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## Research Article

# Fertility Medication Uses and their Effect on Mothers and Children

Alaa Khraiwesh, Aseel Bradea, Anwar Jaradat and Hatem A. Hejaz

Department of Pharmacy, College of Pharmacy and Medical Sciences, Hebron University, P.O. Box 40, Hebron, Palestine

### Abstract

**Background and Objective:** Infertility affects women's lives negatively in different aspects such as their happiness, health, comfort and functioning. Even though male infertility leads to more than half of all cases of global childlessness, the social tonnage of infertility in a woman remains much more than in a man. The study aimed to assess the percentage of Palestinian women who use fertility medications for treating infertility to study the effects and the side effects or any withdrawing backs of infertility medications used on both mothers and children. **Materials and Methods:** A cross-section research study was carried out involving 230 women receiving fertility care at reproductive units. Most of the patients were interviewed with the aid of a questionnaire and the others were filled it online. Data was collected and analyzed with the "Statistical Package for the Social Sciences" (SPSS) version 25. **Results:** About 69% of women who participated in this research study didn't use fertility drugs at all, while 31% of them used them. These women who have used fertility drugs, about 50% of them became pregnant. In general, most of these therapies were safe for both mothers and babies, only little signs and symptoms were developed. It was found that fertility drugs were to be substantially greater effects and efficacy by the marriage length increased and the number of children ( $\alpha < 0.05$ ). **Conclusion:** Infertility medications appear to be common in use in Palestinian women and are a safe and effective way to lower the risk of infertility. That therapy didn't affect seriously either mother or/and fetus.

**Key words:** Infertility, medications, fertility, side effects, pregnancy, women

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**Corresponding Author:** Hatem A. Hejaz, Department of Pharmacy, College of Pharmacy and Medical Sciences, Hebron University, P.O. Box 40, Hebron, Palestine

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**Competing Interest:** The authors have declared that no competing interest exists.

**Data Availability:** All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Infertility is the inability to conceive children and it occurs when a couple cannot conceive after regular unprotected sex for 1 year. Infertility can affect either the male or the female and can be caused by a variety of factors. Disorders in the uterine, ovaries and endocrine systems are the major causes of infertility in females. On the other hand, hormonal disorders, testicular failure and abnormal sperm are the major infertility factors in males<sup>1-3</sup>. Cigarette smoking has been associated with a significant detrimental effect on reproductive function and fertility<sup>4</sup>. Being overweight in women and men may increase the risk of infertility<sup>5</sup>. Age, alcohol use, being underweight and lack of exercise are other factors that may negatively affect fertility. Some medical conditions, environmental and lifestyle factors can also affect fertility<sup>6-8</sup>. Fertility care remains a challenge in most countries, especially in low and middle-income countries. Infertility has social and psychological effects in addition to health. Although both women and men can experience infertility, women in a relationship with a man are often perceived to suffer from infertility, regardless of whether they are infertile or not. Infertility has significant negative social impacts on the lives of infertile couples, particularly women, who frequently experience violence, divorce, social stigma, emotional stress, depression, anxiety and low self-esteem. Women trying to conceive often have depression rates similar to women who have other diseases<sup>9,10</sup>. In some societies, fear of infertility can drape women and men from using contraception if they feel socially pressured to prove their fertility at an early age because of the high social value of childbearing. In such situations, education and awareness-raising interventions to address understanding of the prevalence and determinants of fertility and infertility are essential<sup>2,3</sup>. The lack of access to the standardized concept of primary infertility and the particular methodology for assessing infertile women have a substantial effect on the approximate prevalence of infertility<sup>11,12</sup>. In Palestine in the years 1996 and 2006 reports, contraception use accounted for the largest decrease in fertility (16.8% in the West Bank and 14.7% in the Gaza Strip). Postpartum infertility accounted for a 5.4% drop in fertility in the West Bank compared with 3.6% in the Gaza Strip, mainly because of increased duration of breastfeeding. Fewer marriages in younger age groups between 15 and 19 years of age and between 20 and 24 years of age resulted in a 6.7% decline in infertility<sup>13,14</sup>. The analysis found that infertility impacts women's well-being more than men's. Infertile Egyptian women are at increased risk of developing Domestic Violence (DV). Psychological aggression and verbal

harassment are the most popular kinds of DV<sup>13-15</sup>. Results have shown that the most common type of infertility is primary infertility. Most infertile women come from urban residential areas, while the majority of fertile women come from rural areas, while infertile women have married early compared to fertile women. Most women have menarches  $\leq 15$ , many women in the menstrual cycle have the polycystic ovarian syndrome, problems with sperm quality and occlusion of tubules<sup>13,14,16</sup>.

Modern medicine has succeeded in treating many causes of infertility. The treatment method depends on the causes of infertility, whether for the man or the woman or both. Medical treatment of infertility generally involves the use of fertility medications, medical devices, surgery or a combination of both. Many drugs are used for both women and men like clomiphene citrate<sup>17,18</sup>. Intracytoplasmic sperm injection (ICSI) and *in vitro* Fertilization (IVF) are two other options for solving the infertility problem. Another infertility procedure is IVF in which ova are collected from the body of the female, fertilized by semen in the laboratory and returned to the uterus for natural childbirth. The first successful *in vitro* fertilization was conducted in England in 1978. Another treatment, called Gamete Intrafallopian Transfer or Donation is IVF variation. Once the ovaries have been activated and mature oocytes are released, the oocytes are mixed with the sperm and under the oocytes. Zygote intrafallopian transfer is usually reserved for women with cervical injury. ZIFT and IVF have an advantage over Gamete Intrafallopian Transfer (GIFT) in that fertilization have already taken place. Multi-births are a problematic concern associated with these procedures. Several medications, including clomiphene citrate, bromocriptine and human menopausal gonadotropin, have been very active in resolving hormonal imbalances that induce irregular menstrual ovulation. However, these "fertility drugs" often raise the risk of a woman experiencing several births due to the release of more than one egg at ovulation under the influence of the medication. Women with infertility exposure to severe uterine failure or a congenital absence of the uterus may be candidates for uterus<sup>19-24</sup>. The increase in the use of infertility treatment has contributed to an exponential increase in the incidence of twins and triplets in the US<sup>17</sup>. A huge performance was achieved in the first uterine transplant in 2020 for a woman suffering from a childhood uterus, i.e. without a vagina or uterus but with the presence of an ovarian that usually functions<sup>25</sup>. Fertility drugs can treat many issues, increasing the chances of conceiving and carrying the baby to term. Many women experience side effects of fertility drugs, especially those that contain hormones. There are lots of these drugs but there are drugs

that are most commonly prescribed<sup>18,22,23</sup>. Therefore, this study researched to know the rate of the use and the most common fertility medications for treating infertility among Palestinian women and to study the effects and the side effects or any withdrawing backs of infertility medications used on both mothers and children.

## **MATERIALS AND METHODS**

**Study area:** This was a cross-sectional study performed at the Infertility Clinic of the Palestinian Institute of Medical Sciences, Hebron, Palestine and at women from all the Governorate in Palestine.

**Research protocol:** The study was carried out for about one month from September to October, 2020. The study included a total of 230 women, 139 women (60.4%) attending infertility clinics were interviewed with the aid of a standard questionnaire and 91 (39.6%) women have filled it online. The inclusion requirements were women between the ages of 20 years to over 40 years old, from all governorates in Palestine, who were either specifically consulted at the infertility clinic or referred to the general obstetrics and gynaecology clinic for at least 6 months of testing for pregnancy. At the initial consultation, women were invited to participate in the study voluntarily and consent was taken from each patient to participate in the research study. The interview consisted of a thirty-four-item questionnaire developed to study the effects of these treatments on the mother and the infant. Most of the patients were interviewed by a fertility counsellor with the aid of a standardized questionnaire. The questionnaire consisted of two sections. The first part of the questionnaire included participants' demographic and background details such as age, occupational status, couples' educational levels, marriage length, ownership of residential property, residence address, income, fertility and employment status of the spouse. The second part of the questionnaire contains questions about the use of fertility drugs, the therapies used after the use of them in the number of pregnancy times and their effect on both the mother and the child.

The survey questions were multiple choices questions the patients had to decide the correct answers to each question from the choices given for each question. Only there were three questions in the questionnaire were to fill the blanks, the participated women were asked to write the answer for these three questions. The first question is if any other fertility drug is used other than the given medications, the second question

if other side effects other than the side effects given and the last question how is your child was affected by the medicines taken if he has been affected. Some of the questions also about the impact of fertility with marriage length, the correlation between oral contraceptives and infertility and a woman's options to return to use fertility medication again. The Tukey scale was used to find if there is a link between the effects of fertility drugs used by women in Palestine and the degree of their effectiveness and their effect on the mother and child according to age criteria, governorate, educational stage, place of residence, monthly income, nature of employment, length of the marriage and family relationships. The basic demographic parameters and socioeconomic status measurements were reported. The study was also designed to measure the percentage of Palestinian women who use fertility medications for infertility treatment and their effect on the mother and child of the treatment.

**Statistical analysis:** Data was collected and analyzed with the "Statistical Package for the Social Sciences" (SPSS) version 25. An ANOVA test is used to find out if there is a significant difference in group means and the Tukey test is performed to see where a significant difference lies. For quantitative variables, descriptive statistics were used and were expressed as mean, standard deviation or frequencies and percentages. The percentage of respondents responding correctly was stratified according to the size of the SES. The exact test was performed as necessary for comparing categorical results.  $\alpha < 0.05$  was considered for all statistical tests.

## **RESULTS**

In this survey which was conducted on Palestinian women who use fertility medications for treating infertility, Table 1 represents demographic details. This study enrolled 230 women in the study, aged between less than 20 and over 40 years old, who completed the questionnaire. The research study included Palestinian women from the different Governorates in Palestine. Most of the participated women were from the Hebron Governorate ( $n = 161, 72.5\%$ ), followed by Gaza ( $n = 24, 10.8\%$ ) and the rest of the governorates were very close proportions such as Nablus, Ramallah, Bethlehem, Jenin and others (0.9-4.1%). Most women participated in the study, their age between 20-25 years then women aged between 26-30 as shown in Table 1. Many infertile women were less than 20 years of age and above the age of 40 years, i.e., 5.4% ( $n = 12$ ) and 6.3% ( $n = 14$ ), respectively show a low risk of infertility (Table 1). Most of participating women have

Table 1: Characteristics of participants women

	Frequency	Percentage
<b>Governorate</b>		
Hebron	161	72.5
Ramallah	5	2.3
Bethlehem	8	3.6
Jerusalem	6	2.7
Jericho	2	0.9
Nablus	9	4.1
Jenin	3	1.4
Tulkarm	4	1.8
Gaza	24	10.8
Missing	8	
<b>Age</b>		
<20	12	5.4
20-25	82	36.6
26-30	61	27.2
31-35	32	14.3
36-40	23	10.3
>40	14	6.3
Missing	6	
<b>Education level</b>		
School	13	5.8
High secondary school	53	23.7
Diploma	24	10.7
Bachelor degree	122	54.5
Master degree	12	5.4
Missing	6	
<b>Living place</b>		
City	132	58.9
Village	84	37.5
Camp	8	3.6
Missing	6	
<b>Monthly income</b>		
<US\$ 650	66	29.7
US\$ 650-1000	63	28.4
US\$ 1000-1250	45	20.3
US\$ 1250-1550	24	10.8
>US\$ 1550	24	10.8
Missing	8	
<b>Occupation</b>		
Housewife	136	61.3
Student	36	16.2
Government employee	15	6.8
Private employee	23	10.4
Medical field	12	5.4
Missing	8	
<b>Suffering from disease</b>		
Yes	23	10.4
No	198	89.6
Missing	9	
<b>Disease type</b>		
Iron deficiency	1	4.3
Cystic ovarian syndrome	2	8.7
Kidney	1	4.3
Diabetes	6	26.1
Hypertension	3	13
Colon	2	8.7
Migraine	2	8.7
Joint and disk	1	4.3
Urinary tract infections	2	8.7
Thyroid gland	3	13

Table 1: Continue

	Frequency	Percentage
<b>Length of being married</b>		
1-2 Years	64	29.1
3-4 Years	39	17.7
5-6 Years	33	15
7-8 Years	19	8.6
9-10 Years	16	7.3
More than 10 Years	49	22.3
Missing	10	
<b>Number of children</b>		
None	23	10
1 child	70	30.4
2 children	56	24.3
3 children	32	13.9
4 children	25	10.9
5 children	13	5.7
More than 5 children	11	4.8
<b>Is the husband a relative?</b>		
Yes	64	28.8
No	158	71.2
Missing	8	
<b>Number of times have been pregnant</b>		
None	40	
Once	58	30
Twice	60	31
Three times	24	13
Four times	24	13
More than four times	24	13

a bachelor's degree (n = 122, 54.5%), while 53 women (23.7%) only finished their high school and 24 women have diploma degrees. The majority of respondent women aren't working, they are housewives (n = 136, 61.3%), only 5.4% (n = 12) working in the medical field and 17.2% (n = 38) working either in government or private sectors. More than half of participating women living in cities (n = 132, 58.9%), while only 3.6% (n = 8) living in camps and 37.5% (n = 84) living in villages. Only 10.8% (n = 24) of the participated women have a high monthly income (>US\$ 1550) according to standard life in Palestine, while 10.8% (n = 24) have income between US\$ 1250-1550. Most of the participated women have low monthly income as the following: 29.7% (n = 66) their income less than US\$ 650, 28.4% (n = 63) their income between US\$ 650-1000 and 20.3% (n = 45) their income between US\$ 1000-1250 as shown in Table 1. About 89.6% (n = 198) of married women who completed the research survey did not suffer from any disease but a small majority, about 10.5% (n = 23), were suffering from various diseases, most of these diseases were diabetes (26.1%, n = 6), followed by high blood pressure (13%, n = 3), disc and joints (4.3%, n = 1) and thyroid problems (13%, n = 3). There are also other diseases, including urinary tract infections (8.7%, n = 2) and ovarian cysts (8.7%, n = 2) as shown in Table 1. Other characteristics of participating women were present in Table 1 including the length of the marriage period, the number of children, if their

husband is a relative and the number of times been pregnant as follows: Only 49 (22.3%) women have been married more than 10 years, while 64 women (29.1%) have been married 1-2 years, 39 women (17.7%) have been married 3-4 years and 33 (15%) women have been married 5-6 years. Regarding the number of the children they have, only 23 women (10%) didn't have any children, while 70 women (30.4%) have 1 child, 32 women (13.9%) have 3 children, 25 women (10.9%) have 4 children and 11 women (4.8%) have more than 5 children. Most of the participated women in the study (n = 158, 71.2%) their husband is not a relative to them and most of them have been pregnant once or twice (n = 58, 30% and n = 60, 31%), respectively as presented in Table 1.

Around 24% (n = 52) of the 230 women observed had issues with fertility and pregnancy and about 27% (n = 60) of them had infertility in the family, about 69% (n = 158) of women who participated in this research study mentioned that they didn't use the fertility drugs and about 31% (n = 67) of women who suffer from infertility resorted used fertility drugs. In general, 68.6% (n = 48) used fertility drugs when they were not pregnant and 31.4% (n = 22) after their first pregnancy, the majority of women (64%, n = 58) who had a late pregnancy had prior testing performed before taking fertility drugs if the doctor requests this, that facilitated diagnosis and after determining the best treatment in Table 2. More than half of participating

Table 2: Fertility medications

	Frequency	Percentage
<b>Problems with fertility or pregnancy</b>		
Yes	52	23.7
No	167	76.3
<b>Family with infertility or fertility problems</b>		
Yes	60	27.4
No	152	69.4
<b>Used fertility drugs</b>		
Yes	67	30.6
No	158	69
<b>Has fertility drugs covered by health insurance</b>		
Yes	8	8.4
No	87	91.6
<b>Number of times of taking fertility medicines</b>		
Once	38	48.7
Twice	20	25.6
Three times	7	9
Four times	3	3.8
More than four times	10	12.8
<b>In what birth number are fertility drugs used?</b>		
First	48	68.6
Second	13	18.6
Third	4	5.7
Fourth	2	2.9
More than fourth	3	4.3
<b>Number of pregnancies the fertility drugs have been used</b>		
First	48	68.6
Second	13	18.6
Third	4	5.7
Fourth	2	2.9
More than fourth	3	4.3
<b>Pregnant after using fertility drugs</b>		
Yes	56	49.6
No	57	50.4
<b>Tests are taken before taking fertility drugs</b>		
Yes	58	63.7
No	33	36.3
<b>Women who got children after using fertility drugs</b>		
Yes	53	57.6
No	39	42.4
<b>Children affected by fertility drugs</b>		
Yes	4	4.9
No	78	95.1
<b>Women affected by fertility drugs in the long term and symptoms persisted for a long time</b>		
Yes	16	19.3
No	67	80.7
<b>Women want to take fertility drugs in their next pregnancy</b>		
Yes	40	32.8
No	82	67.2
<b>Women signed responsibility form for the use of fertility drugs and negative effects</b>		
Yes	16	13.8
No	100	86.8
<b>Women affected by fertility drugs</b>		
Yes	44	39.6
No	67	60.4
<b>Women visited a doctor after signs and symptoms of fertility drugs</b>		
Yes	40	50
No	40	50



women who used the fertility drugs used them more than one time (51.3%, n = 40) and about 69% (n= 48) took fertility treatments after the first birth. About 50% (n = 56) of the women who used fertility drugs got pregnant after taking fertility drugs and about 58% (n = 53) of the sample subjects gave birth after taking fertility drugs, a high percentage of women 87% (n = 100) did not sign any paper or responsibility form for using fertility drugs or if negative effects occur (Table 2). Few numbers of the women and the children affected by fertility drugs, only 4 children affected and one case only was a serious case which causes a brain paralysis for the baby in the fourth pregnancy of one woman and 44 women affected by the fertility drugs and 16 women also affected by fertility drugs in the long term and symptoms persisted for a long time. A reasonable number of women (n = 44) want to take fertility drugs in their next pregnancy. Half of the women visited a physician for treatment of the signs and symptoms of fertility drugs (Table 2).

Table 3 shows the different signs and symptoms of fertility drugs used. Most of the women affected by fertility drugs used to suffer more than one sign/symptom at the same time. Mood changes, anxiety/worried, breast pain, headache and nausea were the most common signs and symptoms of fertility drugs used in Table 3. Forty-four women suffer from mood change, while 38 women faced anxiety, 31 women have nausea, 22 women have depression, 31 women have a headache and 32 women have breast pain after using fertility medications as represented in Table 3. Participated women suffers also from other signs and symptoms after the use of fertility drugs as follows: Multiple births (n = 8), ovarian hyperstimulation (n = 17), pregnancy loss (n = 11), vomiting (n = 19), tender or softness of breasts (n = 10) and hardening of the breasts (n = 17).

Most of the women who used the fertility drugs did not face any signs and symptoms even by using the medications more than one time. About 26% (n = 17) of the women had fewer symptoms than the first time, 23% (n = 15) had symptoms as the first time and only 15% (n= 10) had symptoms more than the first time Fig. 1.

Letrozole was the most common drug used to cure issues with infertility and fertility among the participated women (n = 29), then Metformin (n = 24), clomiphene citrate (n = 18), bromocriptine (n = 15), gonadotropins (n = 13) and others including golin (n = 6) as shown in Fig. 2.

The analysis of variance was used for the differences in the responses of the study sample members towards fertility drugs used by women and their effectiveness and impact on the mother and child according to the governorate. Table 4 shows the results of the analysis of the differences in the

Table 3: Signs and symptoms of fertility drugs used

Signs and symptoms	Numbers
Mood change	44
Anxiety/worried	38
Nausea	31
Multiple births (more than one child)	8
Depression	22
Ovarian hyperstimulation	17
Pregnancy loss	11
Headache	31
Vomiting	19
Tender or softness of breasts	10
Breast pain	32
Hardening of the breasts	17
No signs and symptoms	16
Others	6

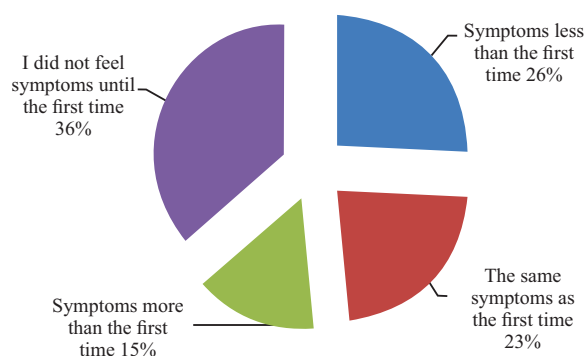


Fig. 1: Symptoms and signs when fertility drugs are used more than once and compared for the first time use

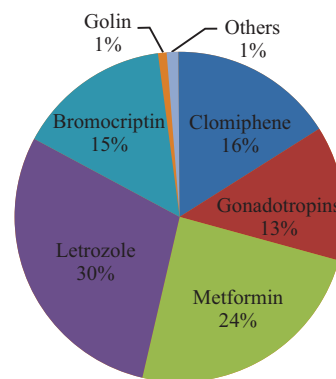


Fig. 2: Fertility drugs used

responses of the study sample members towards fertility drugs used by participated women and the extent of their effectiveness and impact on the mother and child according to the governorate is shown in Table 4.

Table 4 indicate that there are no statistically significant differences at the significance level ( $\alpha \leq 0.05$ ) in the responses of the study sample members towards fertility drugs used by women and their effectiveness and impact on the mother and child according to the governorate, because

Table 4: Analysis of the differences in the responses of the study sample towards fertility drugs used and impact on the mother and child according to the governorate

Groups	Sum of squares	df	Mean square	F	Significant
Between groups	2.783	8	0.348	0.933	0.490
Within groups	79.048	212	0.373		
Total	81.831	220			

Table 5: Analysis of the differences in the responses of the study sample towards fertility drugs used and impact on the mother and child according to age

Groups	Sum of squares	df	Mean square	F	Significant
Between groups	0.438	4	0.110	0.290	0.884
Within groups	82.215	218	0.377		
Total	82.653	222			

Table 6: Analysis of the differences in the responses of the study sample towards fertility drugs used and impact on the mother and child according to the duration of the marriage

Groups	Sum of squares	df	Mean square	F	Significant
Between groups	6.298	5	1.260	4.328	0.001
Within groups	62.283	214	0.291		
Total	68.581	219			

the value of the statistical significance related to this is 0.490, meaning that this value is greater than the value of alpha (0.05).

Analysis of variance was used for the differences in the responses of the study sample members towards fertility drugs used by women and their effectiveness and impact on the mother and child according to age in Table 5.

Table 5 indicate that there are no statistically significant differences at the significance level ( $\alpha \leq 0.05$ ) in the responses of the study sample members towards fertility drugs used by women and their effectiveness and impact on the mother and child depending on age, because the value of the statistical significance related to this is 0.884, meaning that this value is greater than the value of alpha (0.05).

The results of the univariate analysis of the differences in the responses of the study sample members towards fertility drugs used by women and their effectiveness and impact on the mother and child according to the educational stage, place of living, monthly income, profession, disease, duration of the marriage, relative relation, number of children, were also carried out using NOVA/ Tukey test. The analysis showed there are no statistically significant differences for most of these factors except for the duration of the marriage and the number of children.

Table 6 indicate that there are statistically significant differences at the significance level ( $\alpha \leq 0.05$ ) in the responses of the study sample members towards fertility drugs used by women and their effectiveness and impact on the mother and child depending on the duration of the marriage, because the value of the statistical significance related to this is 0.001 (Table 6), meaning that this value is less than the alpha value (0.05).

To study the differences about fertility drugs used by women and their effectiveness and impact on the mother and

child depending on the duration of the marriage, the Tukey test was used for two-dimensional comparisons, where the numbers in the table represent the differences in the arithmetic circles and the following Table 7 shows the results of this test.

Table 7 indicate that there are statistically significant differences at the significance level if  $\alpha \leq 0.05$  in the responses of the study sample members to the differences in fertility drugs used by women and their effectiveness and impact on the mother and child depending on the duration of the marriage. So to look up the difference between the group from 1-2 years and the group from 3-4 years, the means differ by 0.00066, the confidence interval associated with this difference is (-0.2154, 0.2167) and that the comparison has  $\alpha$  value of 0.995. So in this case would conclude that there was no significant difference between these two groups. To look up the difference between the group from 1-2 years and the group from 5-6 years, the means differ by -0.03972, the confidence in terval associated with this difference is (-0.2676, 0.1882) and that the comparison has  $\alpha$  value of 0.731. So in this case would conclude that there was no significant difference between these two groups. To look up the difference between the group from 1-2 years and the group from 7-8 years, the means differ by -0.34845, the confidence interval associated with this difference is (-0.6263, -0.0706) and that the comparison has  $\alpha$  value of 0.014. So in this case would conclude that there was a significant difference between these two groups. To look up the difference between the group from 1-2 years and the group from 9-10 years, the means differ by -0.40061, the confidence interval associated with this difference is (-0.6978, -0.1034) and that the comparison has  $\alpha$  value of 0.008. So in this case would conclude that there was a significant difference between these two groups. To look up the difference between the

Table 7: Differences in fertility drugs used by women and their effectiveness and impact on the mother and child depending on the duration of the marriage

Multiple comparisons		Dependent variables					LSD	
							95% confidence interval	
(I) VAR00024	(J) VAR00024	Mean difference (I-J)	Std. error	Significant	Lower bound	Upper bound		
From 1-2 years	From 3-4	0.00066	0.10959	0.995	-0.2154	0.2167		
	From 5-6	-0.03972	0.11562	0.731	-0.2676	0.1882		
	From 7-8	-0.34845*	0.14095	0.014	-0.6263	-0.0706		
	From 9-10	-0.40061*	0.15079	0.008	-0.6978	-0.1034		
	More than 10	-0.34347*	0.10241	0.001	-0.5453	-0.1416		
From 3-4 years	From 1-2	-0.00066	0.10959	0.995	-0.2167	0.2154		
	From 5-6	-0.04038	0.12760	0.752	-0.2919	0.2111		
	From 7-8	-0.34911*	0.15093	0.022	-0.6466	-0.0516		
	From 9-10	-0.40127*	0.16016	0.013	-0.7170	-0.0856		
	More than 10	-0.34413*	0.11577	0.003	-0.5723	-0.1159		
From 5-6 years	From 1-2	0.03972	0.11562	0.731	-0.1882	0.2676		
	From 3-4	0.04038	0.12760	0.752	-0.2111	0.2919		
	From 7-8	-0.30873*	0.15536	0.048	-0.6150	-0.0025		
	From 9-10	-0.36089*	0.16435	0.029	-0.6848	-0.0369		
	More than 10	-0.30375*	0.12149	0.013	-0.5432	-0.0643		
From 7-8 years	From 1-2	0.34845*	0.14095	0.014	0.0706	0.6263		
	From 3-4	0.34911*	0.15093	0.022	0.0516	0.6466		
	From 5-6	0.30873*	0.15536	0.048	0.0025	0.6150		
	From 9-10	-0.05216	0.18305	0.776	-0.4130	0.3087		
	More than 10	0.00498	0.14580	0.973	-0.2824	0.2924		
From 9-10 years	From 1-2	0.40061*	0.15079	0.008	0.1034	0.6978		
	From 3-4	0.40127*	0.16016	0.013	0.0856	0.7170		
	From 5-6	0.36089*	0.16435	0.029	0.0369	0.6848		
	From 7-8	0.05216	0.18305	0.776	-0.3087	0.4130		
	More than 10	0.05714	0.15534	0.713	-0.2490	0.3633		
More than 10 years	From 1-2	0.34347*	0.10241	0.001	0.1416	0.5453		
	From 3-4	0.34413*	0.11577	0.003	0.1159	0.5723		
	From 5-6	0.30375*	0.12149	0.013	0.0643	0.5432		
	From 7-8	-0.00498	0.14580	0.973	-0.2924	0.2824		
	From 9-10	-0.05714	0.15534	0.713	-0.3633	0.2490		

\*Mean difference is significant at the 0.05 level

group from 1-2 years and the group more than 10 years, the means differ by -0.34347, the confidence interval associated with this difference is (-0.5453, -0.1416) and that the comparison has an  $\alpha$  value of 0.001. So in this case would conclude that there was a significant difference between these two groups. Could look up any comparison of the other groups of durations of the marriage with different groups in the next lines of Table 7 in the same way. The fifth column gives the  $\alpha$  value, which when is much greater than 0.05 is certainly not significant as in the case of the first three groups of the duration of the marriage, so conclude there is no difference between these groups and the fertility drugs used by women and their effectiveness and impact on the mother and child. But, in the last three groups of the duration of the marriage, the  $\alpha$  values are significant because they are less than 0.05 in those groups. The lowest  $\alpha$  value is when the duration of marriage is more than 10 years, then when the duration of marriage is from 9-10 years and then when the duration of marriage is from 7-8 years (Table 7). Thus, the

differences are in favour of the marriage period of more than 10 years, then of the marriage period of 9-10 years and then of the marriage period of 7-8 years. In general, the differences are in favour of the marriage period of these three groups (more than 6 years) compared to the duration of marriage of fewer than 6 years. In other words, from Table 7, it is noted that the differences are in favour of the marriage period of more than 10 years compared to the duration of marriage of fewer than 6 years. It is also noted that the differences are in favour of the marriage period of 9-10 years, compared to the marriage period of fewer than 6 years and it is noted that the differences are in favour of the marriage period of 7-8 years, compared to the marriage period of fewer than 6 years.

Table 8 shows the results of the analysis of the differences in the responses of the study sample members towards fertility drugs used by women and the extent of their effectiveness and impact on the mother and child according to the number of children. Table 8 indicate that there are statistically significant differences at the significance

Table 8: Analysis of the differences in the responses of the study sample towards fertility drugs used and impact on the mother and child according to the number of children

Groups	Sum of squares	df	Mean square	F	Significant
Between groups	3.960	5	0.792	2.587	0.027
Within groups	61.539	201	0.306		
Total	65.498	206			

Table 9: Differences in fertility drugs used by women and their effectiveness and impact on the mother and child depending on the number of children

Multiple comparisons						
Dependent variables						
LSD						
(I) children	(J) children	Mean difference (I-J)	Std. error	Significant	95% confidence interval	
					Lower bound	Upper bound
1.00	2.00	0.03235	0.09920	0.745	-0.1633	0.2280
	3.00	-0.18384	0.11807	0.121	-0.4167	0.0490
	4.00	-0.24692	0.12892	0.057	-0.5011	0.0073
	5.00	-0.35823*	0.16711	0.033	-0.6877	-0.0287
	> 5	-0.34615	0.17946	0.055	-0.7000	0.0077
2.00	1.00	-0.03235	0.09920	0.745	-0.2280	0.1633
	3.00	-0.21619	0.12262	0.079	-0.4580	0.0256
	4.00	-0.27927*	0.13309	0.037	-0.5417	-0.0168
	5.00	-0.39058*	0.17035	0.023	-0.7265	-0.0547
	> 5	-0.37850*	0.18248	0.039	-0.7383	-0.0187
3.00	1.00	0.18384	0.11807	0.121	-0.0490	0.4167
	2.00	0.21619	0.12262	0.079	-0.0256	0.4580
	4.00	-0.06308	0.14770	0.670	-0.3543	0.2282
	5.00	-0.17439	0.18198	0.339	-0.5332	0.1845
	> 5	-0.16231	0.19339	0.402	-0.5436	0.2190
4.00	1.00	0.24692	0.12892	0.057	-0.0073	0.5011
	2.00	0.27927*	0.13309	0.037	0.0168	0.5417
	3.00	0.06308	0.14770	0.670	-0.2282	0.3543
	5.00	-0.11131	0.18920	0.557	-0.4844	0.2618
	> 5	-0.09923	0.20020	0.621	-0.4940	0.2955
5.00	1.00	0.35823*	0.16711	0.033	0.0287	0.6877
	2.00	0.39058*	0.17035	0.023	0.0547	0.7265
	3.00	0.17439	0.18198	0.339	-0.1845	0.5332
	4.00	0.11131	0.18920	0.557	-0.2618	0.4844
	> 5	0.01208	0.22668	0.958	-0.4349	0.4591
>than 5	1.00	0.34615	0.17946	0.055	-0.0077	0.7000
	2.00	0.37850*	0.18248	0.039	0.0187	0.7383
	3.00	0.16231	0.19339	0.402	-0.2190	0.5436
	4.00	0.09923	0.20020	0.621	-0.2955	0.4940
	5.00	-0.01208	0.22668	0.958	-0.4591	0.4349

\*Mean difference is significant at the 0.05 level

level ( $\alpha \leq 0.05$ ) in the responses of the study sample members to fertility drugs used by women and their effectiveness and impact on the mother and child depending on the number of children, because the value of the statistical significance related to this is 0.027 (Table 8), meaning that this value is less than the alpha value (0.05).

To study the differences about fertility drugs used by women and their effectiveness and impact on the mother and child depending on the number of children, the Tukey test was used for two-dimensional comparisons, where the numbers in the table represent the differences in the arithmetic circles and the following Table 9 shows the results of this test.

Table 9 shows the results of the Tukey test for two-dimensional comparisons about fertility drugs used by women in Palestine and their effectiveness and impact on the mother and child according to the number of children. Similarly, Table 9 indicate that there are statistically significant differences at the significance level when  $\alpha \leq 0.05$  in the responses of the study sample members to the differences in fertility drugs used by women and their effectiveness and impact on the mother and child depending on the number of children. So to see the difference between the group that has one child and the group that has two children, the means differ by 0.03235, the confidence interval associated with this difference is (-0.1633, 0.2280) and the comparison has  $\alpha$  value

of 0.745. So in this case would conclude that there was no significant difference between these two groups. To see the difference between the group that has one child and the group that has three children, the means differ by -0.18384, the confidence interval associated with this difference is (-0.4167, 0.0490) and the comparison has an  $\alpha$  value of 0.121. So in this case would conclude that there was no significant difference between these two groups. To see the difference between the group that has one child and the group that has four children, the means differ by -0.24692, the confidence interval associated with this difference is (-0.5011, 0.0073) and the comparison has an  $\alpha$  value of 0.057. So in this case would conclude that there was no significant difference between these two groups. To see the difference between the group that has one child and the group that has five children, the means differ by -0.35823, the confidence interval associated with this difference is (-0.6877, -0.0287) and the comparison has an  $\alpha$  value of 0.033. So in this case would conclude that there was a significant difference between these two groups. To see the difference between the group that has one child and the group that has more than five children, the means differ by -0.34615, the confidence interval associated with this difference is (-0.7000, 0.0077) and the comparison has an  $\alpha$  value of 0.055. So in this case would conclude that there was no significant difference between these two groups. Could look up any comparison of the other groups of the number of children with different groups in the next lines of Table 9 in the same way. The fifth column gives the  $\alpha$  values, which when is much greater than 0.05 is certainly not significant as in the case of the first three groups of the number of children, so conclude there is no difference between these groups and the fertility drugs used by women and their effectiveness and impact on the mother and child. Table 9 shows the results of the Tukey test for two-dimensional comparisons about fertility drugs used by women in Palestine and their effectiveness and impact on the mother and child according to the number of children. In Table 9, it is noted that the differences are in favour of those who have 5 children versus those who have one or two children as well as in favour of those who have 4 children versus those who have two children and in favour of those who have more than 5 children versus those who have two children. But, in the last groups of the number of children who have four or five and more than five children, the  $\alpha$  values are significant because they are less than 0.05 in those groups. The lowest  $\alpha$  value is when the women have 5 children, then when the duration of marriage when they have 4 children and then when they have more than five children (Table 9). Thus, the differences are in favour

of 5 children, then of 4 children and then of more than 5 children. In general, the differences are in favour of the number of these three groups (who have more than 3 children) compared to the number of children less than 3 children. In other words, from Table 9, it is noted that the differences are in favour of those who have 5 children versus those who have one or two children as well as in favour of those who have 4 children versus those who have two children and in favour of those who have more than 5 children versus those who have two children.

## **DISCUSSION**

Infertility is one of the most common problems prevalent in Palestine, which suffers from the social and emotional outlook due to delaying child bearing for a few years<sup>25-28</sup>. Drugs to treat infertility are usually very widely used to increase the chances of fertility and childbearing. Therefore, it is necessary to study the effect and effectiveness of these medicines on both the mother and the child. In this research study, studied the fertility medicines used by the women to assess the percentage of Palestinian women who use fertility medications for treating infertility and the side effects or any withdrawing backs on both mothers and children by the drugs used. The current study was carried out according to several criteria and characteristics. The study demonstrated that the effect and effectiveness of these medicines are safe for both the mother and the child and these treatments were helpful to increase the chances of childbearing and there are no serious side effects during their uses in pregnancy or after childbirth. It was found that one of the most prominent reasons which lead to infertility was the long period of marriage and the high number of children. The infertility medicines were used to treat the problems of fertility caused by these two criteria as it was observed that the response to these treatments reduces infertility and increases the chances of childbearing. Most of the women who used fertility medicines had multiple pregnancies (such as twins, triplets or more than that). The research study included only 230 Palestinian women, which they have filled out the questionnaire and these participated women were divided into two groups. The first one they use the infertility drugs and another group of women who don't use the infertility drugs. The research study included Palestinian women from different Governorates in Palestine. The participated women are the majority from Hebron and other women from other governorates have participated including Jerusalem, Bethlehem, Jenin, Ramallah, Tulkarm, Gaza, Qalqilya, Nablus and Jericho.

The main reasons for women didn't use the infertility drugs are fear of their side effects or they think that these drugs will not get the desired aims. Only a few women delivered their babies with minor side effects. Only one woman mentioned that her baby had brain paralysis in her fourth pregnancy. Other women hesitate to take any fertility medication because either they didn't need it or they want to experience natural pregnancy but some women want to use the drugs or repeat to use them if they needed. It is important mentioning that the Palestinian Government and private hospitals or medical centres have the facilities for the treatment of infertility.

There were statistically significant differences in the response of the subjects of the study sample towards the fertility drugs used by women and the extent of their effectiveness and their effect on the mother and child according to the duration of the marriage and the number of children. Besides the marriage length, infertility was more observed among those with a high number of children. There was no significant statistical difference between infertility and ages of women, educational levels, monthly income and other variables. The effect of fertility medicines on children was found to be very slight as about 95% of them were not affected by these drugs. Thus, the drugs were safe for both the mother and the child. However, the common causes of infertility depend mainly on both the length of the marriage period and the number of children. It is true that in this research study the fertility medicines were safe for both mother and child as mentioned but the use of such fertility-stimulating drugs after many times pregnancy showed minor side effects and in a few cases unsolicited side effects, such as cerebral palsy in a child. The participants' individuals who suffer from fertility and pregnancy problems and required treatment as such, the majority pay for the treatment from their pocket, the health insurance pay only for a few of them. Although the data analysis showed that fertility treatments were safe for both mother and baby, there are many possible side effects associated with the use of fertility drugs. The mood change is the most common symptom, followed by nausea and anxiety (Table 3). About a third of the sample studied who used the fertility drugs more than once did not feel side effects until the first time, while about a quarter of them was suffering from the same symptoms as the first time. A few women taking these medications may be affected by long-term side effects, especially mood changes. A reasonable number of women were affected and felt with same symptoms even by using fertility drugs many times. Only one-third of women using fertility drugs are considering

undertaking and repeating to get pregnant, while the largest number of them disagreed with repeating the attempt.

Clomiphene and metformin in some studies are considered the first line of treatment for infertility<sup>29,30</sup>. But, in another study, it is reported that clomiphene citrate is the first-line treatment of infertility and letrozole is the second-line.<sup>31</sup> A study by Legro *et al.*<sup>32</sup>. showed that letrozole is a more effective medication for ovulation induction than clomiphene in women with polycystic ovary syndrome. This made letrozole the first-line medication to treat infertility. Different studies reported that Letrozole is associated with specifically impaired memory<sup>33</sup>, mood disturbances, somnolence, anxiety, fatigue and hot flashes<sup>34-36</sup>. Clomiphene reported having some undesirable side effects, including changes in mood and flushing and resistance<sup>37</sup>. Current results are consistent with these studies as in our study the medications used have similar side effects like mood changes, anxiety/worried, headache and nausea. These adverse effects in the current study were the most common signs and symptoms of fertility drugs used. Besides, in our study, letrozole was the most common drug used to cure issues with infertility and fertility among the participated women. It was also found that the second most used fertility drug is metformin, then clomiphene citrate, then bromocriptine and the least used drug was gonadotropins. This is quite different from the mentioned studies as it is reported that Clomiphene is the second most drug use, not metformin. The current study determined the effect of fertility drugs used to treat and reduce the prevalence of infertility and fertility problems in Palestine. It was found that the decrease in fertility was related to the length of the marriage and the increase in the number of children. The study also determined that the economic status, educational level and nature of work did not affect fertility using assisted reproductive treatments. There was knowledge among women about the medicines used and the accompanying side effects as few women suffer from swelling in the limbs due to fluid accumulation, These medicines have no long-term effects. The study shows that the women who have taken these therapy didn't have major side effects the symptoms were slight on mothers and also the medicines didn't affect the babies. There were mixed opinions about the desire to return to use these drugs again as the majority did not prefer to repeat their use despite the absence of negative side effects on both the mother and the child. To the best of our knowledge, this is the first study in Palestine to study fertility medication uses and their effect on mothers and children. The study covered the topic from different angles but on the other hand, this study had some limitations. First, used a convenient

sampling for participants' selection. Moreover, most of the study subjects are from the Hebron governorate. Because most of the participants are only from one area, current findings may not accurately reflect all the issues. Furthermore, the cross-sectional design that was adopted in the current study did not allow for testing between variables accurately. The recall bias and language level of complexity could not be eliminated due to limitations in such studies especially for online sample surveys as a face-to-face study is usually more accurate. Finally, the sample size is quite small, therefore to get more accurate results further study needed to be carried out with a larger sample size, considering the participants from over governorate and should be a face-to-face interview study.

### **CONCLUSION**

Fertility therapy appears to be common in use in Palestinian women and effective in reducing infertility problems. The length of the marriage and the rise in the number of children were some of the most significant factors contributing to infertility, which contributed to the emergence of multiple pregnancies (twins). Most Palestinian women of various social, economic and educational standards are unaware of the risk of neglecting the treatment of infertility and fertility problems. The side effect of infertility drugs on both the mothers and their babies were minor or none even on long-term uses. There is an important necessity to clarify the effects and effectiveness of using fertility drugs for Palestinian women to enhance childbearing chances reduce the spread of this problem and thus reduce the negative perception directed for women by not embracing a child. It is also important to guide women and to show the importance of the use of these medicines as they are safe to a sufficient degree.

### **SIGNIFICANCE STATEMENT**

This study discovered fertility medication uses and their effect on mothers and children among Palestinian that can be beneficial to the ministry of health, patients and as a scientific base for further investigations to determine the efficacy and safety of these drugs which might contribute to better integration of public health. This study will help the researchers to uncover the critical areas of fertility medication use and their side effects that many researchers were not able to explore. Thus a new theory on fertility medication uses and their side effects and to affect positively the various aspect of women's lives may be arrived at.

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