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Title:

Risk factors associated with infertility and recurrent miscarriage among Palestinian females at the Gaza strip

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DEDICATED

To

My great mother who love me, who raised me, supported me, and taught me every thing I know.

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List of abbreviations

Abbreviation	Full word
AAV	Human adeno-associated virus
ACE	Angiotensin-converting enzyme
aCL	Anticardiolipin antibodies
APA	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
AR%	Attributable Risk Percent
C. trachomatis	*chlamydia trachomatis*
CI	Confidence interval
FSH	Follicle-stimulating hormone
FVL	Factor V Leiden
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IgG	Immunoglobulin Gamma heavy chains
IgM	Immunoglobulin Mu heavy chain
IMA	Immunologically mediated abortion
LAC	Lupus anti-coagulant
LH	Luteinizing hormone
MTHFR	Methylenetetrahydrofolate reductase
NSFG	National Survey of Family Growth
OR	Odds ratio
P	Probability value
PAI-1	plasminogen activator inhibitor-1
PAR%	Population Attributable Risk Percent
PCOS	Polycystic ovary syndrome
RM	Recurrent miscarriage
RPL	Recurrent pregnancy loss
RR	Relative risk
SPSS	Statistical Package for the Social Sciences
T4	Thyroid gland hormones
TSH	Thyroid Stimulating Hormone
US	United States
WHO	The world health organization

Abstract

Background: the inability to have children is frequently considered a personal tragedy and a curse for the couple, impacting on the entire family and even the local community. In Palestine and specially in the Gaza strip there is no documented reports or scientific wok explaining the risk factors associated with infertility and recurrent miscarriage.

Aim: the present work aims to identify the risk factors associated with infertility and recurrent miscarriage among Palestinian women in the Gaza strip.

Subjects and methods: the cases were selected randomly from those referring to Al Basma fertilization center seeking for medical management of infertility or recurrent miscarriage. While, apparently healthy fertile females who are attending public and private clinics for family planning issues were included as control group. The main tools of the present study included close ended questionnaire, interviews, ultrasound, related hormonal biochemical analysis, and thrombophilic picture.

Different statistical tests were performed included: odd ratio (OR) and its corresponding 95% confidence interval (95% CI); attributable risk percent (AR%), and population attributable risk percent (PAR%).

Results: the result of the present study showed that, about three fourth of the women who referred to the infertility clinic are seeking for treatment from infertility and about one fourths are seeking for treatment from recurrent miscarriage, the highest percentage (44.8%) of the cases were from the Gaza Governorate.

When referring to social-geographical locality the majority of the cases and the controls were from the major cities of the Gaza strip. Regarding to the age characteristics of the study population, a significantly higher mean age was reported in women with recurrent miscarriage as compared to the women with infertility. Also, the percentage of women with recurrent miscarriage and age greater than 30 years old is significantly higher than the corresponding percentages in the infertility and control groups.

Regarding to occupation, the percentage of working women in the infertility group (18.3%) and in the recurrent miscarriage group (24.6%) are significantly higher than the percentage of working women in the control group (8.7%).

According to the medical and clinical characteristics of the study population, the menstruation cycle of women, showed significantly higher percentages in those with irregular menstrual cycle in the infertility and recurrent miscarriage groups as compared to the control group. The percentage of the infertile women (18.3%) with retrieved uterus was significantly higher than those in the control group (2.6%) as well as the recurrent miscarriage group (4.9%), and the percentages of polycystic ovarian syndrome were significantly higher in infertility (17.8%) and recurrent miscarriage (23.0%) groups as compared to control group (1.7%). Also abnormities in fallopian tubes showed higher percentages in infertility (13.0%) and recurrent miscarriage (11.5%) groups as compared to control group. On the other hand, endometriosis showed a significantly higher percentage among the recurrent miscarriage group (11.5%) as compared to both the control (0.9%) and infertility (4.1 %) groups. However, percentage of uterus fibroids was significantly higher in the infertility group as compared to control group.

Regarding to Sex hormonal abnormalities, it was found that sex hormones abnormities were significantly higher in the infertility (47.3%) and recurrent miscarriage (57.4%) groups as compared to control group.

The percentage of women with previous surgical operation in the abdomen were higher in both infertility (20.1%) and recurrent miscarriage (34.4%) groups as compared to control (4.3%) group.

A higher percentages of vaginal infections were reported in the women of the infertility (45.0%) and recurrent miscarriage (44.3%) groups as compared to control group.

About 45.6% of the women in the infertility group and 70.5% in the recurrent miscarriage group are exhibiting one or more of the thrombophilic disorders.

It was concluded that the most common factors that lead to infertility and recurrent miscarriage include: Thrombophilic disorder, sex hormone abnormalities, vaginal infections, social and living stresses, abdominal surgical operation, PCOS, retroverted or tilted or tipped uterus, sexually transmitted diseases, fallopian tube damage or blockage, O blood group, working women, days of menstruation, endometriosis, presence of uterus fibroids, thyroid gland abnormality, irregularly of menstruation and family history.

Key word: Infertility, Recurrent miscarriage, Gaza strip, odds ratio, attributable risk percent, population attributable risk percent.

الملخص

عوامل الخطورة المصاحبة للعقم والإجهاض المتكرر لدى السيدات في قطاع غزة

تعتبر عدم القدرة على إنجاب الأطفال مأساة شخصية ونقمة للزوجين، مما يؤثر على الأسرة بأكملها، بل وعلى المجتمع المحلي. في فلسطين وخاصة في قطاع غزة لا يوجد هناك أي تقارير موثقة أوعلمية تبحث في عوامل الخطورة المرتبط بالعقم والإجهاض المتكرر لدى النساء.

يهدف العمل الحالي إلى تحديد عوامل الخطورة المرتبطة بالعقم والإجهاض المتكرر بين النساء الفلسطينيات في قطاع غزة. تم اختيار الحالات بشكل عشوائي من السيدات اللاتي يقمن بمراجعة مركز البسمة للإخصاب وأطفال الأنابيب، في حين تم اختيار المجموعة الضابطة من الإناث اللواتي لديهن أطفال واللواتي يحضرن إلى العيادات العامة والخاصة من أجل قضايا تنظيم الأسرة والفحوصات العامة. وكانت النسبة بين الحالات والضوابط هي 1:2 وكان هناك مطابقة قدر الإمكان من ناحية السن والسكن والحالة الاجتماعية. وشملت الأدوات الرئيسية لهذه الدراسة الاستبيان ،المقابلات ، الموجات فوق الصوتية أوالتصوير فوق الصوتي، التحاليل البيوكيميائية والهرمونية، والفحوصات الجينية لمشاكل تجلط الدم.

أظهرت نتائج الدراسة الحالية أن نحوثلاثة أرباع (169 / 230 ، 73.5 ٪) من النساء اللواتي يتوجهن إلى عيادة العقم يسعين للعلاج من العقم، وحوالي ربع (61 / 230 ، 26.5 ٪) يبحثن عن العلاج من الإجهاض المتكرر، وأعلى نسبة (44.8 ٪) من الحالات كانت من محافظة غزة.

عند الإشارة إلى التوزيع الجغرافي، أظهرت النتائج أن الغالبية العظمى من الحالات (144 / 230 ، 62.6 ٪) والضوابط (64 / 115 ، 55.7 ٪) من المدن الرئيسية في قطاع غزة.

عند النظر إلى الفئة العمرية، وجدت النتائج أن الوسط العمري لحالات الإجهاض المتكرر لدى النساء أعلى بكثير بالمقارنة مع النساء المصابات بالعقم. أيضا، فإن النسبة المئوية للنساء المصابات بالإجهاض المتكرر للفئة العمرية التي تزيد عن ثلاثين عاما هي أعلى بكثير من النسب المقابلة في مجموعتي العقم والضوابط. فيما يتعلق بعمل السيدة، فإن نسبة النساء العاملات في مجموعة العقم (18.3 ٪) وفي مجموعة الإجهاض المتكرر (24.6%) وهي أعلى بكثير من نسبة النساء العاملات في المجموعة الضابطة (8.70٪).

وفقا للناحية الصحية والسريرية لدى النساء ، أظهرت النتائج أن هناك نسبة مرتفعة كثيرا من النساء اللاتي يعانين من عدم انتظام الدورة الشهرية في مجموعتي العقم والإجهاض المتكرر مقارنة مع مجموعة التحكم. وكانت نسبة النساء المصابات بالعقم واللاتي يعانين من مشكلة الرحم المقلوب هي(18.3 ٪) وهي أعلى بكثير من تلك الموجودة في المجموعة الضابطة (2.6 ٪) وكذلك مجموعة الإجهاض المتكرر (4.9 ٪). أما النسبة المئوية لتكيس المبيض فكانت أعلى بشكل ملموس في العقم (17.8 ٪) والإجهاض المتكرر بالمقارنة مع المجموعة الضابطة (1.7 ٪).

أظهرت النتائج أيضا أن تشوهات قناة فالوب قد ظهرت بنسبة (13.0 ٪) في حالت العقم ونسبة (11.5 ٪) في حالت الإجهاض المتكرر بالمقارنة مع المجموعة الضابطة. من ناحية أخرى ، أظهرت النتائج أن بطانة الرحم الهاجرة أعلى بكثير بين مجموعة الإجهاض المتكرر (11.5 ٪) بالمقارنة مع المجموعة الضابطة (0.9 ٪) ومجموعة العقم (4.1 ٪). في حين أن نتائج تليفات الرحم قد ظهرت بنسبة كبيرة في مجموعة العقم بالمقارنة مع المجموعة الضابطة.

أما بالنسبة لنتائج فحص الهرمونات الجنسية فقد أظهرت النتائج أن النسبة الأعلى في الخلل الهرموني موجودة لدى مجموعة الإجهاض المتكرر (57.4 ٪) ومجموعة العقم (47.3 ٪) بالمقارنة مع المجموعة الضابطة. وكانت النسبة المئوية للنساء اللاتي تعرضن لعمليات جراحية سابقة في منطقة البطن مرتفعة في مجموعتي الإجهاض المتكرر (34.4 ٪) والعقم (20.1 ٪) بالمقارنة مع المجموعة الضابطة (4.3 ٪). ووجد أن نسبة مرتفعة من الالتهابات المهبلية توجد في كل من النساء اللاتي يعانين من العقم (45.0 ٪) والإجهاض المتكرر مقارنة بالمجموعة الضابطة (44.3 ٪).

النتائج الأكثر أهمية في هذه الدراسة هي فيما يتعلق باضطرابات أحد أو أكثر من عوامل تجلط الدم ذات البعد الوراثي، فلقد أظهرت النتائج أن حوالي (45.6 ٪) من النساء في مجموعة العقم و(70.5 ٪) في مجموعة الإجهاض المتكرر بعانين من اضطرابات في وحدا أو أكثر من عوامل تجلط الدم ذات البعد الوراثي

نستنتج من هذه الدراسة أن العوامل المؤدية إلى العقم والإجهاض المتكرر كثيرة ومتعددة وتشمل كلا من: الاعتلال في تجلط الدم، الالتهابات المهبلية، الحالة الاجتماعية والمعيشية، العمليات الجراحية في البطن، ومتلازمة تكيس المبايض، ميل أو انقلاب الرحم، الأمراض المنقولة جنسيا، تشوهات وانسداد قناة فالوب، فصيلة الدم، عمل المرأة، عدد أيام الدورة الشهرية وانتظامها، بطانة الرحم الهاجرة، وجود أورام أو تليفات في الرحم، اعتلال الغدة الدرقية، اعتلال الهرمونات الجنسية والسجل العائلي.

كما أننا و من خلال هذه الدراسة نوصى بالإعداد الجيد والفحص المبكر لكافة السيدات اللاتي يرغبن بالحمل تجنبا لكثير من إهدار الوقت و المال و لتحديد و دراسة و معالجة أسباب أو عوامل تساهم في حدوث العقم أو الإجهاض المتكرر مبكرا.

I-Introduction

Conception and pregnancy are complicated processes involving many biologic factors and phases. The man and the women need to produce healthy sperm and eggs respectively. The cervical mucus needs to be healthy and abundant so that the sperm can travel up through the cervical canal to the uterus and fallopian tubes. The fallopian tubes need to be open and accessible so that the sperm can reach the egg. The sperm has to be able to fertilize the egg when they make contact. The fertilized egg (the embryo) has to be able to implant in the woman's uterus; and, finally, both the embryo and the woman's uterine environment need to be healthy and strong for the baby to come to term. If any one of the biologic factors is impaired or damaged in any way, infertility can result **(World Health Organization,WHO, 1991; Buckett & Bentick, 1997).**

Infertility is the inability to conceive and become pregnant after 12 months of regular, unprotected sex at the time of ovulation. Infertility is not a "woman's" problem. It is a medical problem of the male or female reproductive system and affects men and women equally. In about one third of cases, the cause is traced to the woman, another third of cases are traced to the man. The rest are caused by unknown factors or a physiological incompatibility **(Frank, 1993)**. Infertility is a common medical condition, affecting approximately 6 million people in the United States every year. It is estimated that about 10% to 15% of couples who try to conceive are unable to do so after 1 year. Twelve months may seem like an arbitrary length of time, but it makes sense given that most fertile couples become pregnant within a year. So if a couple

does not conceive after a year of effort, it is likely that the man, the woman, or both are infertile **(Mosher 1998).**

Recurrent miscarriage is traditionally defined as three or more consecutive miscarriages occurring before 20 weeks post-menstruation **(Bulletti *et al.*, 1996; Bricker and Farquharson, 2002)**. Around 1% of fertile couples will experience recurrent early pregnancy losses **(Berry *et al.*, 1995).** The risk of recurrence increases with the maternal age and number of successive losses **(Brigham *et al.*, 1999; Andersen *et al.*, 2000).** Thus, the number of previous miscarriages and maternal age are the most important covariates, and they have to be taken into account when planning therapeutic trials. The ideal trial should have stratification for the number of previous miscarriages and maternal age, with randomization between control and experimental treatments, within each stratum as recommended in previous work **(Christiansen *et al.*, 2005).**

The most common cause of female infertility is an ovulation disorder. Other causes of female infertility include blocked fallopian tubes, polycystic ovary syndrome (PCOS) and endometriosis. While in recurrent miscarriages it is believed that the vast majority of these early losses are due to genetic or chromosomal problems with the fetus. Recurrent miscarriage have been directly associated with maternal thrombophilic disorders **(Rey *et al.*, 2003),** parental chromosomal anomalies **(Franssen *et al.*, 2005),** and structural uterine anomalies and indirectly with maternal immune dysfunction and endocrine abnormalities **(Carrington *et al.*, 2005).** However, as the majority of recurrent miscarriage cases following investigation are classified as idiopathic, that is, no identifiable cause in either partner, it is generally

accepted that within the idiopathic group there is considerable heterogeneity and it is unlikely that one single pathological mechanism can be attributed to their recurrent miscarriage history **(Stirrat, 1990; Foka *et al.*,2000; Jauniaux *et al*.,2006).**

Problem Statement

One of the most important and underappreciated reproductive health problems in developing countries is the high rate of infertility and childlessness **(Bergstrom, 1992; Leke *et al.*, 1993)**. The inability to have children is frequently considered a personal tragedy and a curse for the couple, impacting on the entire family and even the local community. Negative psychosocial consequences of childlessness are common and often severe **(Daar and Merali, 2002; Dyer, 2005)**. In many cultures, including the Arabic oriental, womanhood is defined through motherhood and infertile women usually carry the blame for the couple's inability to conceive. Childless women are frequently stigmatized, resulting in isolation, neglect, domestic violence and polygamy **(Gerrits, 1997; Papreen *et al.*, 2000; Richards, 2002; Wiersema *et al.*, 2006).**

Although good documentation of the prevalence of infertility is lacking, the WHO estimates that there are 60-80 million infertile couples worldwide with the highest incidence in some regions of Sub-Saharan Africa which is said to have an "infertility belt" wrapped around its center as infertility rate may reach 50% compared to 20% in Eastern Mediterranean region and 11% in the developed world **(Fathalla *et al.*, 2006; Boivin *et al.*, 2007).**

In Palestine and specially in the Gaza strip there is no documented reports or published scientific wok that investigated the prevalence and risk factors associated with infertility and recurrent miscarriage. Moreover, the demographic records published by the Palestinian Central Bureau of Statistics revealed a significant decline in fertility rates which reached 4.6 births per woman in Palestine during 2004 , of which 4.1 in the West Bank and 5.8 in Gaza Strip. While fertility rate in Palestine was 6.0 births per woman in 1997.

General objective

The general objective of the study is to identify and quantify the risk factors associated with infertility and recurrent miscarriage among Palestinian women in the Gaza strip.

The specific objectives are:

- To highlight the most common risk factors for infertility and recurrent miscarriage.
- To find any association between the different risk factors that lead to infertility and recurrent miscarriage.
- To provide the community and the health care providers with the first scientific data about the risk factors for infertility and recurrent miscarriage in the Gaza strip.

II. Review of Literature

II.1. Infertility

II.1.1. Definitions

Epidemiological definition of infertility is not very specific, because the substantial fraction of couples defined as infertile if they had not conceived after one year of unprotected intercourse, go on to conceive without ever receiving any treatment. Thus, the levels of infertility obtained using this epidemiological definition of infertility will lead to higher estimates of infertility, compared to estimates obtained. Demographers have modified the epidemiological definition of infertility as "the inability of a non-contracepting sexually active woman to have a live birth". Demographers have shifted the endpoint from conceptions to live births, because it is difficult to collect complete data about conceptions in population based studies **(Larsen, 2000).**

Infertility is the inability of a sexually active couple, not using any birth control, to get pregnant after one year of trying **(Marcell & Robert, 2005).** The clinical definition of infertility is currently known as 1 year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycles **(Gnoth *et al*., 2005).**

Infertility is also defined as failure to conceive after one year of regular unprotected sexual relationship. Infertility is classified as primary, when there is no history of pregnancy having occurred, or secondary when inability to conceive occurs after one or more successful pregnancies **(Mokhtar *et al*.,2006). Safarinejad in 2007** defined infertility as a disease or condition of the reproductive system that interferes with the ability to conceive. While **Bhattacharya in 2009** defined it as the inability to conceive following 12–24 months of exposure to pregnancy.

II.1.2. Prevalence of infertility

The world monthly conception rates are 20% to 25% in normal young couples actively attempting pregnancy. **Guttmacher in 1956** reported that 85% of normal couples conceived after 1 year of trial, and 93% after 2 years. More recently **Page in 1991** surveyed 250 couples by mail and found that of the 82% who responded to his inquiry, 20 to 35% took longer than 1 year to conceive. At present in the United States, approximately 10 to 20% of couples are infertile **(Jewelewiez & Wallach , 1991).**

Not like the etiology of infertility the exact prevalence of infertility in community cannot be addressed by WHO study, because the WHO study centers were not selected at random and they were not representative of their region or country, and for instance, Africa was represented by only four centers in Ibadan (Nigeria), Lusaka (Zambia), Nairobi (Kenya) and Yaounde (Cameroon), respectively. Also, all infertile couples probably did not seek treatment and both partners were probably not diagnosed in all infertile couples. For these two criteria, no study has provided national estimates of the prevalence of primary and secondary infertility **.**

Twenty eight African countries were analyzed by **Larsen** to show the incidence of primary and secondary infertility, it was found that elevated levels of secondary infertility prevail in most countries. Secondary infertility for women age 20–44 ranges from 5% in Togo to 23% in Central African Republic **(Larsen, 2000).**

Infertility affects more than 3 million couples in the United States. About 40% of cases are due to female factors, 30% are due to male factors, 20% are a

combination of both, and in about 10% the cause is unknown **(Marcell & Robert, 2005). Mosher in 1998** found that 65% of the infertile females in the United States had primary infertility and 35% had secondary infertility**.**

WHO, 1996 estimates that the highest incidence of infertility are found in some regions of Sub-Saharan Africa which is said to have an "infertility belt" wrapped around its center as infertility rate may reach 50% compared to 20% in Eastern Mediterranean Region and 11% in the developed world. The prevalence of infertility in Egypt has been estimated to be between 10 to15% among married couples and causes of infertility can be found in about 90% of infertile cases, and in about 10% of couples the causes is not explained **(Mokhtar *et al*.,2006).**

Infertility prevalence is characterized by a very large geographical variability. Prevalence depends on many reasons include the age group examined, the definition of infertility, geographical areas involved, the composition of the population studied, the selection criteria, and the method of the study used**.** About 25% of European and American couples suffer from reproductive disorders. In industrialized countries the lifetime prevalence of infertility in populations of women who have tried to have children is 16-26%, and the prevalence of infertility increased with age. The national estimate of primary infertility in Iran was 4.6%. The primary infertility increased significantly from 2.6 to 4.3 to 5.5% for the 1985–1989, 1990–1994 and 1995–2000 marriage cohorts. The prevalence of secondary infertility was 3.4% **(Safarinejad, 2007).** Data collected by WHO through demographic and health surveys in developing countries estimated that 186 million married women (excluding China) were infertile in the year 2002, however, the full scale of the problem is not known **(Safarinejad, 2007; Bhattacharya, 2009).**

II.1.3. Etiology of infertility

Conception and pregnancy leading to a live birth depend on complete, interdependent integration of anatomic, physiologic, and immunologic factors acting in concert. In addition to anatomic integrity of female reproductive tract, the women require a functionally intact hypothalamic pituitary, ovarian axis, regular ovulatory cycles, normal folliculogenesis and ovulation, and an effective lutel phase **(Jewelewiez & Wallach, 1991). Marcell & Robert, in 2005** mentioned that for pregnancy to occur, several things have to happen :

- An egg must develop in the woman's ovary.
- The egg has to be released each month into the fallopian tube (ovulation).
- A man's sperm must fertilize the egg in the fallopian tube at specific time.
- The fertilized egg must be able to travel through the fallopian tubes and attach (implant) in the lining of the uterus.

II.1.4.The risk factors for infertility

II.1.4.1. Age

The females with age of menarche more than 16 years have high risk to develop infertility than those with age of menarche less than 16 years. Also the age of marriage was a significant predictor for primary infertility **(Mokhtar *et al.*,2006).**

Safarinejad in 2007 found from analyzed sociodemographic data collected from Iran, that the age is most strongly correlated with the likelihood of infertility, also infertility is an age-dependent disorder, possibly resulting from physiological changes associated with the ageing process. The prevalence of infertility increased from 4% in women aged 15–24 years old to 17% in those

>39 years old. Also 40-50 years old women are likely to experience fertility problems four times more when compared with women aged 15–24 years old**.**

II.1.4.2. Menstrual cycle disturbances

Since the menstrual cycle is considered the really clearest reflection of a female's hormonal status, and as the bleeding that occurs basically marks the shedding of the previously prepared uterine lining and thus the end of the ovulatory cycle, a female's menstrual history is of great importance in initially assessing the problem of apparent infertility. Thus frequency and the regulatory of periods, their heaviness in loss and the amount of pain, or their scantiness, or even absence, will all be considered as indicator whether ovulation is occurring predictably or perhaps not at all**.** The regulatory of menstrual cycle is of great importance in the study of infertility. It was found that irregular and unpredictable menstruation will indicate that hormonal production is fluctuant and inconsistent so it suggests that ovulation is failing to occur regularly each month.

Scanty periods may demonstrate a failure in uterine lining build-up, and this is due to a reduction in progesterone released from the ovarian follicle, or even show that no follicle (and therefore no egg cell) is being produced at all**.** Heavy periods with sever pain may suggest that there are fibroids in the uterine wall, which by their presence prevent implantation and thus a pregnancy, even though ovulation and conception may have occurred.

Also painful menstruation with sever discomfort all over the low abdomen and pelvis may indicate endometriosis, which by its scar formation has blocked off the tubes, ovaries or parts of the pelvic cavity with adhesions. This disorder may prevent all probabilities of conception despite regular production each month of a

healthy egg cell. Persist vaginal losses of bleeding or red /brown discharge may mean that there is disease of cervix or a uterine polyp (could be infection) that similarly prevents access of otherwise healthy sperm to a healthy egg cell higher up in the uterine tubes. From that we take in consideration that a woman's menstrual history will say a lot about her internal and fertility status **(Gann,1988).**

Giwercman *et al.*, in 1994 found that many abnormal cycles may be associated with infertility**,** also most of secondary infertile females had menstrual irregularities **(Mokhtar *et al*.,2006).**

II.1.4.3. Blocked fallopian tubes

One of the more difficult conditions that occur is the tubal blockage. The uterine tubes are narrow and relatively small in length about four to six centimeters and the sperm have to swim up the uterine cavity to them, enter either one or both, and gain access to an egg cell from the ovary at the far end of the tube, or pelvic cavity. The fertilized cell then has to proceed downward over a period of four to five days to gain access to the uterine cavity. Therefore, any blockage or disease of the tubes is a major barrier to developing pregnancy **(Gann, 1988).** Tubal disease may be a factor in 30 to 50% of infertility **(Jewelewiez & Wallach, 1991).**

II.1.4.4. Cervical mucus problems

Cervical factor accounts for 5 to 10% of infertility. Sperm receptivity of the cervical mucus is of prime importance **(Jewelewiez & Wallach, 1991).**

II.1.4.5. Endometriosis

Endometriosis is defined as the presence of endometrial-like glands and stroma outside the uterine cavity, most commonly implanted over visceral and peritoneal surfaces within the female pelvis. It exhibits disturbances of cellular proliferation,

cellular invasion and neoangiogenesis. The exact prevalence of endometriosis in the general population is not clear, the prevalence in female of reproductive age is estimated between 10 and 15%, where **Marcoux *et al.*, in 1997** found that endometriosis affects 2.5 to 3.3% of women of reproductive age, and is diagnosed in 20 to 68% of the women studied for infertility.

Endometriosis usually associated with a range of pelvic pain symptoms such as chronic dysmenorrhoea, premenstrual abdominal and pelvic pain, back pain, dysuria, dyschezia and dyspareunia. However, the relationship between different pains and endometriosis is not clearly understood and there is poor correlation between the severity of pain symptoms and anatomical staging of the disease.

The main visible features of the minimal and mild stages of endometriosis are peritoneal or ovarian endometriotic implants and filmy adhesions on the fallopian tubes or ovaries. The causal link between these lesions and infertility is much debated, as is the value of resection or ablation of these lesion consider as a treatment for infertility **(Marcoux *et al.*, 1997; Al-Jefout *et al.*, 2009). Labbok, *et al.*, in 1998** found that all stages of endometriosis were associated with infertility, **Fujishita** observed that pelvic endometriosis was usually associated with infertility **(Mokhtar *et al.*, 2006).**

The diagnosis of endometriosis is a major stumbling block for both clinical management and research studies of this enigmatic disease. At this moment, there is no simple, reliable, non-invasive way for diagnosis of endometriosis, although there are a number of studies currently underway to try and identify 'biomarkers' of this disease. Symptoms like chronic pelvic pain and infertility may suggest the presence

of endometriosis; however, laparoscopy is still required for confirmation or exclusion **(Al-Jefout *et al*., 2009).**

II.1.4.6. Polycystic ovary syndrome (PCOS)

The polycystic ovary syndrome remains one of the most common hormonal disorders in women, with a prevalence estimated between 5 and 10 %. Variance in prevalence among populations may reflect the effect of ethnic origin, race, and other environmental factors on the phenotype. Women with the polycystic ovary syndrome always have some aberration in gonadotropin secretion as compared with women who have normal menstrual cycles. However, since gonadotropin concentrations vary over the menstrual cycle and are released in a pulsatile manner into the circulation, a single measurement of luteinizing hormone(LH), and follicle-stimulating hormone(FSH) provides little diagnostic sensitivity. Thus, in routine clinical practice, abnormal gonadotropin levels (an elevated level of luteinizing hormone or an elevated ratio of luteinizing hormone to follicle-stimulating hormone) need not be documented to diagnose the polycystic ovary syndrome.

It was found that hypertension develops in some women with the polycystic ovary syndrome during their reproductive years, and sustained hypertension may develop in later life in women with the disorder. Reduced vascular compliance and vascular endothelial dysfunction were noted in most women with the polycystic ovary syndrome. Also, the degree of impairment in vascular reactivity is significantly greater than can be explained by obesity alone. Insulin-lowering therapies appear to improve the vascular endothelial dysfunction in patients with the polycystic ovary syndrome **(Ehrmann, 2005).**

Polycystic ovarian syndrome (PCOS) is thought to be the commonest cause of anovulatory infertility. **Mc Donald *et al.*, in 1993 and Franks in 1995** found that women with PCOS were at increased risk of infertility and menstrual irregularities. **Mokhter *et al.*, in 2006** found that there was significant association between PCOS and primary infertility, about one third of women with primary infertility had PCOS.

II.1.4.7. Lifestyle factors

Several lifestyle factors may affect reproduction, including habits of diet, clothing, exercise, and the use of alcohol, tobacco, and recreational drugs also exposure to textile dyes, lead, mercury and cadmium, volatile organic solvents and pesticides has been also associated with infertility **(Mokhtar *et al.*, 2006)**. Industrialization, environmental pollution, use of chemicals and repeated exposure to hazardous materials, adversely affect reproductive health. The changes in the life style and new tendencies observed during the tedious socio-economical changes had considerable influence on childbearing rate in the world **(Safarinejad, 2007).**

II.1.4.8. obesity

The fertility of obese women compared to normal weight women is lower in natural cycles and infertility treatment cycles. It also reported that even a small weight loss in an ovulatory obese infertile women, achieved in a group setting over a six month period, resulted in an improvement in ovulation, pregnancy rate and pregnancy outcome, self-esteem and endocrine parameters **(Clark, 1998).** The cause of obesity in the PCOS remains unknown, but obesity is present in at least 30 percent of cases, and in some times the percentage is as high as 75. Women in the United

States with the PCOS generally have a higher body weight than their European counterparts. This reason is considered as an explanation for the increase in the incidence of the PCOS in the U.S. population (an increase that parallels the increase in obesity) **(Ehrmann, 2005).**

II.1.4.9.Infection

In the last 30 years, sub clinical infection due to several microorganism have been implicated in infertility. Two types of mycoplsma *Mycoplsma hominis and Ureaplasma urealyticum*, have been recovered from the genital tract. Several studies have reported a greater prevalence of genital mycoplasma in cervical mucus and semen of infertile couples than in normal controls **(Jewelewiez & Wallach, 1991).** Chronic cervicitis may be, low grade, but it may damage the cervical canal and secretary glands that form the mucus, rendering the cervix inhospitable to sperm or partially blocked **(Gann, 1988).**

Another microbe can cause infertility is the *Chlamydia trachomatis* which is an obligate intracellular gram-negative like bacterium and an important cause of sexually transmitted diseases worldwide. Many Chlamydial infections are asymptomatic, and re-infections are common. If not treated, Chlamydia has a high tendency to remain persistent in inflamed tissues of the upper genital tract of patients with pelvic inflammatory disease. Prolonged inflammation may lead to tissue scarring and occlusion of Fallopian tubes. Although **Morre *et al.*, in 2002** found that many women are infected with *Chlamydia* trachomatis, only a minority will develop tubal factor infertility**,** but **Mei *et al.*, in 2009** found that women with Chlamydia trachomatis IgG antibodies had developed severe tubal infertility.

II.2. Recurrent miscarriage (RM)

II.2.1. Definitions

Recurrent miscarriage (RM) or recurrent pregnancy loss (RPL) is defined as three or more losses before 20 weeks' gestation. It is a common clinical problem that affects approximately 1% of all women of reproductive age **(Lim *et al*., 1999; Sullivan *et al*., 2003). Kovalevsky *et al*., in 2004** defined recurrent miscarriage as 2 or more spontaneous abortions**.** In other words recurrent miscarriage, is traditionally defined as three or more consecutive miscarriages occurring before 20 weeks post-menstruation **(Jauniaux *et al*., 2006).**

II.2.2. Prevalence

The exact prevalence of RM varies between different researchers. Recurrent miscarriage is recognized to arise in 22–31% of chemically and clinically documented human pregnancies, the rate may be as high as 60–78% if one takes into account these abortions occurring within the first month of conception, which usually go undetected by patients. The incidence of infertility has been estimated to be 10–15% of all couples, and 70% of all pregnancies fail to go to term; 50–60% are lost within the first month of pregnancy and may go unnoticed. Compared with the general population, a higher frequency of spontaneous abortion has been observed in infertile couples, as well as a higher prevalence of infertility among recurrent spontaneous aborters. There is a two to threefold increased rate of spontaneous abortion in women attempting pregnancy at age ≥40 years and also an increased risk of chromosomal abnormalities **(Bulletti *et al.*, 1996; Wang *et al.*, 2004).**

Lim *et al.*, in 1999 found that the prevalence of RM among pregnant women varies between 0.5–1%. While **Kovalevsky *et al.*, in 2004** found that RM affects approximately 5% of women of reproductive age**.** Recurrent miscarriage affects 12–15% of all pregnancies. Eighty percent of miscarriages occur before 12 weeks of gestation, and the majority are due to chromosomal abnormalities **(Lashen *et al.*, 2004).** About 1% of fertile couples will experience recurrent early pregnancy losses. The risk of recurrence increases with the maternal age and number of successive losses. Also the prognosis is not better for couples with prior live birth. Thus, the number of previous miscarriages and maternal age are the most important covariates, must to be taken into account when planning therapeutic trials **(Jauniaux *et al.*, 2006).**

II.2.3.Causes of recurrent miscarriage (RM)

Many etiologic factors have been implicated in recurrent miscarriage, including genetic abnormalities, endocrine disorders, endometriosis, infection, uterine anomalies, and autoimmune disorders. Recently, a relationship has been identified between the molecular phenotype of skewed X chromosome inactivation and recurrent early pregnancy loss **(Bulletti *et al*., 1996; Sullivan, 2003).**

Always not one reason lead to recurrent miscarriage, most women with recurrent pregnancy loss probably have several risk factors for miscarriage, these factor could be considered acquired or inherited one **(Foka *et al.* ,2000; Jauniaux *et al*., 2006).** An increased incidence of early and recurrent fetal loss has been suggested in women with inherited thrombophilia, including Factor V Leiden deficiency, activated protein C resistance, prothrombin G20210A and protein S deficiency.

However, other authors have found no association between maternal thrombophilia and pregnancy loss **(Kovalevsky *et al*., 2004; Jauniaux *et al*., 2006).**

Recurrent miscarriage has been directly associated with parental chromosomal anomalies, maternal thrombophilic disorders and structural uterine anomalies but indirectly with maternal immune dysfunction and endocrine abnormalities. Acquired maternal thrombophilic disorder is a well-recognized cause of RM, so women with a history of three or more early pregnancy losses, should be tested for lupus anti-coagulant (LAC) and anticardiolipin antibodies (aCL), known collectively as antiphospholipid antibodies (APA), to exclude an antiphospholipid syndrome (APS) **(Jauniaux *et al*., 2006).**

II.2.3.1. Genetic abnormalities

The genetic component may play a role in the a etiology of abortion, specifically when clinically evident genetic anomalies have been ruled out by the determination of parental karyotype from peripheral leukocytes test. **Tulppala *et al*., in 1993** determined parental karyotype and revealed chromosomal aberrations in 6 out of 63 couples, 4.8% of whom experienced recurrent spontaneous abortion. It must take in consideration that the maternal age is a better predictor of chromosome abnormality, specifically trisomy, than a history of live births or miscarriages (**Bulletti *et al*., 1996).** Higher rates of miscarriage and congenital anomalies are reported in a group of obese women **(Clark, 1998).**

Although several causes of RM have been established, more than 50% of them remain unexplained. This is a challenging issue for both patients and physicians **(Lim *et al*., 1999; Kovalevsky *et al*., 2004).** Thrombophilia have been suggested as

a possible cause of RM. Hereditary thrombophilia are a group of genetic disorders of blood coagulation resulting in a hypercoagulable state, which lead to abnormal placentation. In Early pregnancy this may manifest as spontaneous loss, in later pregnancy, thrombophilias have been associated with complications such as preeclampsia, intrauterine growth restriction, placental abruption, and stillbirth. Researcher found that the 2 most common causes of this hereditary thrombophilias are factor V Leiden (FVL) and prothrombin gene (G20210A) mutations. Factor V Leiden is a point mutation at (G1691A) that altered factor V, which is resistant to inactivation by protein C(aPCr), this results in a hypercoagulable state with a 5- to 10-fold risk of thrombosis in heterozygotes and an 80-fold risk in homozygotes**.** This disorder is common in Caucasian 3-7%. Factor V Leiden is responsible for 20% to 40% of isolated thrombotic events and 40 to 45% of familial thrombophilias.

Many studies have investigated the relationship between FVL and RM, and the majority found an association between them, with odds ratios ranging from 0.5 to 18**.** The G20210A polymorphism is common in the population but it responsible for 6.2% of recurrent miscarriage**.** It was also found that the G20210A mutation affects 1% to 4% of the US population. Its prevalence is highest among whites of Southern European decent. This mutation is associated with a 20 to 50% rise in prothrombin plasma levels. Affected women have a 3-fold increased risk of venous thrombosis, and a higher chance of myocardial infarction and cerebral thrombosis than non-carriers. Also many studies of G20210A have shown conflicting associations with RM **(Foka *et al.*, 2000; Kovalevsky *et al.*, 2004)**.

II.2.3. 2. Endocrine disorders

Recurrent spontaneous abortion is a multifactorial disorder. Endocrine abnormalities may be responsible in a substantial proportion for these abortions **(Bussen *et al.* ,1999).** Abnormal systemic endocrine disorders have been suggested as being associated with recurrent miscarriages, including insulin-dependent diabetes mellitus, thyroid disorders, luteal phase defects and hyper secretion of LH with polycystic ovaries **(Lim *et al*., 1999).**

A-Diabetes mellitus

The relation between diabetes mellitus and recurrent miscarriage still a point of controversy between different researchers. Few studies have examined specifically the role of diabetes mellitus in recurrent miscarriage. A review of more than 50 such studies from 1950 to 1986 found no correlation between spontaneous miscarriage and pre-conceptual or gestational diabetes. However, other authors have shown a significant increase in the rate of spontaneous miscarriage in pregnant women with poorly controlled insulin-dependent diabetes mellitus, who had a miscarriage rate of 45% in comparison with 15% in pregnant diabetic women with good control. This negative effect of poorly controlled diabetes on pregnancy occurs as a result of abnormal glucose metabolism **(Lim *et al,* 1999).**

B-Thyroid disorders

There is some evidence that thyroid autoimmunity may be associated with recurrent miscarriage. Anti thyroid antibodies have been suggested to be a predictor of pregnancy loss in randomly chosen obstetric populations, since their presence had been observed to be correlated with a higher rate of spontaneous miscarriage **(Lim et al, 1999).**

C-Luteal phase defects

Luteal phase defect means that there is functional inadequacy of the corpus luteum to produce appropriate amounts of progesterone which lead to inadequate endometrial maturation and probable functional defects in the early maintenance of the implanting embryo. An adequately functional corpus luteum is necessary for implantation and early growth of the embryo. Studies show that the removal of the corpus luteum prior to week 7 of gestation results in induction of abortion in most cases **(Lim *et al.*, 1999).**

Progesterone appears to be necessary to support an early pregnancy. Its potential role in women with habitual abortion due to luteal phase deficiency has been suggested, and for this reason progesterone has been used for this purpose for several decades; however, its efficacy has not yet been fully demonstrated. Although there was no significant correlation between progesterone and choronic gonadotrophin concentrations and pregnancy outcome, there may be possible molecular basis for suboptimal progesterone production in women with spontaneous abortion. So it is important to know that progesterone is an adjunctive marker for prediction of early pregnancy outcome **(Bulletti *et al*., 1996).** Most previous studies have focused on the association between recurrent spontaneous abortion and luteal phase defects, based on retarded endometrium **(Bussen *et al*. ,1999)**

D- Hypersecretion of Lutinizing hormone with polycystic ovaries

Hypersecretion of LH may contribute to miscarriage. The adverse effect of a high pre-pregnancy LH concentration on fertility and outcome of pregnancy has been seen both in women with previously successful pregnancies and in women with a history of recurrent miscarriage **(Bulletti *et al*.,1996).**

Lim *et al.*, in 1999 found that LH hyper secretion in women with polycystic ovaries

has been implicated in recurrent miscarriages. The exact reason for that is sill unknown, although various mechanisms have been proposed. One hypothesis is that a raised follicular phase LH causes premature resumption of meiosis in the oocyte (by antagonizing the action of oocyte maturation inhibitor), resulting in premature maturation of the oocyte at ovulation. Another hypothesis show that the high serum LH acts on the theca cells of the ovarian stroma to increase production of androgens which may be responsible for pregnancy loss**.**

E-Other factors

Some studies have suggested that a prolactin disorder might be responsible for some cases of the so-called 'unex- plained' habitual abortion **(Bulletti *et al*., 1996).**

II.2.3.3. Endometriosis

The role of endometriosis in recurrent pregnancy loss is still controversial. A high incidence of spontaneous abortion in infertile women with endometriosis has been found, but more recent studies suggested that the majority of spontaneous abortions associated with endometriosis are not a direct result of the endometriosis. Also many cases of unexplained infertility are associated with undiagnosed endometriosis **(Bulletti et al.1996).**

II.2.3.4. Infection

The role of maternal and fetal infections in recurrent first- trimester loss is still also controversial. Most studies tried to find association between abnormal flora in the lower genetic tract vagina and cervices, and recurrent miscarriage **(Bandy *et al*., 2005).** Positive detection of *Ureaplasma urealyticum* was found to be significantly

higher in women with spontaneous abortion than in the control group, also the detection rate of *Ureaplasma urealyticum* increased parallel with the number of spontaneous abortions. It was also found that *Chlamydia trachomatis* was indicated as a possible cause of spontaneous abortion. Among women with a positive or active infection of *Chlamydia trachomatis*, 41% had suffered at least one spontaneous abortion, and this result from the immunological reaction of specific bacterial protein **(Bulletti *et al*., 1996).** Also virus plays role in the causes of recurrent miscarriage, it was found that infection with human adeno-associated virus (AAV), cytomegalovirus virus and papilloma virus (HPV), cause recurrent miscarriage **(Bulletti *et al*., 1996; Bandy *et al*., 2005).** Finally, **Frisk & Diderholmin in 1992** have demonstrated that Coxsackie B virus serotypes 1-ç may be an important causative agent in spontaneous abortions, which has been independently associated with maternal HIV-1 antibody, maternal syphilis seroreactivity and vaginal colonization with group B streptococci **(Bulletti *et al*., 1996).**

II.2.3.5. Anatomical disorder

Uterine anomalies, congenital or acquired cervical incompetence, intrauterine synechiae (Ascherman's syndrome), and fibroids are all commonly considered to be closely associated with spontaneous abortion, although there is still controversy about their incidence, classification and role in reproductive failure and treatment**.** Congenital anomalies of the uterus include partial or complete absence or hypoplasia, uterus unicornis, uterus didelphys, uterus bicornis, uterus septus and uterus subseptus **(Bulletti et *al*., 1996; Bandy *et al*., 2005).**

The incidence of congenital uterine defect may range from 1.8-37.6% and cause recurrent miscarriage **(Bandy *et al*., 2005). Ashton *et al*., in 1988** reported a

frequency of uterine abnormalities of 1.9% in the entire female population, and the incidence of uterine abnormalities associated with recurrent miscarriage has been reported to be between 15 and 30%, depending on the definition used **.**

II.2.3.6. Autoimmune disorders

Immunologically mediated abortion (IMA) is a clinical disease caused by an abnormal maternal immune reaction against embryonic paternal antigens. Usually, maternal and/or embryonic regulating factors protect the embryo from the immunological reaction of the mother. The immunological system may reject the embryo by two different mechanisms, depending on the phase of the maternal–embryonic interaction. During preimplantation and until the end of the implantation period. Different type of antibody and cell-mediated immunorejection is a mechanism postulated to cause IMA **(Bulletti *et al.*, 1996)**. Autoimmune factor cause fetal rejection in 30% women with recurrent miscarriage**(Bandy *et al.*, 2005).**

III. Materials and Methods

The present study was conduced in order to identify the risk factors associated with infertility and recurrent miscarriage among Palestinian females in Gaza strip. The cases (infertile women and women with recurrent miscarriage) were selected randomly from those referring to Al Basma fertilization center seeking for medical management of infertility or recurrent miscarriage. While, apparently healthy fertile females who are attending public and private clinics for family planning issues were included as control group. We excluded any female who received any medication or surgery to induce pregnancy from the control group. Cases to controls ratio was 2:1 and they were age and location matched as much as possible. The main tools of the present study included close ended questionnaire, interviews, ultrasound or sonography, related hormonal biochemical analysis, and thrombophilic picture.

III.1. Study design

The present work was designed as a case-control study aiming at the investigation of the possible risk factors associated with infertility and recurrent miscarriage among Palestinian females at the Gaza strip.

III.2. Target population and sample size

The targets of the present study were the women who are suffering from infertility or recurrent miscarriage in Gaza Strip. The controls were the women who are attending public and/or private clinics for family planning issues and they were matched to cases based on age and to some extent to locality. During Jan 2010 to May 2010, 230

women who refereed to Al Basma fertilization center, Gaza, due to infertility or recurrent miscarriage were included. Control were 115 apparently healthy mothering women.

III.3. Study tools

III.3.1. Questionnaire interview

An important part of data was collected by using close-ended questionnaire which was constructed and conducted in Arabic language. Details about the components of the questionnaire are included in Annex (page79). The questionnaire was designed to include major components: socio-demographic and general characteristics; gynecological and obstractic profile; other health characteristics; health complains and medical history of the subjects. The items and components of the questionnaire were arbitrated and validated at three levels. The first was criterion related validity that depended on the construction of questionnaire items after reviewing the related literature. The Second was content validity; the questionnaire was checked by university scientists and gynecological and obstractic experts. The objectives of the study were attached with the questionnaire form. Some of the items were added, some modified and some were excluded. The third level is through piloting procedure, where 10 women were questioned and interviewed (they were not included in the study) the questionnaire content was also modified for confusion, redundancy and time factors.

III.3.2. Ultrasound or sonography

After the completion of the questionnaire, the women were clinically investigated by the gynecologist for the status of the reproductive system using ultrasound-based

diagnostic imaging technique, the diagnostic sonography is Ultrasound **ALOKA SS D-1000.** The sonography provided an evaluation about morphological characteristics of women ovary and uterus. The main points of interest were: retroverted or tilted or tipped uterus; polycystic ovary syndrome; abnormalities of fallopian tube (damage or blockage); endometriosis; and presence of uterus fibroids.

III.3.2. Vaginal and urinary infections

The gynecologist also evaluated the women for any vaginal infections by withdrawing vaginal discharges using sterile swaps which were investigated for the causative microorganisms at the microbiology laboratory (culture technique). For, infection with toxoplasmosis, venous blood samples were withdrawn and tested for the presence of the toxoplasmosis specific IgG antibodies using the commercial kit of toxoplasma IgM enzyme immunoassay test kit catalog number: IGMT-96. In addition fresh urine specimens were investigated microscopically for microbiological infections.

III.3.4. Hormonal analysis

After diagnostic sonography, the women were directed to the medical laboratories for hormonal analysis which included the sex and thyroid hormones: Prolactin ST AIA-PACK PRL; Follicle Stimulating Hormone (FSH) ST AIA-PACK FSH; Luteinizing Hormone (LH) ST AIA-PACK LH II; Estrogen ST AIA-PACK ESTRODIOL; and Thyroid Stimulating Hormone (TSH) ST AIA-PACK TSH

III.3.5. Thrombophilic profile

Further to the above mentioned examinations, the thrombophilic profile of the women were investigated for any heterozygosity or hemozygosity in one or more of the genes affecting the coagulation factors in the clotting cascades. These genes are methylenetetrahydrofolate reductase (MTHFR); plasminogen activator inhibitor-1 (PAI-1); angiotensin-converting enzyme (ACE); Factor V; Factor X; and prothrombin. The molecular tests of the thrombophilic profile were performed at the molecular laboratory of Al Basma fertilization center.

III.4. Data treatment and statistical analysis

The statistical test and analysis of the present work comprised a major part of the methodology. Different statistical tests were followed and performed to assess the risk factors for such case-control cross sectional study. These tests included: odd ratio (OR) and its corresponding 95 % confidence interval (95 % CI); attributable risk percent (AR%), and population attributable risk percent (PAR%).

III. 4.1. Odds Ratio

The odds ratio is one of a variety of statistics tools used to assess the risk of a certain outcome (or disease) if a particular factor (or exposure) is present. Simply odds ratio measures the association between exposures and outcomes. It is a way of comparing whether the probability of a certain event or disease is the same for two groups or not. The odds ratio is a relative measure of risk, informing the investigator how much more likely it is that somebody who is exposed to the factor under study will develop the outcome as compared to somebody who is not exposed.

The odds ratio is the ratio of the odds of an incident occurring in one group to the odds of it occurring in a second group. The odds ratio compares the relative odds in each of the included groups. These groups are classified as dichotomous groups and might be men and women, an experimental group and a control group, or any other two non-overlapping entities. Odds ratio refers to the ratio between subjects within a population expressing a trait or not, relative to their exposure to a related risk.

When performing odds ratio, epidemiologists generally construct a 2x2 table as demonstrated below:

Risk factor or Exposure	**Disease or outcome**		
	Yes (Diseased)	**No (Not Diseased)**	**Total**
Yes (exposed)	**a**	**b**	**a+b**
No (not exposed)	**c**	**d**	**c+d**
Total	**a+c**	**b+d**	**a+b+c+d**

where:

- '**a**' represents those in the exposed population who experienced the disease or outcome of interest.
- '**b**' is the exposed population who did not experience that disease or outcome of interest.
- '**c**' represents those in the non exposed population who experienced the disease or outcome of interest.
- '**d**' represents those in the non exposed population who did not experience the
- disease or outcome of interest.

Simply odds ratio is calculated directly form the contiguity 2X2 table as:

$$\text{Odds ratio} = \frac{ad}{cb}$$

III. 4.1.1. Interpreting Odds Ratios

An odds ratio of 1 indicates that the condition or disease under investigation is equally likely to occur in both groups which means no association between exposure and outcome. If the odds are greater than 1 then the disease or the outcome is more likely to happen than not (a positive association between the exposure and the outcome of interest). While, if the odds are less than one then the disease or the outcome is less likely to happen than not (a negative association between the exposure and the outcome of interest).

Odds ratios can be strengthened in measuring association through calculation of 95% confidence intervals (CI) around the measured odds ratio. Realizing that the odds ratio is an estimate of the true odds ratio, therefore if the 95% CI includes the value 1, this implies that the odds ratio obtained in the study is statistically consistent with a true odds ratio of 1, and investigator cannot properly accept that the true odds ratio is different from 1 (statistically non significant association). This is why one might see the odds ratio for a risk factor calculated as 1.2, implying an increased risk, but if the 95% CI is 0.9 to 1.5 (including the value 1), the risk will be considered "not statistically significantly different." Therefore 95 % CI that do not contain 1 indicate a statistically significant association between exposure and out comes.

III.4.2. Relative risk and attributable risk percent

III.4.2.1. Relative Risk

Relative risk (RR) is the calculated ratio of incidence rates of a disease or outcome in two non-overlapping groups, those exposed to a factor of interest and those not exposed. RR is usually performed to determine whether exposure to a certain risk factor is associated with an increase, decrease, or no change in the disease or outcome prevalence when compared to those without the exposure to the proposed risk factor. RR is considered as a reliable statistical measure of the strength of the association between a risk factor and an outcome. In cases where RR associated with a possible factor is more than 1, then this proposed factor is considered as a risk factor. However, when RR is less than 1, then the factor is called a protective factor. While, if RR equals 1, then thee is no association between factor and outcome.

III.4.2.2. Attributable risk percent

In epidemiological health studies, RR helps in determining whether and how strongly a precursor (proposed factor) is associated with a particular outcome. However, a more powerful measure is the attributable risk percentage (ARP) which is used to determine how much of the disease or an outcome may be attributable to a particular risk factor in a certain population exposed to that factor. ARP is considered as a valuable tool because it offers estimates of the relative impact of the disease that could be achieved if the risk factor is reduced or eradicated.

-Calculation of attributable risk percent (ARP)

Attributable risk percent (ARP) is a calculation that can be derived from attributable risk, and it gives the fraction of cases attributable (and avoidable) to this exposure in relation to all cases.

Thus, attributable risk percent is sometimes called the risk difference, or percent of excess risk, the percent of excess risk that is "attributed" to the exposure.

attributable risk percent (ARP) = [(P1 – P2) / P1] x 100

P1 = the proportion of exposed with the disease = (a/a+b).

P2 = the proportion of non exposed with the disease = (c/c+d).

III.4.2.3 Population attributable risk (PAR) and population attributable risk percent (PARP)

Although attributable risk percent helps in estimating the excess risk among the exposed that can be attributed to the risk factor, however, from a public health perspective it is often more useful to modulate the attributable risk in terms of the whole population. Therefore, health epidemiologists are interested in knowing the proportion of all cases of a disease in the total population that could be attributed to the exposure to the risk factor. This is called the population attributable risk and when expressed as a percent it is known as the population attributable risk percent. Determining the population attributable risk percent allows health epidemiologists to calculate what percent of a disease could possibly be prevented if a risk factor were to be removed or decreased from the population.

The terms population attributable risk (PAR) and population attributable risk percent have been described as the decline in occurrence that would be observed if the population were entirely unexposed, compared to that of the exposure pattern.

- Calculation of population attributable risk percent (PARP)

PARP = $[(P_0 – P_2)/ P_0] \times 100$

Where:

P_0 = the proportion of all individuals with the disease or outcome of interest in the population = (a + c / a + b + c + d).

P_2 = the proportion of individuals with the disease or outcome of interest who do not exposed to risk factor= (c / c + d).

The data from the questionnaire, and from the medical laboratories were tabulated, encoded and statistically analyzed using the Statistical Package for the Social Sciences (SPSS) version 15 and the medical calculator (MedCalc) Version 9.2.0.1.

IV. Results

The present work included 230 women who referred to Al Basma fertilization center for proper management and treatment from infertility or recurrent miscarriage. Additionally, 115 apparently healthy fertile women were selected randomly from obstetric gynecology clinics and other medical centers, and they were considered as control group of the study. The control were almost age matched to the cases, with case to control ratio of 2:1. In this section, the results of the work will be presented as cross tabulation tables to mention the number and frequencies of the subjects according to the different factors and characteristics, odd ratio (OR) and its corresponding 95 % confidence interval (95% CI), and attributable risk percent (ARP), and population attributable risk percent (PARP). The significancy of the differences between the groups with respect to exposure to the factor of interest was determined according to the statistical analysis of the OR and its 95% CI. An OR greater than 1 implies a positive association between the exposure and the condition of interest; an odds ratio less than 1 implies a negative association. An odds ratio of 1, implies no association between the exposure and the condition. In our work the OR presented is an estimate of the true odds ratio, and if the 95% CI includes the value 1, this implies that the OR obtained is not significantly different and so the factor will not be considered as a risk factor.

IV.1. Distribution and general characteristics of the study population

IV.1.1. Distribution according to Governorate

The distribution of the cases and controls according to governorate is mentioned in Table 1. About three fourth (169/230, 73.5%) of the women who referred to the infertility clinic are seeking for treatment from infertility and about one fourths

(61/230, 26.5%) are seeking for treatment from recurrent miscarriage. The highest percentage (44.8%) of the cases were from the Gaza Governorate, followed by the Northern Governorate 17.8%, Midzone14.8%, Khanyounis 13.5%, and the lowest percentage (9.1%) from Rafah Governorate.

Table (1): Distribution of the cases and controls according to Governorate

Governorate	Control		Infertility		Recurrent Miscarriage	
	number	%	number	%	number	%
North	20	17.4	31	18.3	10	16.4
Gaza	45	39.1	68	40.2	35	57.4
Mid-zone	17	14.8	24	14.2	10	16.4
Khanyounis	22	19.1	30	17.8	1	1.6
Rafah	11	9.6	16	9.5	5	8.2
Total	**115**	**100**	**169**	**100**	**61**	**100**

IV.1.2. Distribution according to social-geographical locality

In terms of the type of the socio-geographical locality (Table 2), the majority of the cases (144/230, 62.6%) and the control (64/115, 55.7%) were from the major cities of the Gaza strip. Statistically significant differences were reported in the prevalence of infertility and recurrent miscarriages between the different localities: city, village, and camps. The prevalence of infertility and recurrent miscarriages were significantly ($P < 0.05$) higher in cities and camps as compared to villages, and it shows 60.4% and 37.3% for infertility and 68.9% and 29.5% for recurrent miscarriages respectively as compared to the matching items in villages.

Table (2): Distribution of the study population according to the type of the social-geographical locality

locality	Normal		Infertility		Recurrent miscarriage	
	number	%	number	%	number	%
City	64	55.7	102	60.4*	42	68.9*
Camp	32	27.7	63	37.3*	18	29.5*
Village	19	16.6	4	2.4	1	1.6
Total	**115**	**100**	**169**	**100**	**61**	**100**

* Statistically significant as compared to villages

IV.1.3. Age characteristics of the study population

The age characteristics of the study population are mentioned in Table 3, with overall mean age of 27.61± 5.91 years and overall median of 27 years. However, a significantly higher mean age was reported in women with recurrent miscarriage as compared to the women with infertility, p value = 0.001, and as compare to the control groups, p value = 0.0001. However no significant differences were reported in the mean age of infertile women and control group, p value = 0.091. Moreover, the percentage of the women with recurrent miscarriage and age greater than 30 years old is significantly higher than the corresponding percentages in the infertility and control groups, p values = 0.002 and 0.0001 respectively.

Table (3): Age characteristics of the study population

	Control N= 115	Infertility N= 169	Recurrent miscarriage N= 61
Mean ±SD	26.3 ± 5.6	27.5 ± 5.7*	30.4 ± 6.3**
Median	27	27	30
> 30 years	24 (20.9 %)	42 (24.9%)	28 (45.9 %)**
<30 years	91(79.1%)	127 (75.1%)	33 (54.1%)

* significantly different from control
** significantly different from infertility and also control groups

IV.1.4. Level of education and occupation of the study population

Regarding the level of education and the working of the subjects (Table 4), the three groups are showing an almost homogenous distribution with respect the education level (p values > 0.05). while significant differences were reported among the three groups for the working and non working women (p values < 0.05). The percentage of working women in the infertility group (18.3%) and in the recurrent miscarriage group (24.6%) are significantly higher than the percentage of working women in the control group (8.7%).

Table (4): level of education and occupation of the study population

	Normal N= 115		Infertility N= 169		Recurrent Miscarriage N= 61	
	number	**%**	**number**	**%**	**number**	**%**
Level of Education						
School	80	69.6	124	73.4	39	63.9
Graduate	35	30.4	45	26.6	22	36.1
Working of Women						
Working	10	8.7	31	18.3*	15	24.6*
Not working	105	91.3	138	81.7	46	75.4

* significantly different from control

IV.2. Medical and clinical characteristics of the study population

IV.2.1. Characteristics of women menstruation

The evaluation of the menstruation cycle of the women is illustrated in Table 5. Significantly higher percentages of women with irregular menstrual cycle were reported in the infertility and recurrent miscarriage groups as compared to the control group, with p values of 0.04 and 0.005 respectively. Regarding the heaviness of the menstrual cycles, there were no significant differences between the three groups (p value > 0.05). However, the length of menstrual cycle showed more multifaceted results. For menstrual cycles less than 5 days, the percentage of the women in the infertility group showed significantly higher percentage than control and miscarriage groups ($p < 0.05$). While, for longer menstrual cycles more than 6 days, the percentage of the women in the miscarriage group showed significantly higher percentage than control and infertility groups ($p < 0.05$).

Table (5): Characteristics of women menstruation

	Normal N= 115		Infertility N= 169		Recurrent Miscarriage N= 61	
	number	**%**	**number**	**%**	**number**	**%**
Regularity of menstruation						
Irregular	4	3.5	17	10.1*	10	16.4*
Regular	111	96.5	152	89.9	51	83.6
Severity of menstruation						
Heavy	12	10.4	7	4.1	5	8.2
Normal	103	89.6	162	95.9	56	91.8
Length of menstruation						
Less than 5 days	6	5.2	21	12.4*	1	1.6
5-6 days	95	82.6	121	71.6	45	73.8
More than 6 days	14	12.2	27	16.0	15	24.6 *

* significantly different from control

IV.2.2. Morphological characteristics of women ovary and uterus

Ovary and uterus morphological and anatomical characteristics are presented in Table 6, where the groups of the cases showed heterogeneous results as compared to control and also as compared to each other. The percentage of the infertile women (18.3%) with retrieved uterus was significantly higher than those in the control group (2.6%) as well as the recurrent miscarriage group (4.9%), with p values of 0.0001 and 0.03 respectively, while no significant differences between recurrent miscarriage and control groups (p-value = 0.629). The percentages of polycystic ovary syndrome were significantly higher in infertility (17.8%) and recurrent miscarriage (23.0%) groups as compared to control group (1.7%), p values = 0.0001. Also abnormities in fallopian

tubes showed a similar pattern, with significantly higher percentages in infertility (13.0%) and recurrent miscarriage (11.5%) groups as compared to control group (0.9 %), with p values of 0.0001 and 0.016 respectively. On the other hand, endometriosis showed a significantly higher percentage among the recurrent miscarriage group (11.5%) as compared to both the control (0.9%, p = 0.001) and infertility (4.1%, p = 0.015) groups. However, percentage of uterus fibroids was significantly higher in the infertility group as compared to control group (p value = 0.003).

Table (6): Morphological and anatomical characteristics of women ovary and uterus

	Normal N= 115		**Infertility N= 169**		**Recurrent Miscarriage N= 61**	
	number	**%**	**number**	**%**	**number**	**%**
Retroverted or tilted or tipped uterus						
Yes	3	2.6	31	18.3*#	3	4.9
No	112	97.4	138	81.7	58	95.1
Polycystic ovary syndrome						
Yes	2	1.7	30	17.8 *	14	23.0*
No	113	98.3	139	82.2	47	77.0
Abnormalities of fallopian tube (damage or blockage)						
Yes	1	0.9	22	13.0*	7	11.5*
No	114	99.1	147	87.0	54	88.5
Endometriosis						
Yes	1	0.9	7	4.1	7	11.5*#
No	114	99.1	162	95.9	54	88.5
Presence of uterus fibroids						
Yes	0	0	12	7.1*	2	3.3
No	115	100	157	92.9	59	96.7

* significantly different from control
# infertility significantly different from miscarriage

IV.2.3. Sex and thyroid hormonal abnormalities

The classification of the study population according to the presence of abnormalities in sex hormones (LH, FSH, Prolactine, TSH, Estrogen) and thyroid gland (T4) hormones are presented in Table 7. Sex hormones abnormities were significantly higher in the infertility (47.3%, p= 0.001) and recurrent miscarriage (57.4%, p =0.0001) groups as compared to control group. While for thyroid gland hormone abnormalities, only infertility group showed a significantly higher percentage (7.7%, 0.007) than control group. Recurrent miscarriage group (3.3%) showed a non significant difference as compared to control group (p value = 0.467).

Table (7): Hormonal abnormalities of the study population

	Normal N= 115		**Infertility N= 169**		**Recurrent Miscarriage N= 61**	
	number	**%**	**number**	**%**	**number**	**%**
Sex hormones abnormalities						
Yes	5	4.3	80	47.3*	35	57.4*
No	110	95.7	89	52.7	26	42.6
Thyroid gland abnormality						
Yes	1	0.9	13	7.7 *	2	3.3
No	114	99.1	156	92.3	59	96.7

* significantly different from control

IV.2.4. Medical history of the study population

A relevant items about the medical history of the study population that could be considered are shown in Table 8. Thy included: history of abdominal surgical operation, family history of infertility, history of ectopic pregnancy, and history of molar pregnancy. The percentage of women with previous surgical operation in the abdomen were higher in both infertility (20.1%, p=0.0001) and recurrent miscarriage (34.4%, p= 0.0001) groups as compared to control (4.3%) group. Also the percentage in recurrent miscarriage were significantly higher than the percentage in the infertility group, p value = 0.009. The percentage of women with family history of infertility was higher only in the infertility group (8.3%) as compared to control group (1.7%), p value = 0.015. while for history of ectopic pregnancy the groups of recurrent miscarriage (4.9%) showed significantly higher percentage than control (0.9%) group, p value = 0.016. However, non of the study population reported any history of molar pregnancy.

Table (8): Medical history of the study population

	Normal N= 115		**Infertility N= 169**		**Recurrent Miscarriage N= 61**	
	number	**%**	**number**	**%**	**number**	**%**
History of abdominal surgical operation						
Yes	5	4.3	34	20.1*	21	34.4*#
No	110	95.7	135	79.9	40	65.6
Family history of infertility						
Yes	2	1.7	14	8.3 *	2	3.3
No	113	98.3	155	91.7	59	96.7
History of ectopic pregnancy						
Yes	1	0.9	0	0	3	4.9*
No	114	99.1	169	100	58	95.1
History of molar pregnancy						
Yes	0	0.0	0	0.0	0	0.0
No	115	100	169	100	61	100

* significantly different from control
# miscarriage significantly different from infertility

IV.2.5. Medical presentation (status, situation)

The medical presentation of the cases and the controls at the time of the study is demonstrated in Table 9, and included: vaginal and urinary infections, sexually transmitted diseases (Chlamydia), and toxoplasmosis. A higher percentages of vaginal infections were reported in the women of the infertility (45.0%) and recurrent miscarriage (44.3%) groups as compared to control group (p value <0.05), while no significant differences were reported within the three groups regarding urinary infections (p value >0.05). On the other hand the women in the infertility group exhibited significantly higher percentage regarding the infection with Chlamydia (7.1%, p= 0.011) as compared to control group, however no significant differences were reported in the recurrent miscarriage (3.3%, p=0.454) group. While no significant differences were reported within the three groups regarding toxoplasmosis infections (p value >0.05).

Table (9): Medical presentation (status, situation) of the study population

	Normal N= 115		**Infertility N= 169**		**Recurrent Miscarriage N= 61**	
	number	**%**	**number**	**%**	**number**	**%**
Vaginal infections						
Yes	18	15.7	76	45.0*	27	44.3*
No	97	84.3	93	55.0	34	55.7
Urinary infections						
Yes	8		21	12.4	6	9.8
No	107		148	87.6	55	90.2
Sexually transmitted disease (Chlamydia)						
Yes	1	0.9	12	7.1*	2	3.3
No	114	99.1	157	92.9	59	96.7
Toxoplasmosis						
Yes	1	0.9	8	4.7	3	4.9
No	114	99.1	161	95.3	58	95.1

* significantly different from control

IV.2.6. Thrombophilic disorders

Table 10 showed the distribution of thrombophilic disorders among the study population of the present study. About 45.6% of the women in the infertility group and 70.5% in the recurrent miscarriage group are exhibiting one or more of the thrombophilic disorders screened. These percentages were significantly higher (45.6%, 70.5% respectively) when compared to the control group, and the percentage in the miscarriage groups is also significantly higher than that in the infertility group. The detailed distribution of the thrombophilic disorders among cases are presented in Table 11.

Table (10): Thrombophilic disorders among the study population

	Normal N= 115		**Infertility N= 169**		**Recurrent Miscarriage N= 61**	
	Number	**%**	**number**	**%**	**number**	**%**
Overall thrombophilic disorders						
Yes	1	0.9	77	45.6*	43	70.5*#
No	114	99.1	92	54.4	18	29.5

* significantly different from control
\# miscarriage significantly different from infertility

Table (11): Prevalence of the different types of thrombophilic disorders among cases

Type of thrombophilic disorders	Infertility N= 169		Recurrent miscarriage N= 61	
	number	%	number	%
Methylenetetrahydrofolate reductase (MTHFR)				
Normal	127	75.1	32	52.5
Homozygous/ heterozygous abnormal gene	42	24.9	29	47.5*
Plasminogen activator inhibitor-1 (PAI-1)				
Normal	150	88.8	52	85.2
Homozygous/ heterozygous abnormal gene	19	11.2	9	14.8
Angiotensin-converting enzyme (ACE)				
Normal	138	81.7	44	72.1
Homozygous/ heterozygous abnormal gene	31	16	17	23
Factor X				
Normal	169	100	56	91.8
Homozygous/ heterozygous abnormal gene	0	0	5	8.2*
Factor V				
Normal	157	92.9	51	83.6
Homozygous/ heterozygous abnormal gene	12	7.1	10	16.4*
Prothrombin				
Normal	163	96.4	53	86.9
Homozygous/ heterozygous abnormal gene	6	3.6	8	13.1*

* significantly different from infertility

IV.3. Risk assessment : Odd ratio and population attributable risk percentage

For each of the factors assessed in the present study, the odd ratio is calculated and if the value of 1 is not among the 95% CI of the odd ratio then the population attributable risk percentage (PAR%) was calculated for that factor. Therefore NA refers to factor that has no significant risk on infertility or miscarriage.

IV.3.1. Risk factors for infertility

As indicated in Table 12, the risk factors for infertility were sorted in decreasing order. Thrombophilic disorders were found to have the highest risk for infertility in the Palestinian women at Gaza, with APR and PARP of 54.76% and 24.95% respectively, meaning that about one-fourth of infertility cases in the Palestinian women in Gaza could be attributed to one or more of the thrombophilic disorders. Sex hormones abnormalities were the second common risk factor for infertility with ARP and PARP of 52.48% and 24.83% respectively. While Vaginal infections ranked as the third common risk factor for infertility with ARP and PARP of 39.46% and 17.75% respectively, followed by social stresses, abdominal surgical operation, PCOS, and retroverted uterus Further risk factors were also reported, with lesser ARP and PARP are mentioned in Table 12. However other factors were not found to have significant effect as a risk factor of infertility in Palestinian women in Gaza.

Table (12): Odd ratio, ARP and PARP for infertility

Risk factor	Odd Ratio	Odd Ratio 95% CI	ARP	PARP
Thrombophilic disorder	95.41	13.02-699.20	54.76	24.95
Sex hormone abnormalities	19.78	7.68- 50.92	52.48	24.83
Vaginal or infections	4.40	2.45-7.92	39.46	17.75
Social and living stresses	4.15	1.86-9.24	34.41	8.14
Abdominal surgical operation	5.45	2.10-14.64	36.79	7.4
Polycystic ovary syndrome (PCOS)	12.19	2.85-52.13	41.16	7.31
Retroverted or tilted or tipped uterus	8.39	2.50-28.15	39.46	7.24
Sexually transmitted diseases (Chlamydia)	9.35	2.16-40.40	39.11	5.55
Fallopian tube damage or blockage	17.06	2.27-128.47	41.12	5.35
O blood group	3.81	2.11-6.87	36.5	5.12
Women working	2.36	1.11-5.03	24.89	4.57
Days of menstruation <5	2.58	1.01-6.60	27.98	4.14
Endometriosis	10.30	1.33-79.44	38.26	3.17
Presence of uterus fibroids	8.71	1.12-67.97	42.28	3.0
Thyroid gland abnormality	9.50	1.23-73.67	37.78	2.91
Irregularly of menstruation	3.10	1.02-9.48	28.61	2.88
Family history	5.10	1.14-22.90	33.9	2.81
Women age > 30	1.25	0.71-2.22	NA	NA
Locality (urban)	1.21	0.75-1.96	NA	NA
Days of menstruation > 6	1.37	0.69-2.75	NA	NA
Severity menstruation	0.37	0.14-0.97	NA	NA
Level of education	1.21	0.71-2.04	NA	NA
Urinary infections	1.90	0.81-4.45	NA	NA
Toxoplasmosis	5.66	0.70-45.92	NA	NA
Hypertension	1.02	0.17-6.21	NA	NA
Diabetes mellitus	1.02	0.17-6.21	NA	NA

IV.3.2. Risk factors for recurrent miscarriage

The risk and non-risk factors for recurrent miscarriage in Palestinian women in Gaza strip are presented in Table 13 and arranged in a decreasing order. Like infertility, thrombophilic disorders were found to have the highest risk for recurrent miscarriage in the Palestinian women in Gaza strip, and that about two-thirds of recurrent miscarriage cases could be attributed to one or more of the thrombophilic disorders, with ARP and PARP of 86.05% and 60.66%, respectively. Sex hormones abnormalities occupied the second common risk factor for recurrent miscarriage among the Palestinian population in Gaza strip, with ARP and PARP of 78.15% and 44.84%, respectively. While vaginal infections ranked as the third common risk factor for recurrent miscarriage with ARP and PARP of 56.74% and 25.12% respectively, followed by women age > 30 years, abdominal surgical operation, PCOS, women working, social and living stresses, and long and irregular menstruation. Additional risk factors were also reported, with lesser PAR%, and are mentioned in Table 13. While, other factors were not found to have significant effect as a risk factor of infertility in Palestinian women in Gaza.

Table (13): Odd ratio, ARP, PARP for recurrent miscarriage

Risk factor	Odd Ratio	Odd Ratio 95% CI	ARP	PARP
Thrombophilic disorder	272.33	35.27-2102.87	86.05	60.66
Sex hormone abnormalities	29.62	10.57- 82.95	78.15	44.84
Vaginal or infections	4.28	2.10-8.73	56.74	25.12
Women age > 30	3.22	1.64-6.32	50.58	23.22
Abdominal surgical operation	11.55	4.08-32.69	66.98	23.06
Polycystic ovary syndrome (PCOS)	16.83	3.68-76.96	66.43	15.25
Women working	3.42	1.43-8.19	49.23	12.11
Social and living stresses	3.98	1.57-10.14	52.04	11.94
Days of menstruation > 6	2.35	1.05-5.28	37.86	9.46
Irregularity of menstruation	5.44	1.63-18.17	55.93	9.17
Sexually transmitted diseases (Chlamydia)	8.53	1.75-41.55	60.09	7.88
Fallopian tube damage or blockage	14.78	1.77-123.14	63.27	7.26
O blood group	2.63	1.26-5.48	23.55	4.81
Locality (Urban)	1.76	0.92-3.39	NA	NA
Days of menstruation <5	0.30	0.04-2.57	NA	NA
Severity menstruation	0.77	0.26-2.29	NA	NA
Level of education	0.78	0.40-1.50	NA	NA
Family history	1.92	0.26-13.94	NA	NA
Thyroid gland abnormality	3.86	0.34-43.50	NA	NA
Retroverted or tilted or tipped uterus	1.93	0.38-9.87	NA	NA
Endometriosis	1.90	0.12-30.92	NA	NA
Presence of uterus fibroids	3.86	0.34-43.50	NA	NA
Urinary infections	1.46	0.48-4.42	NA	NA
Toxoplasmosis	5.90	0.60-57.95	NA	NA
Hypertension	1.97	0.45-3.26	NA	NA
Diabetes mellitus	1.92	0.26-13.94	NA	NA

V. Discussion

The inability to have a baby or conceive after at least a year of regular sexual intercourse without the use of contraceptives, can be due to causes that lie either in the man or the woman or both. In developing and specially in Middle Eastern Arabic countries, high rate of infertility and childlessness are considered as the most important and underappreciated reproductive health problems **(Bergstrom, 1992; Leke *et al.*, 1993)**. Although Infertility is frustrating enough, but what's even worse is becoming pregnant only to have all hopes, optimisms and dreams end in miscarriage. The inability to have children is habitually considered a personal tragedy and a bother for the couple, affecting the entire family and even the local community, which may lead to negative psychosocial severe consequences **(Daar and Merali, 2002; Dyer, 2005)**. In many cultures, including the Arabic oriental, womanhood is defined through motherhood and infertile women usually carry the responsibility for couple's inability to conceive or having a baby. Childless women are commonly stigmatized, resulting in isolation, disregard, and disrespect **(Gerrits, 1997; Papreen *et al*., 2000; Richards, 2002; Wiersema *et al.*, 2006).**

The world health organization (WHO) estimates that there are 60-80 million infertile couples worldwide with the incidence of 20% in Eastern Mediterranean Region and 11% in the developed world **(Fathalla *et al.*, 2006 ; Boivin *et al.*, 2007).** In Palestine and specially in the Gaza strip there is no documented reports or published scientific wok that investigated the magnitude and risk factors associated with infertility and recurrent miscarriage. Moreover, the demographic records published by the Palestinian Central Bureau of Statistics revealed a significant decline in

fertility rates which reached 4.6 births per woman in Palestine during 2004, of which 4.1 in the West Bank and 5.8 in Gaza Strip **(PCBS).** While fertility rate in Palestine was 6.0 births per woman in 1997. Although of the considerable prevalence of childlessness worldwide and specifically in developing countries, however, identification of the underlying causation is the key to successful treatment and solving the problem in considerable number of cases. The present work aimed for the indentifying the risk factors associated with infertility and recurrent miscarriage among Palestinian women in the Gaza strip.

In the results section (previous section) we presented the tables as distribution and frequency tables (Tables 1-11) with regard to the different factors involved of the present study. While, the tables that summarized the risk factors (in terms of Odds ratio, ARP, PARP) for infertility and recurrent miscarriages were presented as the last tables (Tables 12 &13). However, in the discussion section we will discussed the factors both from the distribution and riskiness point of view.

V.1. Distribution and general characteristics of the study population

V.1.1. Governorates and localities

The majority (62.6%) of the cases (infertile and women with recurrent miscarriages) of the present work were from the Gaza and North Governorates (Table 1). Although this is concomitant with the population distribution at the different Governorates of Gaza strip, however, we could not attribute this to the prevalence or the incidence of infertility or miscarriages in the different governorates. This is due to the fact that the cases were sampled from Al Bassma fertilization center which is located in Gaza city and closer to North Governorate than other Governorates.

Therefore, geographical conclusions could not be withdrawn about the incidence of infertility or recurrent miscarriages at the different Governorates of Gaza strip.

However, in terms of the type of the socio-geographical locality, results showed statistically significant differences in the prevalence of infertility and recurrent miscarriages between the different localities, with significantly higher prevalence in cities and camps as compared to villages. Our results are concomitant to the results from Egypt and published by the Egyptian Fertility Care Society 1995 & **Mokhtar et al., 2007;** from Ethiopia of **Haddis & Sahleyesus 2010** who showed a higher prevalence of infertility in urban and suburban areas as compared to rural areas. However, in developed countries (Alabama, USA) no significant differences were reported **(Sherrod, 2004).** As indicated by the odds ratio (1.21, 1.76) and its 95% CI (0.75-1.96, 0.92-3.39), the geographical locality was not a significant risk factor for either infertility nor miscarriage (respectively) among Palestinian women in Gaza strip.

V.1.2. Age of the study population

The results of the present study revealed a significantly higher mean age of recurrent miscarriage group as compared to the infertility group (p value = 0.001). Moreover, the percentage of the women in recurrent miscarriage group with age greater than 30 years old is significantly higher than the corresponding percentages in the infertility and control groups (p values = 0.002 and 0.0001, respectively).

Although women age of > 30 years old was found to be among the risk factors of infertility in different populations **(Heffner 2004),** however in the Palestinian

women in Gaza strip this was not a significant risk factor for infertility and our results revealed no significant effect of women age on infertility (Odds ratio = 1.25 and 95% CI = 0.71-2.22).

On the other hand, women age > 30 years was found to be among the risk factors associated with recurrent miscarriage in Palestinian women in Gaza strip. A woman of the present work was 3.22 times more likely to miscarry when she is 30 years old or over. As PARP for recurrent miscarriage was 23.22%, therefore, this percentage of miscarriages could be reduced if childbearing occurs before the age of thirty years old.

The effect of advancing maternal age as a risk of recurrent miscarriage was addressed at different studies from different populations. As a woman grows old, her chances of experiencing miscarriage increase. At 20 years of age, the rate is less than 10%, however, starting from thirties the risk (about 25%) increases progressively and it reaches about 50% at the age of 45. The increased risk of recurrent miscarriage with advanced maternal age could be due to the higher risk of producing aneuploid embryos, resulting in implantation failure. Biologically, this could be attributed to the fact that all of the woman's eggs are present at birth, however, over time, the chromosomes within the egg are less likely to divide properly, resulting in cells with too many or too few chromosomes. This high miscarriage rate contributes significantly to decreasing fertility among older women **(Hook *et al.*, 1983; La Rochebrochard & Thonneau, 2002; Heffner 2004).**

V.1.3. Level of education

The education level of the women was not considered among the risk factors neither of infertility nor of recurrent miscarriage for Palestinian women in Gaza strip, with Odds ratios of 1.21, 95% CI 0.71-2.04, and 0.78. 95% CI 0.40-1.50, respectively. Our results of the Palestinian population are concomitant to the results from the united kingdom **Maconochie *et al.*, 2007** who did not report significant association of level of education to recurrent miscarriage. While our results were in disagreement with the results of **Mokhtar *et al.*, 2006** who showed the educational level as a major risk factors for women infertility in Egyptian population. According to Egyptian study women with low educational level had double the risk of infertility as compared to women with high level of education **(Mokhtar et al., 2006)**. Also the data of the National Survey of Family Growth (NSFG) in the USA and to the population-based study from Northern Sweden suggested that infertile women are less likely to have an education level beyond high school **(Hirsch & Mosher 1987; Kalmuss 1987; Wulff et al., 1997).**

V.1.4. Women working

For infertility and recurrent miscarriage, the working of the Palestinian women was found to be among the risk factors that could significantly affect the rate of incidence of these disorders, with profound effect of working on recurrent miscarriage than infertility. The Odds ratio was 2.36 with 95% CI of 1.11-5.03 for infertility group, meaning that the inability of childbearing is 2.36 times more likely in working women than non working women. In terms of PARP 4.57% of infertility in Palestinian women in Gaza could be avoided or reduced if women stay not working during her plan for childbearing. More efficiently will be with regard to

recurrent miscarriage where 12.11% of the cases could be avoided when woman is not working. The current results are agreed to the results of different studies for different populations. **Tuntiseranee *et al.*, (1998)** showed that Long working hours is a risk factor for sub fecundity especially for women. While, in United Kingdom **Maconochie *et al.*, (2007)** did not find significant association between women working and recurrent miscarriage.

V.2. Medical and clinical characteristics of the study population

V.2.1. Women menstruation

The present work demonstrated the irregularity of menstruation as one of the significant risk factors associated with infertility and recurrent miscarriage with odds ratios of 3.10, 95% CI =1.02-9.48 and 5.44, 95% CI = 1.63-18.17, respectively. PARP 2.88% and 9.17% of the infertility and recurrent miscarriage cases, respectively could be passed up if regularity of menses is achieved before marriage through correction of cases. The results also revealed a significant risk of shorter menstrual cycle on infertility while longer menstrual cycle is a significant risk for recurrent miscarriage. In terms of PARP, 4.14% and 9.46% of infertile females and recurrent miscarriages, respectively might be eliminated when managing the length of the menstrual cycle of the women. The results are concomitant with the results of the Egyptian population where irregularity of menstruation was find as the second most population attributable risk factor on infertility **(Mokhtar et al., 2006)**. Also, **Giwercman, *et al* (1994); mohsen *et al.*, 2001; Ronda *et al.*, 2009** reported that the incidence of infertility among women with abnormal cycles were significantly higher than those with regular cycles.

V.2.2. Morphological characteristics of women ovary and uterus

Abnormalities in ovary and uterus are considered among the significant risk factors for infertility and recurrent miscarriage in Palestinian women in Gaza strip. These ovarian or uterine significant risk factors were: polycystic ovary syndrome, retroverted uterus, fallopian tube damage, endometriosis and uterus fibroids, which for infertility showed PARP of 7.31%, 7.24%, 5.35%, 3.17%, 3.0%, respectively. However, for recurrent miscarriage only polycystic ovary syndrome, and fallopian tube damage are considered as significant risk factors and showed PARP of 15.25% and 7.26% respectively. **Mokhtar *et al.*, 2006** showed that 15.4% of infertility cases are preventable by treating PCOS. **Philippov *et al.*, 1998** demonstrated tubal patency as most frequent (36.5%) causes of female infertility in Western Siberia.

In a Population study about the causes, treatment, and outcome of infertility in England performed by **Hull *et al.*, 1985,** fallopian tube damage and endometriosis were a major risk factors of infertility and they accounted for 14 and 6.0%, respectively of the infertility causes of the studied population. While the study of **Hull 1987** attributed about 21% of infertility cases to PCOS. Moreover, **Kousta1 *et al.*, 1999** suggested PCOS to contribute to the causes of sub-fertility in women with regular menses.

Ovarian and uterine morphological abnormalities were reported as a major risk factors for infertility and / or recurrent miscarriage in our Palestinian population in Gaza strip, Therefore these percentages of infertility and / or recurrent miscarriage could be minimized by managing the cause of ovary or uterine abnormalities.

V.2.3. Sex and thyroid hormonal abnormalities

As mentioned in the results chapter, sex hormones abnormities were significantly higher in the infertility and recurrent miscarriage groups, however thyroid hormone abnormalities were significantly more frequent in infertility group only. Sex hormone abnormalities ranked the second major risk factor for infertility and recurrent miscarriage with odds ratio of 19.78, and 29.62, respectively. When referring to tables 12 and 13, about one-fourth infertility cases and half of recurrent miscarriage cases in the Palestinian women in Gaza strip could be preventable by correcting or adjusting the sex hormones of the women before the plan of childbearing.

The studies addressing the sex hormones abnormalities as a risk factor for infertility and/or recurrent miscarriage are abundant. **Zargar *et al.*, 1997 and Biller, 1999** showed that hyperprolactinemia is associated with an increased production of prolactin, and often leading to reproductive dysfunction. While **Vasadze *et al.*, 1984** reported an endocrine forms of infertility as a risk factor for the failure to carry a subsequent pregnancy to term, and therefore inability for childbearing. The ovulation disorders due to sex hormones abnormalities or imbalance were considered by **Illions *et al.*, 1998** as a major factor of women infertility in American population, by **Thonneau *et al.*, 1991** in French population and by **Razzak & Wais 2002** in Iraqi population. Interestingly, about 76% of female infertility in Madagascar were attributed to sex hormone disturbances **(Ravolamanana *et al.*, 2001).** The significant effect of hypersecretion of LH before conception on the occurrence of miscarriage, which offers the possibility of a simple predictive test for women before pregnancy, and could also be used to identify patients with an

endocrine abnormality that can be remedied **(Regan et al., 1990)**.

V.2.4. Medical history of the study population

The percentage of women with previous surgical operation in the abdomen were higher in both infertility and recurrent miscarriage groups as compared to control group. Also the percentage in recurrent miscarriage were significantly higher than the percentage in the infertility group. The Odds ratios of women with previous surgical operation in the infertile and recurrent miscarriage groups showed significant values and were 5.54 and 11.55, respectively, with PARP of 7.4% and 23.06%, respectively. These significant PARP should be considered well by the surgeons when they are dealing with abdominal surgical operations so the female reproductive organs and ducts remain intact during their abdominal cutting and sealing. The abdominal surgical operation was addressed significantly as a risk factor in different studies. For example**, Mokhtar *et al* 2006** showed that infertility increased by 5 folds in women with abdominal surgery. **Monk *et al.*, 1994; Robertson & Lefebvre 2010** showed how adhesions after abdominal surgical operations increased the rates of infertility and abortions in women. Abdominal adhesions following surgical operations and involving the ovaries or fallopian tubes are accounting for 15-20% of female infertility cases. Abdominal adhesions could lead to women infertility by preventing fertilized eggs from reaching the uterus, where fetal development takes place. Also, adhesions can kink, twist, or pull out of place the fallopian tubes where eggs are stored and released to the uterus **(Dharmananda 2010; Robertson & Lefebvre 2010).** Also the family history was a risk factor for infertility but not for recurrent miscarriage , and women with family history of infertility are 5 times more likely to be infertile than those of women with

no family history, with PARP of 2.81% for the Palestinian population in Gaza.

V.2.5. Medical presentation (status, situation)

Higher percentages of vaginal infections were reported in the women of the infertility and recurrent miscarriage groups, while no significant differences were reported regarding urinary infections. In the Palestinian population women with vaginal infections are 4.40 times more likely to be infertile and 4.28 times more likely to develop recurrent miscarriages than women with no vaginal infections. Moreover, 17.75% and 25.12% of the infertility cases and recurrent miscarriage cases in the Palestinian women in Gaza strip could be prevented or avoided when women treated from vaginal infections before conception, Therefore, for women who are planning to conceive, they must be investigated for any vaginal infections and treated before going ahead with conception. The negative effects of vaginal infections on development of infertility and/ or abortion have been addressed by different researchers **(Healy *et al.*, 1994; Guerra-Infante *et al.*, 2003; Mania-Pramanik *et al.*, 2008).**

V.2.6. Thrombophilic disorders

The most effective risk factor for infertility and recurrent miscarriages among the Palestinian women in Gaza strip is the thrombophilic disorders. In Table 10 of the results it was obvious that, a significantly 45.6% of the women in the infertility group and 70.5% in the recurrent miscarriage group are exhibiting one or more of the thrombophilic disorders screened as compared to control group. Moreover the percentage in the miscarriage groups is also significantly higher than that in the infertility group.

When these percentages are discussed in terms of odds ratio and PARP, the magnitude of the thrombophilic problem became more disquieting and frightening. For infertility, woman with thrombophilic disorders is 95.41 times more likely to be infertile than those with normal clotting functions. While this become more and more distressing when mention that woman is 272.33 times more likely to recurrently miscarry if she has one or more of the thrombophilic disorders. It is worthwhile mentioning that, about one-fourth of infertility cases and about 60% of recurrent miscarriages in the Palestinian women in Gaza are attributed to thrombophilic disorders. Therefore testing and managing these thrombophilic disorders in the women before planning to conceive are highly recommended. The crucial effects of thrombophilic disorders on conception and pregnancy outcome have been addressed properly in scientific works **(Middeldorp 2007, Ferroni *et al.*, 2010; Jeddi-Tehrani *et al.*, 2010; Kujovich, 2010). Kupferminc *et al.*, 1999** demonstrated an increased frequency of genetic thrombophilia in women with complications of pregnancy, while **Coulam *et al.*, 2006** revealed that multiple thrombophilic gene mutations rather than specific gene mutations are risk factors for

recurrent miscarriage. However, **Goodman *et al.*, 2006** identified the most common mutations that affecting recurrent pregnancy loss.

Behjati *et al.*, 2006 investigated the common mutations behind infertility and recurrent miscarriage in Iranian population. They showed that the frequencies of Factor V Leiden mutation in patients with infertility and recurrent miscarriage were 30.6%, 20.0%, respectively which were significantly higher than that of their control group. Also, they observed a significantly higher Methylenetetrahydrofolate reductase (MTHFR) mutation rate (63.1%) in patients with recurrent miscarriage as compared to controls.

In the Palestinian women in the west bank the results of the scientific study conducted by **Hussein *et al.*, 2010** showed strong association of factor V Leiden polymorphism among primary aborters compared to secondary aborters or control groups.

Different treatment protocols depending on administration of anticlotting drugs were adopted and experienced with an encouraging and promising successful rates in infertile and recurrent miscarriage cases, which exceeded 80% in some populations **(Szilágyi *et al.*, 2006; Davies *et al.*, 2009; Laskin *et al.*, 2009; Trisolini *et al.*, 2009)**.

VI. Conclusions

- The age of women is of great importance and must be taken in account by gynecologist when treating infertility or recurrent miscarriage among Palestinian females in the Gaza strip.
- Long working hours must be avoided by women who seek to have a baby because our study found that, the working of Palestinian female is considered among the risk factor that affected the rate of infertility and recurrent miscarriage.
- The incidence of infertility and recurrent miscarriage among women with abnormal cycles were significantly grater than in those with regular one.
- Abnormalities in ovary and uterus are considered among the significant risk factor for infertility and recurrent miscarriage among Palestinian females in the Gaza strip.
- Also sex and thyroid hormone abnormalities are considered one of the risk factors for infertility and recurrent miscarriage among Palestinian females in the Gaza strip.
- The medical history of subject (previous surgical operation) is of great important and one of the risk factor.
- Infertility and recurrent miscarriage among Palestinian female in the Gaza strip, could be prevented or avoided if women treated from vaginal infection before conception.
- The most effective risk factor for infertility and recurrent miscarriages among the Palestinian women in Gaza strip is the thrombophilic disorders.

VII. Recommendation

- The percentage of recurrent miscarriage among Palestinian females in the Gaza strip could be reduced if child bearing occurs before the age of thirty years old.
- Palestinian females in the Gaza strip must avoid long working hours during pregnancy.
- Women menstruation cycle must be taken in consideration when treating infertility and / or recurrent miscarriage.
- Percentages of infertility and / or recurrent miscarriage could be minimized by managing the cause of ovary or uterine abnormalities.
- Sex hormones testing is considered a predictive test for women before pregnancy, and could also be used to identify patients with an endocrine abnormality that can be cured.
- Abdominal surgical operation in women must be precise and accurate to avoid complication effect, which may lead to infertility or recurrent miscarriage.
- The family history is of great importance and must be taken in account when treating infertility.
- Women in Gaza Stripe who are planning to conceive, must be investigated for any vaginal infection and treated before going ahead with conception.
- Testing and managing for thrombophilic disorders must be taken in women before planning to conceive.

VIII. References

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Risk factors associated with female infertility and recurrent miscarriage

عوامل الخطورة المصاحبة للعقم النسائي والإجهاض المتكرر

الجزء الأول: المقابلة الشخصية

هل هناك عقم	o نعم				o لا
نوع العقم	o أولي				o ثانوي
هل هناك إجهاض متكرر	o نعم				o لا
عدد حالات الإجهاض المتكرر	.....				
المحافظة	o الشمال	o غزة	o الوسطى	o خان يونس	o رفح
مكان السكن	o مدينة	o قرية	o معسكر		
العمر (سنة الميلاد)	.....				
الدورة الشهرية	o منتظمة			o غير منتظمة	
الدورة الشهرية	o شديدة			o طبيعية	
عدد أيام الدورة الشهرية	..... يوم				
المستوى التعليمي (عدد سنوات الدراسة)	o جامعي فأكثر	o دبلوم	o ثانوية عامة	o أقل من ثانوية عامة	o ابتدائي
الزوج يعمل	o نعم			o لا	
السيدة تعمل	o نعم			o لا	
نوع العمل	.....				
هل هناك مشاكل وحالات عقم في العائلة	o نعم			o لا	
هل هناك عمليات جراحية سابقة في منطقة البطن	o نعم			o لا	
هل هناك اعتلال في الغدة الدرقية	o نعم			o لا	
هل تعاني المريضة من أمراض ضغط الدم	o نعم			o لا	
هل تعاني المريضة من السكري	o نعم			o لا	
هل هنا مشاكل وضغوطات حياتية واجتماعية	o نعم			o لا	
هل هناك تاريخ مرضي لحمل خارج الرحم (history of an ectopic pregnancy)	o نعم			o لا	
هل هناك تاريخ مرضي لحمل عنقودي (molar pregnancy)	o نعم			o لا	

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الجزء الثاني: الفحص الطبي

شكل الرحم والأنابيب وتليفات الرحم	o طبيعي	o غير طبيعي
هل الرحم مقلوب إلى الخلف أو مائل retroverted (tilted or tipped) uterus	o نعم	o لا
هل هناك تعدد تكيس مبيضي (polycystic ovarian syndrome)	o نعم	o لا
هل هناك انسداد أو تعطل في قناة فالوب fallopian tube damage or blockage	o نعم	o لا
بطانة الرحم الهاجرة (endometrioses)	o نعم	o لا
هل هناك تليفات في الرحم (fibroids)	o نعم	o لا

الجزء الثالث: الفحص المخبري

هل هناك خلل هرموني	o طبيعي				o غير طبيعي	
فحص الهرمونات	o Estrogen	o LH	o FSH	o Prolactine	o TSH	o AMH
هل هناك أمراض منقولة جنسياً مثل Chlamydia	o نعم			o لا		
هل هناك إصابة toxoplasmosis	o نعم			o لا		
هل هناك مشاكل في تجلط الدم Thrombophilia	o نعم	o لا	o MTHFR	o PAI	o ACE	
			o Factor x	o Factor v	o Prothrombin	
فصيلة الدم blood group	.....					
هل هناك التهابات مهبلية أو التهابات عنق الرحم	o نعم			o لا		
هل هناك التهابات في مجرى البول	o نعم			o لا		