife). After the semen liquefaction, centrifugation was done slowly at 1000–1500 rpm (g Force 1.350- 2.454) and the supernatant was discarded. This step was repeated 1-2 times according to the sample. The remaining sperms were over layered with 1 cc of culture medium (G-GAMATETM vitrolife) and stored inside an incubator at 37^{o}C for 30- 60 minutes; so, the most actively motile sperms will migrate to the supernatant and be used for IUI. The post-preparation semen parameters then evaluated and 0.7 ml of the prepared semen sample was loaded on an IUI injection catheter. The above-mentioned steps were conducted by two well-trained lab technicians. All pre- and post-preparation semen parameters were recorded (shown in Table 2).

Intrauterine Insemination Protocol

All the participants were educated about the prohibition of intercourse and the use of non-steroidal anti-inflammatory drugs (NSAIDs) for at least 72 hours before the IUI. 34 to 36 hours after the trigger, a single IUI with the freshly ejaculated prepared husband semen was performed. Without anaesthesia and under aseptic conditions and ultrasound scan guide, the IUI catheter was gently entered into the uterine cavity through the cervical orifice and the prepared semen then injected. According to the protocol, the patients remained supine for 15 minutes and the couples advised to have sexual intercourse the next day. Supplemental natural micronized progesterone vaginal pessary (cyclogest®) was provided during the luteal phase.

Outcome Evaluation

Serum β-hCG test to diagnose pregnancy done for those did not get the menstrual period 14 days after insemination. One week later, an ultrasound scan was performed in the centre for those with positive pregnancy tests to confirm pregnancy, its location, viability and the number of sacs. Clinical pregnancy defined as the presence of intrauterine pregnancy with fetal cardiac activity (FCA). Pregnant patients were followed up in our clinic with full antenatal care services till term. Birth outcome details were obtained for most cases and might be used for further studies.

Main Outcome Measures

Clinical pregnancy rates were analyzed according to wife's age, BMI, pre-treatment infertility related hormones, the duration and type of infertility, tubal patency, the number and size of pre-ovulatory follicles and EMT and pre- and post-preparation semen parameters.

Statistics

All the data entered and analyzed by using SPSS software (version 25). The means of the continuous variables were compared using the independent t-test. The categorical variables were compared for significant differences using the Chi-square test. A P-value of <0.05 was considered to be significant. Logistic regression analysis was used to determine whether there was an association between the dependent variable (clinical pregnancy) and the predictors (clinical and biological characteristics of the couples). Backward regression also applied to find out the most explanatory prognostic factors for predicting IUI success.

RESULT

188 COH/IUI cycles were conducted between August/2015 and January/2019. The female mean age was 34 (6.5) years and the majority aged between 25-35 years; their BMI was 28.8 (5.8). The duration of infertility ranged between 1-17 years and with a mean duration of 5.3 (4) years. The means the basal hormonal values were [FSH: 8 (2.5) IU/ml; LH: 6.3 (3) IU/ml; E2: 48 (21) pg/ml; and normal prolactin and TSH level.

As shown in Figure 1, the most common cause of infertility in both groups (pregnant and non-pregnant) was a female factor, followed by unexplained infertility. PCOS was the most common cause among the female factor in both (75% of pregnant and 60% of non-pregnant).

Both Clomid tables and injectable GnH were used for ovarian stimulation in 64.4% of the cycles. Femara (letrozole) table with injectable GnH was used in 21% of the cycles and the remaining were received injectable GnH alone. On the day of the trigger; the mean number of the mature follicles (measuring ≥17 mm) was 3.3 (2) with a concomitant endometrial thickness of 8 (1.5) mm.

A total of 32 clinical pregnancies were obtained form 188 cycles, with a pregnancy rate of 17.02% per cycle and 19.6% per couple. According to the clinical outcome, the cases were divided into the following categories; the live birth rate was 50.2 %, the rate of miscarriage was 31.2 %. Two cases of ectopic pregnancy (6.25%) were recorded and both patients were undergone laparotomy and salpingectomy. 3 cases of multiple gestations; 2 cases were twins (6.25%) and only one with a triplet pregnancy, and all the cases of multiple gestations were delivered by emergency caesarean section before 34 weeks because of preterm labour in the twins and abruption placenta in the triplet. Almost all the singleton pregnancy delivered at term by elective caesarean section.

Figure 2 illustrates the pregnancy rate by age subgroups; 35.7% of pregnancy was recorded for women less than 26 years; 16.2% was for subgroup of women between 26-35 years; followed by 15.6% of cases for those aging between 36 and 40 years and the least recorded pregnancy rate (13.8%) was for women aged above 40 years.

As shown in Table 2, the husbands of pregnant women were having significantly higher pre-preparation progressive sperm motility and post-preparation total sperm motility than their counterparts. The two groups did not differ in other semen analysis parameters.

Table 3 shows that, with the exception of wife's age, type of infertility, bilateral tubal patency and the endometrial thickness on the day of trigger; There was no significant difference between the pregnant and non-pregnant women in terms of their BMI, duration of infertility, basal hormonal levels, size and number of the preovulatory follicles.

Univariate regression analysis was carried out to determine whether there was an association between pregnancy and the predictors and the results presented in Table 4. The pregnancy was significantly and positively associated with the EMT (OR=1.4, p=0.03), and shows a negatively significant association with wives 'age (OR=0.90, p=0.02). As displayed in Table 4& 5 none of the other studied female pre- and post-cyclic parameters as well as the pre- or post-preparation semen parameters were significantly associated with the occurrence of pregnancy.

Finally, a backward regression was performed to obtain the most explanatory model for clinical pregnancy in the current study; as illustrated in Table 6; According to the final model, younger wife's age (p= 0.016) and a better endometrial development (p= 0.023) were associated with positive pregnancy outcome.

Neither cases of ovarian hyperstimulation syndrome nor cases of congenital anomalies were reported.

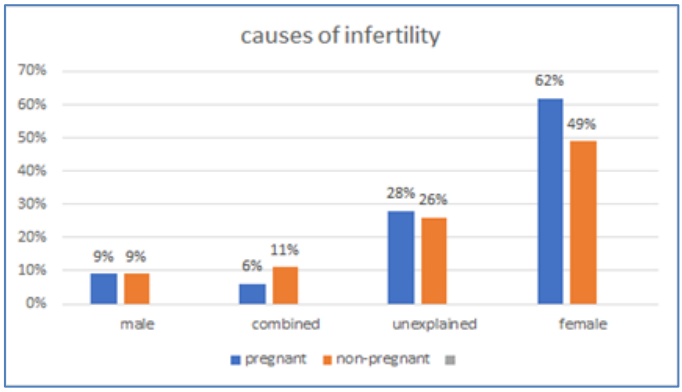

Fig-1: Causes of infertility in the study population

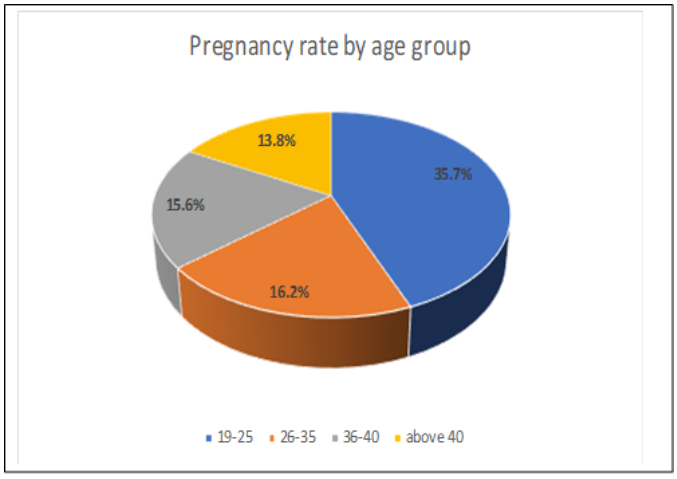

Fig-2: Pregnancy rate according to wifes' age subgroups

Table-1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1- Mild male sub-fertility or male with dysfunctional problems like impotence 2- Female partner with normal pelvic ultrasound scan, 3- Normal hormonal assay with basal FSH not more than 12 ng/ml 4- At least one patent fallopian tube is mandatory	1- Patients who had clinically significant systemic or endocrine disorders. 2- Those with a diagnosis of any space-occupying lesion during HSG or hysteroscopy evaluation such as endometrial polyp, submucous myoma or uterine septum 3- Azoospermia or severely abnormal semen analysis

Table-2: Pre and post preparation semen parameters

Semen analysis	Pre-wash parameters		P-value	Post-wash parameters		P-value
	pregnant	Non-pregnant		pregnant	Non-pregnant	
Sperm count	67.5(43)	63.7(42)	0.6	34.8(24)	29.5(22)	0.2
Total motility	61.8(13)	62(50)	0.9	90.8(6.9)	85.7(12)	0.03*
Progressive motility	43.6(16)	37.8(14)	0.04*	87.8(14)	87.6(52)	0.9
morphology	17.8 (10)	15 (9)	0.1	18(10)	15(8)	0.8

Table-3: Female pre-cyclic and cyclic characteristics

	Pregnant		Non-pregnant		p-value
	Mean (SD)	No. (%)	Mean (SD)	No. (%)	
Wifes' age	32 (7)		34.5 (6)		0.035*
BMI	29.5 (5)		28.4 (5)		0.33
Infertility duration	4.2 (3)		5.5 (4)		0.1
FSH	7.1(2.6)		8 (2.8)		0.1
LH	6.9 (4.7)		5.9 (3)		0.1
E_2	42 (21)		61 (22)		0.8
Endometrial thickness	8.4 (1.4)		7.6 (1.5)		0.02*
Pre-ovulatory follicle size	18.3 (1.2)		18.3(1.8)		0.8
No. pre-ovulatory follicle	3.3 (1.8)		3.3 (2)		0.9
2nd infertility		14/32(43.7%)		58/156 (37.2%)	0.002*
Bilateral tubal patency		28/32(87.5%)		22/156 (14%)	<0.001*

Table-4: Female factors associated with the probability of pregnancy

Covariate	Coefficient	P-value	OR	95% Confidence Interval
Wife' age	- 0.085	0.02*	0.92	0.85, 0.99
BMI	0.4	0.32	1	0.96, 1.1
Infertility duration	- 0.103	0.19	0.9	0.77, 1
Infertility type	0.18	0.66	1.2	0.55, 2.62
Infertility cause	0.06	0.77	0.94	0.63, 1.4
BTP	0.32	0.33	1.4	0.38, 4.9
FSH	0.42	0.15	0.65	0.37, 1.16
LH	0.33	0.12	1.4	0.93, 2.1
E_2	0.007	0.79	1	0.95, 1.1
Endometrial thickness	0.39	0.03*	1.4	0.94, 2.3
Size of pre-ovulatory follicle	0.03	0.84	1.04	0.74, 1.4
No. pre-ovulatory follicle	0.003	0.98	0.99	0.82, 1.2

Table-5: Pre- and post-preparation semen parameter as predictor of pregnancy

Covariate	coefficient	P-value	OR	95% CI
Pre- preparation count	-0.03	0. 1	0.97	0.72, 1.9
Pre- preparation morphology	0.17	0.51	1.2	0.4, 2.5
Pre- preparation total motility	-0.09	0.1	0.9	0.82, 1
Pre preparation -progressive motility	0.09	0.06	1.1	0.98, 1.2
Post-preparation count	0.04	0.25	0.8	0.97, 1.12
Post-preparation morphology	-0.18	0.49	0.8	0.5, 1.4
Post- preparation total motility	0.19	0.06	1.2	0.98, 1.5
Post- preparation progressive motility	-0.03	0.6	0.96	0.82, 1.1

Table-6: Final modal: backward regression

Covariate	Coefficient	P-value	OR	95% Confidence interval
Wifes' age	-0.099	0.016*	0.91	0.83, 0.98
Endometrial thickness	0.35	0.023*	1.4	1.05, 1.9

DISCUSSION

In the current study, the pregnancy rate was 17.02% per cycle and 19.6% per couple. As noticed, the pregnancy rate was higher in the younger age group (<26 years), despite the non-significant difference between pregnant and non-pregnant women with respect to the markers of ovarian reserve (AFC and the basal level of FSH, E2), and number and size of pre-ovulatory follicles. This could be explained by the decline in oocyte quality with aging, which was documented before [15-17].

Those who got pregnant had a significantly higher percentage of secondary infertility and bilateral tubal patency than their counterpart but this did not associate with the achievement of pregnancy after using the univariate regression. The pregnant women were with higher BMI and shorter duration of infertility than non-pregnant ones however the difference did not reach a significant level. The only significant difference between the two groups for the post-stimulation parameters was in the endometrial thickness.

Despite the significant difference in pre-preparation progressive sperm motility and post-preparation total sperm motility between the husbands of pregnant and non-pregnant women; by using logistic regression; neither of these factors affects the pregnancy rate.

After applying backward multivariate regression, most of the studied variables were not significantly affecting the IUI outcome and only women's' age (p= 0.016), and pre-ovulatory endometrial thickness (p=0.023) were significantly affecting the clinical pregnancy rate.

Strength: firstly; it was a prospective study, secondly; all the included patients were Libyan and this might exclude the effect of ethnicity on infertility. The relationship between ethnicity and IVF outcome was investigated, and the clinical pregnancy rate and live birth rate were different between different ethnic groups [16] and this could be applied to the outcome of other assisted reproductive technology (ART). This could be explained by the suggestion that cultural factors might modify ovarian reserve, risk behavior and treatment-seeking for fertility healthcare. Thirdly; to reduce the inter-observed bias, semen analysis and preparation were done by the same technicians. They used the same procedure and reference criteria for semen analysis and preparation for insemination as these procedures may modify sperm characteristics and the result of IUI considerably. Moreover, the follow up during ovulation induction and the insemination were done by three clinicians in the same center.

Weakness, the sample size was the main limitation of the study. As noticed, male factor was low as a cause of infertility among the study cohort and this could be explained by the strict male inclusion criteria, which may affect the predictive value of the male factor in the success rate of IUI.

The clinical pregnancy rate/cycle was 17% and this rate was within the range of 8 and 19.6% reported by previous studies [4-6]. Low pregnancy rate (8.7%) of Kamath *et al* [4] could be a result of their use of strategy aiming for monofollicular development during COH to avoid multiple gestation and OHSS.

In the current study, the live birth rate was 50.2% including the multiple gestations of 9.3%, the rate of miscarriage and ectopic pregnancy was (31.2 %; 9.3% respectively). A study [5] documented a lower pregnancy rate of 12.6% but with a higher live birth rate of 70.6% comparing to ours. A study was done in 2010 [4] reported a lower rate of miscarriage (17%) and ectopic pregnancy rate (4.7%) and no case of multiple gestations as their protocol was aiming for monofollicular development. A higher rate of multiple gestations (13.7%&11%) but a lower rate of miscarriage (23.5%& 22.7%) and ectopic pregnancy (5.9%& 3%) were recorded by other studies [5, 20] respectively.

In our study, wives' age significantly influences the pregnancy rate (p=0.02) supporting previous studies [21, 22]. However, the woman's age did not significantly influence the pregnancy rate as reported by others [23, 24].

In the current work, the highest recorded pregnancy rate (35.6%) was for the age group between 19 and 25 years followed by the nearly same rate for both age groups; 26-35 and 36-40 (16.2% and 15.6% respectively) and for the age group above 40 years the pregnancy rate was only 13.8%. 1038 IUI cycles conducted over 4 years in France [25] reported a pregnancy rate by age group similar to ours of 38.5% and 12.5% for women under 30 and above 40 years respectively. In 1999 a study [22] used the same age group as ours but they reported different pregnancy rates; 18.9%, 26.3, 11.1% and only 5.2% for each group respectively. Nuojua-Huttunen in 1999 [5] reported a low pregnancy rate for women below and above 40 years (13.7% and only 4.1% respectively). Our higher rate of pregnancy for those above 40 years could be because of our strict inclusion criteria (basal FSH $\leq$12 IU/ml and appropriate AFC) and also the exclusion of those with poor response to COH during the follow-up.

The pregnancy rate was higher in women with higher BMI as found in this study, however, as noticed the difference was non-significant (p= 0.33). However, a significantly higher pregnancy rate was reported in women with a higher BMI [24].

Merviel and his workers [25] reported that pre-cyclic FSH level below and above 9.4 IU/L and E_2 level below and over 80 pg/ml had no significant effect on the occurrence of pregnancy. This result was supported by the present study, as basal FSH and E_2 were found to have no effect on pregnancy rate. In contrast, a study [24] documented that pregnancy rate drop with basal FSH level $\geq$ 9 IU/L but the basal E2 above 80 pg/ml was not a relevant pregnancy predictor.

It has been reported that the type of infertility did not show a significant effect on the pregnancy rate [4, 25], and the same was reported in our study. Bilateral tubal patency could not be considered as a predictor for the success of COH and IUI as found in the current study and this was reported by other workers [26, 27].

The short duration of infertility was associated with a higher pregnancy rate however the association was not significant, supporting previous studies [21]. Others [4, 5] reported a significant association between short infertility period and pregnancy rate.

The number and size of preovulatory follicles were not associated with pregnancy in the current study and the same result was documented previously [4]. Others found a significant association between the achievement of pregnancy and the number of mature follicles [24, 25].

The endometrial thickness (EMT) on the day of hCG injection was found to have a significantly positive effect on pregnancy rate in this study supporting a result of previous studies [28, 29]. As the endometrium is considered to be the final site of implantation and therefore, successful pregnancy, so good endometrial development could explain this positive association. These studies reported different values of endometrial thickness at which pregnancy rate was improved; this raises a need for more work to get a cut-off value for EMT for IUI. In contrast to the result of the above-mentioned studies, no evidence for an association between EMT and pregnancy rates was found during OS and IUI as reported in a meta-analysis including 23 studies [30]. The overall quality of the studies included in this meta-analysis was low to moderate and with considerable heterogeneity in the comparisons, making firm conclusions difficult to be made from this meta-analysis.

A decreased pregnancy rate with the severity of oligoasthenoteratospermia was reported [24]. In the present study, none of the studied semen analysis parameters was significantly associated with the success of IUI. Similarly, post-preparation sperm concentration and progressive motility did not affect the pregnancy rate as found by [5]. This could be explained by screening and exclusion of couples with an abnormal semen analysis in both studies.

CONCLUSIONS

Overall, our study confirms the efficacy of COH and IUI with satisfactory clinical pregnancy rates. The strongest predictor of IUI success was the women's age and endometrial thickness on the day of trigger. Larger sample size may help in formulating a better predictive model for IUI success and to have IUI guidelines. This could help couples and clinicians to have better decisions with regards to infertility treatment options.

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