Etiology of Infertility and Treatment Outcome in Couples Aged 40 Years or more in a Non-IVF Setting

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Abstract

Infertility is a global reproductive problem that has a huge impact on a couple's life. Different etiological factors contribute to this problem, and the pregnancy outcomes vary depending on the infertility cause and age of the women. This study aimed to investigate the etiology of infertility and pregnancy outcomes in women aged 40 years or more in a non-IVF setting from January 2015 up to December 2019. This study was a descriptive retrospective cohort study that included 207 infertile patients who attended the infertility clinic in SQUH from 1 January 2015 up to 31 December 2019. Data were collected from the hospital's information system (HIS) and analyzed by using the SPSS program (version 25). There were a total of 207 couples. The study showed that secondary infertility (71.5%) was more prevalent compared to primary infertility (28.5%). About 9.66% of women had live babies after treatment, though the overall pregnancy rate was 12%. Most of the infertility cases were due to female factors (54.1%), followed by male factors (22.7%). The commonest semen characteristic was asthenozoospermia (52.7%). The best outcome was for couples with unexplained infertility where 20.0% of them got normal live babies. The overall live baby rate was 9.66%. Female factors specifically anovulatory disorders remain the commonest cause of infertility. The best outcome was for women with unexplained infertility.

Keywords: Infertility, Age, Pregnancy, Oligospermia, Oman

Introduction

Infertility is a global ongoing reproductive problem that has a huge impact on a couple's life. The World Health Organization (WHO) ranks infertility in the young population as one of the highest serious global disabilities. Although male infertility contributes to many cases of global infertility, it remains a woman's social burden as childbearing is an important and valuable issue in marital relationships (1). Social changes have occurred in the last few decades such as an increase in the age of marriage, postponement of pregnancy over 35 years old seeking pregnancy, and technical advances in treatment (2). The fecundity of women decreases gradually but significantly beginning approximately at age 32 years and decreases more rapidly after age 37 years (3). According to the current evidence, infertility prevalence is around 9% in the normal population (4), but the prevalence in women aged 40 or more is higher according to a report from the UK (5). Though traditionally it is believed that fertility is more related to the age of the female, recent evidence suggests that increased paternal age is also associated with lower fertility, an increase in pregnancy-associated complications, and an increase in an adverse outcome in the offspring (6, 7).

A survey data from 277 demographic and reproductive health surveys found that Couples affected by infertility increased from 42.0 million in 1990 up to 48.5 million in 2010 (8). In addition, infertility diagnosis causes psychological symptoms and affects life satisfaction in couples. To illustrate, wives were found to be significantly more depressed than their husbands in couples diagnosed with female factor infertility (9).

Infertility increases the psychological burden on infertile patients, especially here in Arab countries. To illustrate, A study that was conducted in Oman including 112 Omani women indicates that the presence of PCOS is associated with an increased risk of depression, anxiety, and stress among these women (10). The Arab region is not an exception for women delaying their age of the pregnancy. Regardless of the massive global expansion of infertility treatments including assisted reproductive techniques (ARTs), many parts of the world remain inaccessible to such services (11). Infertility etiologies vary from one country to another according to local demographics (12). A study which was conducted in the southern region of Iran found that varicocele (49.4%) and ovulation disorders (57.5%) were the most common causes of male and female infertility respectively (13).

Another study that was done in Mumbai in India categorized the main infertility etiologies into the following:

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Female factors (46.6%), mostly PCOS and tubal pathology, Male factors (10%), combined causes (10.8%), mostly ovulatory disorders with abnormal semen and unexplained infertility (32.5%) in the overall population (14). However, the etiological factors obviously will be different in women and men of advanced age. Apart from the fact that women older than 40 are likely to need assisted conception, also the outcome of pregnancy must be kept in mind (6). Poor pregnancy outcome from an individual and public health perspective has to be kept in mind in these couples.

Therefore, there is remarkable important to identify the main infertility etiologies in Oman and the pregnancy outcome in couples older than 40. This study will help to modify these risks and counsel infertile patients.

Aim and rationale

This study aimed to investigate the etiology of infertility and pregnancy outcome in infertile couples aged 40 years or more in a non-IVF setting attending Sultan Qaboos University hospital (SQUH) in the Sultanate of Oman from the 1st of January 2015 up to the 31st of December 2019. To the best of our knowledge, there are no published studies done before in Oman addressing the main etiological factors of infertility and its outcome in this age group. Therefore, this study will draw attention to the main etiological risks of infertility in this age group in Oman, taking into consideration that SQUH is a tertiary hospital in the capital Muscat where most of the infertile patients from all regions around Oman are referred to.

Specific objectives

To determine the prevalence of various etiological factors of infertility couples ≥ 40 years of age, from January 2015 up to December 2019. To compare the pregnancy outcome in each etiological group.

Materials and Methods

Setting and Design

This study was conducted in the form of a descriptive retrospective cohort study targeting infertile patients who attended the infertility clinic in SQUH, a government tertiary care unit in the capital city of the Sultanate of Oman, Muscat. The study was conducted from the 1st of January 2015 up to the 31st of December 2019. Ethical approval was obtained from the medical research ethics committee at the college of medicine and health sciences in Sultan Qaboos University on the 30th of April 2020 (MREC #2130) before data collection.

Subjects

The study comprised 207 infertile couples aged 40 years or more, both males and females, Omanis and non-Omanis. We included all patients who were diagnosed with infertility in SQUH during the period from the 1st of January 2015 up to the 31st of December 2019

Data collection

Data for this study were retrospectively collected from the hospital's information system (HIS) Trakcare, the electronic medical record system used in SQUH. The patients' data were collected in an IBM SPSS program (version 25) sheet. Collected data included information about the following: patient's age, sex, region in Oman the patient belongs to, weight, height, primary or secondary infertility, regularity of menstrual history, previous investigations, hormone assays (FSH, LH, prolactin, estrogen, TSH, thyroxine, testosterone, DHEAS, and AMH), results of pelvic imaging (ultrasound, hysterosalpingogram, MRI), semen analysis (including semen volume, sperm count, sperm motility, percentage of abnormal forms), previous surgical procedures, infertility etiology, pregnancy outcome.

Statistical Analysis

Data analysis was carried out using the IBM SPSS program (version 25). Mean, Standard Deviation (SD), and the median was calculated for the male and female patients' age. We used the patients' weight and height to calculate the Body Mass Index (BMI), and then we used a bar chart to represent the different categorized variables of the BMI. Next, frequency tables were used to represent the percentages of different Oman regions, hysterosalpingogram results, surgical procedures that infertile patients underwent, infertility etiologies, specific causes of female infertility, semen characteristics, combined infertility specification in infertile couples. Pie charts were used to represent the type of infertility (primary or secondary), and the regularity of menstrual history. Crosstab was used to compare the pregnancy outcome in each etiological group.

Results

Demographic characteristics

This study included a population of 207 infertile couples who attended SQUH from 1 January 2015 up to 31 December 2019. SQUH is a tertiary hospital in the capital Muscat where most of the infertile patients from all regions around Oman were referred. According to these regions, most of the referred patients were from the Muscat region (43.5%), followed by the Al Batinah region (25.6%). The mean age for males was 46 years old ± 7.62. On the other hand, the mean age for females was 43 years old ± 2.94. The maximum age was for a male patient (70 years old). The weight and height of the patients were used to calculate their BMI. According to the different BMI groups, 44.4% of infertile patients were found to be obese. What is more, 30.4% of the patients were overweight according to Figure 1.
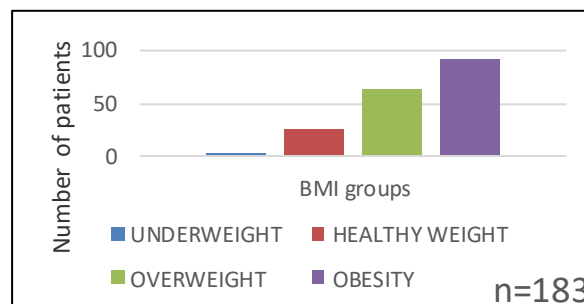

Figure 1. Body mass index distribution in infertile patients

The study results showed that the secondary type of infertility (71.5%) was more prevalent compared to primary infertility (28.5%) as shown in Figure 2.
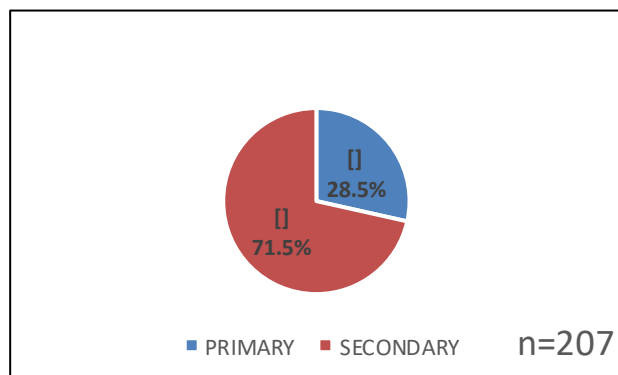

Fıgure 2. Type of infertility in infertile patients

In the present study, the most striking observation to emerge from the data analysis was that most of the infertile women had a regular menstrual history (84.4%), and only 15.6% had an irregular menstrual history. These results are shown here in Figure 3.
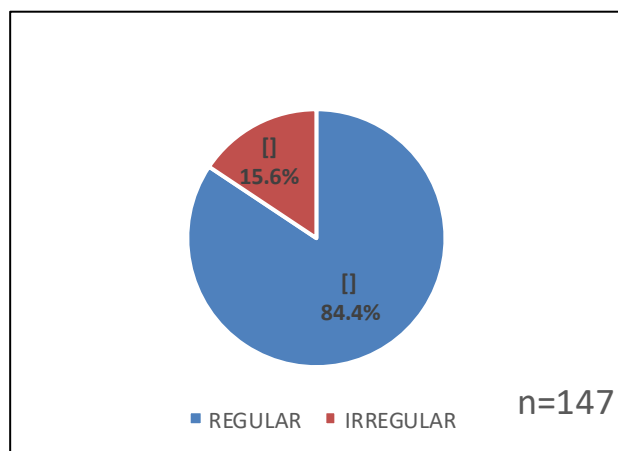

Fıgure 3. Regularity of menstrual periods in infertile women

Investigation results

Hysterosalpingography (HSG) is important imaging used to investigate infertile women. In our study, we found that 9 infertile women (11.7%) had both fallopian tubes blocked, so they were included in our study as tubal factor infertility. About 62% had normal HSG and 26.0% had one tube patent only.

Pelvic ultrasound is another important imaging used to investigate infertile women. Surprisingly, we found that 57 infertile women out of 118 had fibroids. 44.1% of women had a normal study of pelvic ultrasound. Further details are in Table 1.

Table 1. Results of pelvic ultrasound in the infertile women

Pelvic ultrasound findings	Frequency (n=118), n (%)
Normal study	52 (44.1)
Fibroid	57 (48.3)
Endometriosis	4 (3.4)
PCOS	5 (4.2)

PCOS: Polycystic Ovarian Syndrome

The patients had undergone different surgical procedures that are shown in Table 2. Out of 52 patients, 48.1% of infertile females underwent myomectomy. 15.4% had a polypectomy. Six infertile males in the study population underwent excision of varicocele.

Table 2. Surgical procedures that infertile patients had undergone

Surgical procedure	Frequency (n=52), n (%)
Myomectomy	25 (48.1)
Polypectomy	8 (15.4)
Ovarian cyst surgery	5 (9.6)
Excision of varicocele	6 (11.5)
Others	8 (15.4)

Infertility etiologies

The results of our study showed that most of the infertility cases were due to female factors (54.1%). Male factors contributed to about 22.7% of infertility cases, and unexplained infertility prevalence was 19.3%. Eight couples only had combined infertility. Table 3 shows the main four infertility etiologies.

Table 3. Infertility etiologies in the study population

Infertility etiology	Frequency (n=207), n (%)
Female factors	112 (54.1)
Male factors	47 (22.7)
Unexplained infertility	40 (19.3)
Combined infertility	8 (3.9)

Table 4 shows the distribution of various female infertility factors in percentages. Anovulation was the commonest accounting for 58.9% of infertile women. Anovulatory disorders include different conditions like PCOS, Hyperprolactinemia, and reduced ovarian reserve. The second commonest cause of female infertility was tubal factors (19.6%) that include women with both uterine tubes block and women with the previous salpingectomy. In our study, we found that 20 women had uterine factors since they presented with Asherman syndrome, fibroids, adenomyosis, and congenital uterus anomalies. We considered endometriosis as a separate cause of female infertility, and it accounts for 3.6 % of total female cases.

Table 4. Distribution of female infertility factors

Female factor	Frequency (n=112), n (%)
Anovulation	66 (58.9)
Tubal factors	22 (19.6)
Uterine factors	20 (17.9)
Endometriosis	4 (3.6)

The commonest semen characteristic was asthenozoospermia (52.7%) which is a disorder of motility. The results of the semen analysis are shown in Table 5.

Table 5. Semen characteristics in infertile males

Semen characteristic	Frequency (n=55), n (%)
Asthenozoospermia	29 (52.7)
Oligospermia	19 (34.6)
Combination	5 (9.1)
Teratospermia	1 (1.8)
Azoospermia	1 (1.8)

Eight couples in the study population had combined infertility, and these different combinations are specified in Table 6. The commonest combinations were (Asthenozoospermia + Tubal factor) and (Oligospermia + Uterine factor).

Table 6. Combined infertility specification in infertile couples

Infertility combination	Frequency (n=8), n (%)
Asthenozoospermia + Tubal factor	2 (25.0)
Asthenozoospermia + Anovulation	1 (12.5)
Oligospermia + Uterine factor	2 (25.0)
Oligospermia + Endometriosis	1 (12.5)
Oligospermia + Anovulation	1 (12.5)
Combination of sperm abnormality + Anovulation	1 (12.5)

Pregnancy outcome

Table 7 is a crosstab that shows the pregnancy outcome in each etiological group. The outcome of pregnancy was collected whether the patients underwent treatment or not. We split the female infertility factors into four categories to have more reliable and useful data. To keep in mind, the percentage was taken within infertility cause. The overall pregnancy rate outcome was 12%., with 9.66% live babies. The worst outcome was for couples with combined infertility since they did not get any outcome at all. The best outcome was for couples with unexplained infertility where 20.0% of them got normal live babies. The second-best outcome was for females with anovulation as 10.6% of them got normal live babies. Infertile women with tubal factors were more prone to get ectopic pregnancy (9.1%). Miscarriage was a common outcome in women with endometriosis (25.0%).

Discussion
Epidemiology

In this study, we investigated the etiology of infertility and pregnancy outcomes in women ≥ 40 years of age, attending SQUH in the Sultanate of Oman from January 2015 up to December 2019. A study that was conducted in an infertility center in Iran found that the mean ages of infertile women and their husbands were 31.2 ± 5.94 and 35.7 ± 6.70 years, respectively (15). However, there is no data for couples with advanced age except a study published by Tulandi et al in 1981 identified tubal factors in women of 36-40 years and unexplained infertility in women more than 40 years (16).

Table 7. Pregnancy outcome in each etiological group

Infertility cause	Frequency (n=207), n(%)	Pregnancy outcome			
		No outcome	Ectopic pregnancy	Miscarriage	Live baby	Total
	Anovulation	58 (87.9)	1 (1.5)	0 (0)	7 (10.6)	66 (100)
	Uterine factor	19 (95.0)	0 (0)	0 (0)	1 (5.0)	20 (100)
	Tubal factor	20 (90.9)	2 (9.1)	0 (0)	0 (0)	22 (100)
	Endometriosis	3 (75.0)	0 (0)	1 (25.0)	0 (0)	4 (100)
	Male factor	42 (89.4)	1 (2.1)	0 (0)	4 (8.5)	47 (100)
	Combined infertility	8 (100)	0 (0)	0 (0)	0 (0)	8 (100)
	Unexplained infertility	32 (80.0)	0 (0)	0 (0)	8 (20.0)	40 (100)
	Total	182 (87.9)	4 (1.9)	1 (0.5)	20 (9.7)	207 (100)

Note: The percentage was taken within the infertility cause.

However, we focused on advanced age and the mean age was high in both males and females as it was 46 years old ± 7.62 for males and 43 years old ± 2.94 for females. The prevalence of secondary infertility was high in our study and as we know, couples with primary infertility are younger than those with secondary infertility (17). Second, many patients do not tend to seek infertility treatment in the early stages, and some patients prefer to start with traditional medicine and come late to the infertility clinic. Late marriage in the current days might be another reason explaining the high mean age. According to the

different BMI groups, 44.4% of infertile patients were found to be obese. What is more, 30.4% of the patients were overweight. The results of our study support many previous studies which found that women with early onset of obesity tend to develop menses irregularities and infertility later. On the other side, massively obese men tend to have low testosterone levels and reduced spermatogenesis (18). Another study that addresses female obesity and infertility issues showed that obesity is associated with various reproductive sequelae like anovulation, subfertility, and infertility (19).

Pregnancy after weight loss surgery is safe and associated with better pregnancy outcomes (20). What is more, an Indian study found that obese women were more likely to have primary infertility (21).

The type of infertility prevalence whether primary or secondary vary from one country to another. Primary infertility (57.5%) was considered to be more prevalent than secondary infertility 42.5% in younger women (13). In our study, the secondary type of infertility (71.5%) was more prevalent compared to primary infertility (28.5%). Our study results are similar to the one from, Qatar. According to that study secondary infertility (68.4%) was more prevalent than primary infertility (31.6%) (22). Hence, it could be hypothesized that there is a relation between social and economic status and the trends to have more children. In Gulf countries, people tend to have more offspring. As established before, reproductivity of the couples decreases after having offspring, which increases their chance to develop secondary infertility. A study found that the risk of infertility is more after two years of marriage; furthermore, it increases after a second attempt at pregnancy (23).

In our study, the commonest surgical procedure that patients underwent was myomectomy (48.1%). This finding was expected taking into consideration that 48.3% of the infertile women in our study have fibroids detected by pelvic ultrasound. Myomectomy surgery is usually done to improve fertility and pregnancy outcomes. Miscarriage rates are significantly reduced following myomectomy (24).

Various studies have shown that ovulation disorders are the most common female infertility cause. For instance, the anovulation percentage was 57.5% in one study. Our study supports all previous findings as anovulation was the commonest accounting for 58.9% of infertile women especially given their advanced age.

In the current study, we considered endometriosis as a separate cause of female infertility, and it accounts for 3.6% of total female cases. These results match those mentioned in a study that was conducted in England where it stated that endometriosis accounted for infertility in 6% of the total cases (25). The second commonest cause of female infertility was tubal factors (19.6%) that include women with both fallopian tubes blocked and women with the previous salpingectomy. In our study, we found that 20 women had uterine factors since they presented with Asherman syndrome, fibroids, adenomyosis, congenital uterine anomalies.

Unexplained infertility is a diagnosis of exclusion that is made after the failure to evaluate the male and female etiological factors for infertility. The incidence of unexplained infertility in our study, of 207 infertile patients, was 19.3%. In another study that included 120 couples, 34% of the couples had unexplained infertility (13). Another study found that Infertility was unexplained in 28% of the cases (26).

Male factors

We found that the commonest semen characteristic in our study was asthenozoospermia (52.7%) which is a disorder of motility, followed by oligospermia (34.6%). Nevertheless, the findings of our study are not consistent with previous research.

One study documented that oligospermia was the commonest male factor infertility (13). Another study documented that the most commonly diagnosed causes included azoospermia (56.4%) followed by oligospermia (24.5%), while teratozoospermia was only 9.6% (15). These variations in the results might be due to the different techniques used in each lab compared to another. Moreover, the cutoff points used to label asthenozoospermia, teratospermia and oligospermia may differ from one study to another. In our study, asthenozoospermia is said to be when the motile sperms are less than 40% in the collected semen sample.

Pregnancy outcome

We found that the best outcome was 12% overall and in couples with unexplained infertility, 20.0% of them got normal live babies. Pregnancy rates vary depending on the treatment methods. We are describing a non-IVF setting and some women had Intrauterine insemination (IUI). It is beyond our scope to discuss the methods of ovulation induction followed in this manuscript. Live birth rate of 3.9% in 1991 has increased to 6.9% by 2004 according to Kmietowicz et al (6). Ovulation induction with IUI resulted in a live baby in 5.22% per cycle according to Corsan et al. (26).

The pregnancy outcome in our study is very acceptable and has many possible explanations. First of all, some infertile women stopped their follow-up in the infertility clinic when they knew that they were pregnant. Additionally, we did not get information on women who got pregnant with unknown outcomes and women who are currently pregnant under the category.

Limitations

The retrospective nature of the study and missing data is a major limitation. Moreover, this study was conducted in a single hospital only which is SQUH, and no data were collected from the other infertility clinics and hospitals in Oman.

Conclusion

To conclude, the etiologies of infertility vary according to the local demographics, however, female factors specifically anovulatory disorders remain the commonest cause of infertility as expected in this age group. Unexplained infertility had the best pregnancy outcome in this age group.

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Conflict of interests

The authors declare that there is no conflict of interest.

Author contributions

Dr. Fatema did the data collection, analysis and drafted the manuscript and Dr. Gowri supervised her and revised the manuscript for content and clarity.

Ethical issue

There are no ethical issues regarding the manuscript.

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