Sana'a University Journal of Medical and Health Sciences
Vol. 2 | No. 1 | Page 16 – 22 | 2023 | https://jpurnals.su.edu.ye/jchm
ISSN : 2958-7476

Impact of duration of Infertility on the Physiological Viability of Sperms Preparing for Intrauterine Insemination among Yemeni Infertile Males

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ARTICLE INFO
Article history:
Received: October 20, 2022
Accepted: December 18, 2022
Published: January, 2023

Keywords
1. Infertility
2. ART
3. IUI
4. Life Birth Rate

ABSTRACT
Background :The duration of infertility should be considered as a factor that may affect the outcome of assisted reproductive techniques (ART).
Aim :The aim of this descriptive study was to examine the outcome of infertility treatment in relation to duration of infertility.
Methods: Sixty nine couples from Allow in vitro fertilization center (IVF) were involved in this work. Intrauterine insemination (IUI) had been done for all couples using the same ART.
Results: The mean age of men was 29.37±0.16 years and the duration of infertility was 4.38±0.25 years with range of 1-12 years. Higher pregnancy and life-birth rates were demonstrated in males suffering from infertility for less than 4 years as compared to those who had infertility for more than 10 years ($P<0.003$, $r = -0.869$). Moreover, abortion rate was higher in men who had infertility for more than 10 years as compared to those who have infertility for less than 4 years ($P<0.0014$).. The linear life-birth rate, in both IVF centers, shows decrease by increase in the duration of infertility. Conclusion: The researchers conclude that by increase in the duration of infertility the outcome of assisted reproductive techniques – IUI will be decreased markedly. In addition to the duration of infertility, the present work recommended to consider the different techniques of sperm preparation in relation *to the ART outcome.*

CONTENTS

Introduction:

Infertility is defined as inability to conceive after 1 year of un-protective intercourse1,2 Pregnancy represents the successful and timely conclusion of series of physiological events: ovulation of a mature oocyte, production of viable sperm, association of oocyte and sperm in the reproductive tract, making of a viable embryo, embryo carriage into the uterine cavity, and embryo implantation within the endometrial cavity. Any disruption in these essential steps

will lead to infertility [3, 4]. Secondary infertility is defined as the inability to become pregnant, or to carry a pregnancy to term, following the birth of one or more biological children [3]. About 30% of the infertile cases are solely attributed to the male partner, 30% to female partner, 25% of cases are caused by a combination of male and female factors and about 15% unexplained infertility [5, 6]. Most of the infertility treatments are dependent on the underlying cause of infertility [7]. Some infertile couples nevertheless need more complex medical intervention like ARTs which is referred to many methods designed to overcome barriers to natural fertilization [8]. Over all, the estimated number of infertile patients treated by ART is around 20%. The goal is to increase the success rate of ART both in term of achieving pregnancy and in making sure that the pregnancy result in a genetically healthy individual [9]. The duration of infertility should be considered as a factor that may affect the outcome of ART. It is unclear the effect of duration of infertility on the outcome of infertility treatment especially semen characteristics of infertile males undergoing IUI, and this subject, in general, is not completely understood.

Aim of the study:

To examine, retrospectively, the outcome of infertility treatment in relation to duration of infertility in infertile couples from two different centers. This multi-central study would give strong evidence and more confidence in the expected results.

Subjects and Methods

Sixty nine couples from "Allow IVF Center", Sana'a - Yemen was involved in this study. All couples were evaluated by the infertility consultant and their medical history was recorded. Semen sample was obtained by masturbation with collection of the ejaculate into a clean, dry, sterile and wide mouthed Petri-dish; this was done after 3-5 days of abstinence. The container was labeled with date and time, names of patient and his wife, and their file number. The sample was transported to the laboratory immediately and placed in an incubator at 37ºC till complete liquefaction. A drop of 10µL of liquefied and thoroughly mixed semen was taken by Eppendorff automatic pipette, mounted between warm slides and covered with a standard cover slip (22×22) mm. The sample was examined by light microscope under magnification of 40X objectives. The semen was analyzed macroscopically and microscopically using the standardization of World health Organization[10].

The male factor infertility had been treated by conventional treatment of male infertility and involved in the ART. IUI had been done for all couples involved in the present study using the same ART[3]. The overall outcome of this treatment had been analyzed in correlation to their duration of infertility.

were used depending on the nature of the data. In addition to standard statistical methods to determine the mean, standard deviation and standard error of mean (SEM), a typical type of students paired T-test, Chi-square, and Kruskal-Wallis one-way analysis of variance were used for analysis of data. Correlation coefficients were calculated according to Pearson. Data were analyzed using statistical package for the social sciences SPSS 20.5; Inc. Chicago, IL). A power of measurement was considered more than 80% and P-value of less than 0.05 ($P < 0.05$) was as well considered statistically significant. Protocol of the present study was conducted in compliance with human care standards outcome of Allow IVF center and approval of the Ethical Committee of the Faculty of Medicine and Health Sciences. Informed consent was obtained from each participant in the study, confidentiality of gathered information was granted

Results

The mean age of the recruited 69 infertile couples was

29.37±0.16 years and the mean duration of infertility was 4.38±0.25 years The semen samples had been obtained from infertile males and seminal fluid analysis (SFA) was done depending on World Health Organization (WHO) recommended criteria. The percentage of infertile couples with secondary infertility was 76%.

Table (1) showed the parameters of seminal fluid analysis for infertile males classified according to age groups.

Sperm parametes		20-29 years No. 25	30-39 years No. 90	40-49 years No.35	>50 years No.6
Sperm concentration (million/mL)		33.88±2.49	43.29±1.57	45.11±2.83	34.17±5.23
Sperm motility (%)		56±2.89	65±1.37	63.69±3.01	57.5±4.43
Sperm grade activiy (%)	A	3.4±1.31	6.78±1.06	10.23±2.13	0.83±0.83
	B	29.2±2.91	34.94±1.24	30.91±2.3	25.83±6.11
	C	23.4±1.73	23.5±1.01	22.29±1.61	30.83±3.27
	D	43.6±2.85	34.78±1.31	36±3.02	42.5±4.43
Progressie sperm motility (%)		32.6±2.92	41.78±1.6	41.14±3.22	26.67±6.54
Normal sperm morphology (%)		44.6±2.31	52.37±1.5	46.97±2.45	40±2.58
Sperm agglutination (%)		6.52±1.55	8.22±1.14	12.03±2.33	5±3.42
Round cells count		4.56±1.1	5.46±0.71	7.11±1.36	10.5±4.99

It was noticed that the highest sperm concentration (million/mL) was within the two age groups (30-39) years (43.29±1.57) and age group (40-49) years (45.11±2.83). Regarding the percentage of sperm motility, best results were obtained within the same two age groups (30-39) years (65±1.37) and (40-49) years (63.69±3.01). A significant difference (P<0.05) was observed in the percentage of progressive sperm motility grade (A), the best results were noticed among age group (40-49) years (10.23±2.13) and the lowest values were in the age group

≥50 years (0.83±0.83). The best results regarding the percentage of progressive sperm motility grade (B) were noticed in the age group (30-39) years (34.94±1.24) and the lowest values were in age group ≥50 years (25.83±6.11) . The overall percentage of sperm progressive motility (grade A+B) showed a significant difference (P<0.01) with highest percentage in age groups (30-39) years (41.78±1.6), (40-49) years (41.14±3.22) and the lowest value was among age group ≥ 50 years (26.67±6.54) . Furthermore there was a significant difference (P<0.01) regarding the percentage of normal sperm morphology. However, the highest results were within age group (30-39) years (52.37±1.5) compared with the lowest results in the age group ≥ 50 years (40±2.58).

Table 1: The mean of sperms' parameters for infertile males classified according to age group.

Number of infertile males classified according to duration of infertility is showed in

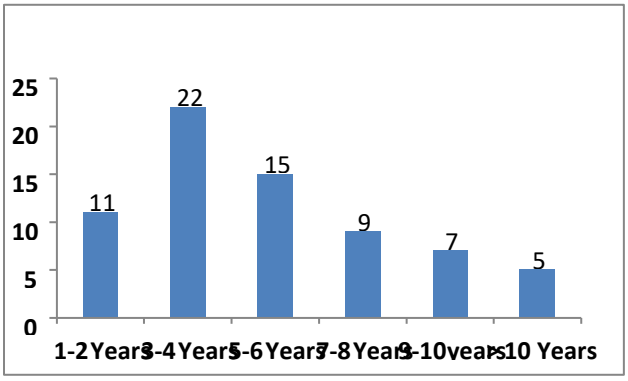


figure 1. It was clear that the largest group of infertile males was with duration of infertility 3-4 years, then the group with duration of infertility 5-6 years. The smallest group 95/69) was observed for infertile males with duration of infertility ≥10 years. Although little variations were assessed for seminal fluid parameters among different groups of infertile males classified according to duration of infertility (Table 2), but it was observed that the percentage of sperm progressive motility grade (A+B) (32.22±6.62) and percentage of normal sperm morphology (44.78±5.43), were the lowest among the group with duration of infertility >11 years. Moreover, the percentage of sperm agglutination (12.22±4.34) and assessed counts of round cells (6.33±2.58) were with highest results in the group of >11 years duration of infertility.

Figure 1: Number of infertile men according to the duration of infertility.

Table 2: The mean of sperm parameters for infertile males classified according to duration of infertility.

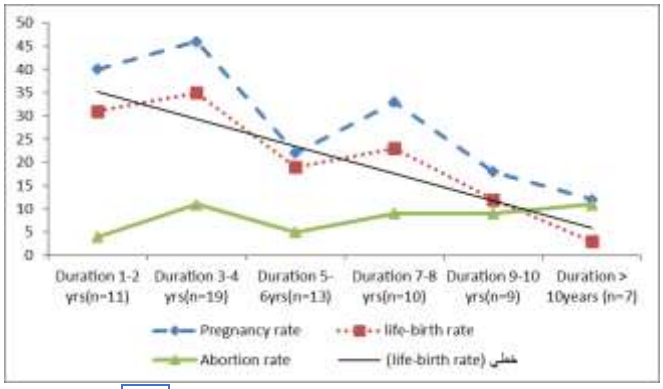
Sperm parameters		1-2 years No. 22	3-4 years No. 47	5-6 years No. 32	7-8 years No. 15	9-10 years No. 17	>10 years No. 19
Sperm concentration (million/mL)		42.58±3.77	42±1.86	41.89±2.33	40.22±5.02	42.13±3.19	32.33±4.25
Sperm motility (%)		62.08±2.31	64.31±1.66	63.89±2.3	61.11±4.78	63.44±4.49	45±6.87
Sperm grade activity (%)	A	6.25±1.48	5.67±1.17	7.44±1.8	8.33±3.79	7.5±2.96	4.22±3.45
	B	34.17±2.23	34.71±1.73	32±2.07	30±3.68	32.19±3.32	25±4.93
	C	21.67±1.72	23.94±1.25	24.17±1.68	23.89±2.64	23.75±2.44	22.78±2.9
	D	37.92±2.31	35.48±1.63	35.83±2.3	37.78±4.32	36.56±4.49	45±6.87
Progressive sperm motility (%)		39.58±2.79	40.87±1.92	39.44±2.75	38.33±5.59	39.69±4.29	32.22±6.62
Normal sperm morphology (%)		47.83±2.71	50.12±1.62	51.25±1.83	51.94±4.84	45.31±4.71	44.78±5.43
Sperm agglutination (%)		9.43±3.11	8.2±1.53	8.49±1.38	7.11±2.25	8.93±3.02	12.22±4.34
Round cells count		5.04±1.84	6.9±1.05	5.61±0.96	3.83±1.47	5.27±1.18	6.33±2.58

The outcome of IUI for infertile males including pregnancy, life birth and abortion rates were demonstrated in the figure 2.

The higher pregnancy and life-birth rates were showed in those males suffering from infertility for duration less than 4 years in compare to those who have duration more than 10 years (P<0.003, r=-0.869). Abortion rate was observed in those men who have duration more than 10 years in compare to those who have

duration of infertility less than 4 years (P<0.0014).

Figure 2: Pregnancy, life-birth and abortion rates, after IUI, among infertile males according to duration of infertility



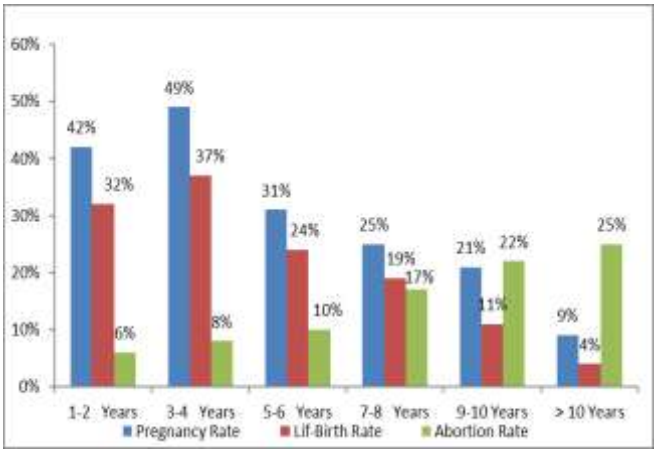


Figure 3: The linear life-birth rate among infertile couple treated by intrauterine insemination due to male factor infertility Yemini infertile couples

Discussion

The results of this study showed that the secondary infertility was more than three times as the primary infertility. This is in a good agreement with that results published by another researchers[11, 12]. This was in disagreement

with the results of this study because the couples who involved in this study, had visited us asking for IUI, which means that they had no intense causes of infertility which made the IUI not a choice of treatment.

Factors cause secondary infertility are less severe than those cause primary male infertility which can result from a variety of conditions included hypothalamo-pituitary disorders, systemic disorders, chronic illnesses, nutritional deficiencies and congenital disorders[13, 14]. A multicenter study reported that chromosomal abnormalities are common in infertile men mostly those with primary infertility, with an incidence of 5.8% as compared to an incidence of 0.5% in the fertile population[15].

A relatively high incidence of asthenozoospermia could be observed in the immunologically infertile males [16], because antisperm antibodies may be sustained and enhanced through bacterial or viral infections [3]. subsequently they may severely alter spermatogenesis [17]. The different causes of male infertility support the results of this study because the causes of primary infertility are more intense in their effects than that of the secondary infertility, and need more sophisticated ways of ART other than IUI [11]. In infertile males with secondary infertility in addition to the previous causes, varicose veins and number of environmental factors including high temperature, inflammatory factors, social habits, drugs, radiation therapy and xenobiotics (pesticides, insecticides) had been shown to have negative impact on testicular function but had been implicated in the decline of sperm quality [18].

The groups of the infertile males with history of infertility of 3-4 years duration are largest groups who attended medical services, in contrast infertile males with history of infertility ≥ 10 years were the smallest group. As the duration of infertility increases, the couples become less interested to seek the medical services. Besides, the psychological factors (depression and hopelessness) play a major role in these cases [1].

Intra-uterine insemination has been practiced widely as an empirical treatment for male factor infertility and as a mean to bypass defects in sperm-cervical mucus interaction [19]. In the present study IUI was performed for 152 couples with mild male factor infertility. Studying the results of this study, the positive IUI outcome was observed in groups who had post-activation sperm parameters of more sperm progressive motility percentage grade (A) and grade (B) and higher percentage of normal sperm morphology as well as less sperm concentration. The sperm quality that is necessary for successful IUI is lower than the WHO threshold values. IUI is an effective therapy for male factor infertility when initial sperm motility is ≥ 30% and the total motile sperm count is ≥ 5million, when the initial values are lower IUI has little chance of success [20]. An average total motile sperm count of 5 million may be a useful threshold value for decision about treating a couple with IUI or IVF [21]. The final post-washed sperm count used for IUI may be considered predictive of the success for pregnancy and allow couples to be informed of the chances of success. Pregnancy rates, were significantly higher among couples with more than (14%) normal sperm morphology than among those of sperm morphology was less than (14%) normal sperm morphology [1, 22].

The greatest enthusiasm supports IUI is when combined with controlled ovarian hyperstimulation (COH) that increases the number of oocytes ready for fertilization. IUI combined with superovulation may increase monthly probability of pregnancy approximately four times compared to that following IUI timed by LH surge [23]. According to the largest available clinical studies, IUI in stimulated cycles with conventional doses of gonadotropin, induce pregnancy in (10-15%) of cases with better results in couples with normal sperm parameters [24]. The use of an ovulation induction agent, clomiphene citrate, human chorionic gonadotropin (hCG) or human menopausal gonadotropin (HMG), increases the success rate of IUI by 10% [3].

The timing of insemination in IUI programmers in relation to other major events

around ovulation or most probably ovulation itself has been suggested as the most important variable affecting the success of this treatment [25]. In addition timing of insemination, number of insemination per cycle may influence the ultimate pregnancy [23]. To maximize the chance of success of IUI, the timing of insemination needs to be closely related to the time of ovulation, ovulation occurred at a mean time of (27.3) hour from onset of LH surge [26]. The normal physiological activity of the reproductive organs gradually decreases with advancing age due to irreversible abnormal physiological changes in the testes that affect the fertilization potential of human spermatozoa. Semen quality, frequency of ejaculation and sperm functions gradually decrease with advancing age. Moreover, the spermatozoa from older men have increased incidence of abnormalities and many children born from older men have an increased chance of abnormalities [27]. With increment duration of infertility, the infertile males become less interested in seeking the medical services. Depression and hopelessness play a major role in those cases. An increment in the duration of infertility to more than 10 years results in reduction in the testicular blood supply especially in the older infertile males and this affects the normal physiology of the testes and epididymis which results in marked elevation of the serum FSH and LH levels [28]. Furthermore there is an increase in the number of pathological spermatozoa which linked to an increase in both age and duration of infertility [19]. Therefore, in this study least positive IUI with 10 years duration of infertility and age ≥ 50 years. The success of IUI is very strongly tied to precise adherence to established methods for everything from preparing the sperms to inseminating the lady. The factors that may influence the results of IUI, age of the couples and duration of infertility, final post-activation sperm parameters, method of preparing the semen, type and composition of the culture media, COH protocols, timing of IUI and accurate selection of couples for IUI with experience of the physician in performing the insemination. In 2010, a study of pregnancy rates performed at infertility centers; it was found that unsuccessful outcomes often were attributed to physician error and a lack of familiarity with procedure [25]. Present study shows a negative relationship between the duration of infertility and outcome of ART include pregnancy and life-birth rates. That is in a good agreement with that study published by Glazener et al in 2000 [29]. The researchers of the present work conclude that by increase in the duration of infertility the outcome of assisted reproductive techniques – IUI in infertile male will decrease markedly.

For further study, the researchers recommend the following:

1.Study the hormonal imbalance in patient with male factor infertility that could be appeared in late inability to achieve pregnancy.

2.Improve the cultural fertility educations of couples whose cannot be parents within 2 years regular unprotected intercourse.

3.Prepare patients psychologically with regard to the duration of infertility more than 8 years before their involvement in the ART.

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