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Title:

Risk factors associated with infertility among Palestinian men in Gaza

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Declaration

I Hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material witch to substantial extent has been accepted for the award of any other degree of the university of other institute, except where due acknowledgment has been made in the text.

Signature	Name	Date
Ali	Ali Abed Alkarim Ashour	

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Dedication

To My great father and mother who love me, who raised me,

To my wife who supported me along the time,

To my baby Karim,

To my brother and sisters,

To all of them I dedicate this work.

Ali

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List of abbreviations

Abbreviation	Full word
ACE	Angiotensin-Converting Enzyme
EDO	Ejaculatory Duct Obstruction
FSH	Follicle Stimulating Hormone
GH	Growth Hormone
IBT	Immunobead Test
IELT	Intravaginal Ejaculatory Latency Time
LH	Luteinizing Hormone
MAR	Mixed Antiglobulin Reaction
MTHFR	Methylenetetrahydrofolate Reductase
OTA	Oligoteratoasthenozoospermia
PAI-1	Plasminogen activator Inhibitor-1
PCBS	Palestinian Central Bureau of Statistics
PCOS	Polycystic Ovary Syndrome
PEDT	Premature Ejaculation Diagnostic Tool
PRL	Prolactin
PUFA	Polyunsaturated Fatty Acid
ROS	Reactive Oxygen Species
SPSS	Statistical Package for the Social Science
STDs	Sexually Transmitted Disease
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization

Abstract

Background: The inability to have children is frequently considered as a personal tragedy and a curse for the couple, affecting the entire family and the local community. In Gaza Strip there is no study document showing the risk factors associated with infertility related to man.

Objective: This study aimed to identify the risk factors associated with infertility among Palestinian men in the Gaza strip.

Material and Method: The cases of the study (N = 328) were selected randomly from those referring to Al-Basma fertilization center seeking for medical management of infertility. Questionnaire interview, urology diagnostic, related hormonal analysis and sonography were the tools of study.

Result: The result showed that in 347 (53.2%) of the cases the cause of infertility was related to woman, while in 293 (41.7%) the cause of infertility was related to man. In addition in 35 (5.0%) the cause of infertility is related to both man and woman. The majority of the cases 139 (42.3%) were lived in Gaza Governorate followed by the other Governorates .

Regarding age, most of the cases 237 (72.2 %) were younger than 30 years old. The education status of the study population showed that 209 (63.7 %) of cases finished their high school.

Medical and clinical characteristics of the cases, revealed that prolactin hormones abnormities hyperprolactinemia were found in 14 (4.2 %) the infertile men. Azoospermia was the highest sperm problem reported among the infertile men 83 (25.3 %).

According to psychological problems 12 (3.6 %) of the infertile cases reported to premature ejaculation. Varicocele infections were reported in 32 (9.7 %) of infertile men. However large number 60 (18.2 %) of cases Suffered from compound infertility.

Conclusion: The most major risk factors that lead to infertility among Gazan men include: sex hormone abnormalities, sperm problems, varicocele, azoospermia, oligospermia, premature ejaculation, infection, sexually transmitted diseases.

Key word: Infertility, Men, Risk factors, Gaza strip.

عوامل الخطورة المصاحبة للعقم لدى الرجال في قطاع غزة

ملخص البحث

تعتبر عدم القدرة على إنجاب الأطفال مأساة شخصية ونقمة للزوجين، مما يؤثر على الأسرة بأكملها، بل وعلى المجتمع المحلي. في قطاع غزة لا يوجد هناك أي تقارير موثقة أو علمية تبحث في عوامل الخطورة المرتبطة بالعقم لدى الرجال.

يهدف العمل الحالي إلى تحديد عوامل الخطورة المرتبطة بالعقم بين الرجال الفلسطينيين في قطاع غزة. تم اختيار الحالات 328 بشكل عشوائي من الحالات التي قامت بمراجعة مركز البسمة للإخصاب وأطفال الأنابيب وشملت الأدوات الرئيسية لهذه الدراسة المقابلة الشخصية، فحص وتشخيص الجهاز التناسلي والبولي، ، التحاليل الهرمونية و التصوير التلفزيوني.

أظهرت نتائج الدراسة الحالية أن 347 (53.2 ٪) من الحالات كان سبب العقم فيها النساء وحوالي 293 (41.7 ٪) من الحالات كان السبب فيها الرجال و35 (5.0 ٪) من الحالات اجتمع الزوج والزوجة في حدوث العقم. وكانت النسبة الأعلى 139 (42.3 ٪) من الحالات تسكن في محافظة غزة.

فيما يتعلق بالخصائص العمرية للحالات فإن نسبة الرجال الذين تقل أعمارهم عن 30 سنة 293 (72.2 ٪) هي الأعلى . فيما يخص المستوى التعليمي فإن نسبة الرجال الذين أنهو الثانوية العامة فأكثر كانت الأعلى 209 (63.7 ٪) .

وفقا للناحية الصحية والسريرية لدى الرجال ، أظهرت نتائج فحص الهرمونات ارتفاع في نسبة الرجال الذين يعانوا من ارتفاع مستوى هرمون الحليب 14 (4.2 ٪). النسبة الأعلى من مشاكل السائل المنوي كانت للأشخاص الذين يعانوا من فقد النطاف 83 (25 ٪). من الناحية الفسيولوجية 12 (3.6 ٪) من الحلات كانت تعاني من القذف المبكر.

سجلت نسبة عالية من الأشخاص المصابين بدوالي الخصيتين ودوالي الحبل المنوي 32 (9.7 ٪) ، النسبة الأعلى للأشخاص العقيمين كانت تعاني من عوامل عقم مضاعفة (أكثر من عامل معا ، مثال حالات تعاني من العقم بسبب مشاكل هرمونية ومشاكل فسيولوجية معا).

نستنتج من هذه الدراسة أن العوامل المؤدية إلى العقم بين الرجال في غزة متعددة وتشمل كلا من: الاعتلال في وظائف الهرمونات الجنسية، مشاكل وأمراض السائل المنوي، دوالي الخصيتين ودوالي الحبل المنوي، فقد النطاف، قلة النطاف، القذف المبكر، العدوى والأمراض الناتجة عن الالتهابات.

الكلمات الافتتاحية: العقم، الرجال، قطاع غزة، عوامل الخطورة.

CHAPTER I

INTRODUCTION

I-Introduction

Infertility is the inability to conceive and become pregnant after 12 months of regular, unprotected sexual intercourse 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).**

Traditionally, the diagnosis of male infertility is based upon the conventional semen profile, constructed according to recognized guidelines **(WHO, 1992; Van den Eede, 1995).** This profile incorporates information on the volume of the ejaculate, the concentration of spermatozoa, their motility and their morphological appearance. Unfortunately, a number of significant shortcomings limit the diagnostic value of this assessment. Marked inter-ejaculate variability is a major problem in the assessment of human semen **(Scwartz *et al.*, 1979; Mallidis *et al.*, 1991)**, and many aspects of the profile are subjective, and have not traditionally been subjected to quality control, with disconcerting evidence of inconsistency between laboratories **(Neuwinger and Nieschlag, 1990; Cooper et al., 1992, Matson, 1995).**

Although WHO has issued a range of 'normal' values, these are not evidence-based, either in terms of their diagnostic value, nor in terms of their relationship to the normal fertile population. As a consequence, many couples with 'unexplained' infertility can be shown to have defective sperm function when appropriately sensitive assays are used, and some couples with subnormal conventional semen parameters have normal sperm function **(Irvine and Aitken, 1986; Glazener *et al*, 1987; Anonymous, 1996).** It is perhaps more logical for individual laboratories to define their own normal ranges, with reference to their normal fertile population.

Notwithstanding the difficulties in diagnosis out- lined above, the WHO has proposed a scheme for the diagnostic classification of the male partner of the infertile couple **(Rowe *et al.*, 1993).** This approach is of enormous value as a basis for standardization, and for comparative multicenter studies. However, many of the male diagnostic categories are of a descriptive nature (e.g. idio-pathic oligozoospermia) or of controversial clinical relevance (e.g. male accessory gland infection).

It is important to recognize that a number of general epidemiological factors will have a bearing on a couple's fertility. Examples of this include age, there being clear evidence that the age of the female partner is a major determinant of fertility **(Joffe and Li, 1994b; Templeton *et al.*, 1996)**, although the impact of male age is less certain. Smoking by both partners is highly relevant, there being evidence that smokers have lower sperm concentrations than non-smokers **(Joffe and Li, 1994b; Vine *et al.*, 1994, 1996)**. Occupational, environmental and genetic factors may also be highly relevant. Moreover, recent advances in our understanding of the causes of male infertility, particularly in the area of genetic problems, mean that this classification is now in need of review **(Najmabadi *et al.*, 1996; Vogt *et al.*, 1996).**

Problem statement

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. The infertility consider a one of the most important reproductive health problems in developing countries **(Bergstrom, 1992; Leke *et al.*, 1993)**. 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).**

In Palestine, and especially in the Gaza Strip there is no documented reports or published scientific work that investigated the prevalence and risk factors associated with infertility and. 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 the risk factors associated with infertility among Palestinian men in the Gaza Strip.

The specific objectives are:

- To highlight the most common risk factors for infertility among Gazan men .
- To provide the community and the health care providers with the first scientific data about the risk factors for infertility in men in the Gaza Strip.

CHAPTER II

Review of Literature

II. Review of Literature

II.1. Infertility

II.1.1. Definitions

One of the most serious social problems facing developed countries today is the declining birth rate, although it is generally not well recognized that the number of infertile couples is on the rise in these countries. While both social (i.e., social progress for women and the resulting increase in the age at which women marry) and environmental (i.e., pollution and global warming) factors are behind part of the increase in the number of patients with infertility, infertility in the male partner contributes to approximately half of all cases.

Infertility is a 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.

Demographers have modified the epidemiological definition of infertility as "the inability of a non-contracepting sexually active woman to have a live birth". **(Larsen, 2000).**

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).**

II.1.2. Prevalence of infertility

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 procreate 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 *et al*., 2002a,b, 2004, 2005; Umezulike and Efetie, 2004; Dyer, 2007).** In many cultures, womanhood is defined through motherhood and infertile women usually carry the blame for the couple's inability to conceive. Moreover, in the absence of social security systems, older people are economically completely dependent on their children. Childless women are frequently stigmatized, resulting in isolation, neglect, domestic violence and polygamy **(Gerrits, 1997; Sundby, 1997; Papreen *et al*., 2000; van Balen and Gerrits, 2001; Richards, 2002; van Balen, 2002; Araoye, 2003; Hollos, 2003; Wiersema *et al*., 2006).**

Only a limited number of papers report on the prevalence of infertility in developing countries. According to **Boivin *et al*. (2007).**

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**.**

Although good documentation of the prevalence of infertility is lacking, it is generally believed that more than 70 million couples suffer from infertility worldwide **(Fathalla, 1992; Boivin *et al*., 2007).**

There are wide variations in the published data on the prevalence of resolved male infertility, with rates of 5-14% being cited for resolved primary infertility, and 3-12% for resolved secondary infertility. For unresolved infertility, rates of 3-9% and 3-7% have been quoted for primary and secondary infertility respectively.**(Irvine 1998).**

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 and diagnosis of infertility

In a large study performed by the WHO Task Force on the Diagnosis and Treatment of Infertility, 8504 infertile couples in 33 different countries were examined through a standard approach in all participating centres **(Cates *et al*., 1985; WHO, 1987).** In Africa, over 85% of women had an infertility diagnosis attributable to an infection

compared with 33% of women worldwide. In another study from sub- Saharan Africa, a history of sexually transmitted diseases was reported by 46% of participating men **(Gerais and Rushwan, 1992)**. A study of 5800 couples in 33 World Health Organization centres in 25 countries showed that almost 50% of the African couples and 11–15% of other patients in other parts of the world had infectious tubal disease **(Sciarra, 1994)**.

Studies from non-African developing countries on the causes of infertility are lacking but available data would indicate that infection-related causes also play a prominent role **(Barten, 1978; Makush *et al*., 2000)**.

Moreover, infectious diseases other than sexually transmitted diseases may also cause infertility.

The diagnosis of male infertility is based upon the conventional semen profile, constructed according to recognized guidelines **(WHO, 1992; Van den Eede, 1995).** This profile incorporates information on the volume of the ejaculate, the concentration of spermatozoa, their motility and their morphological appearance. Unfortunately, a number of significant shortcomings limit the diagnostic value of this assessment. Marked inter-ejaculate variability is a major problem in the assessment of human semen **(Scwartz *et al.*, 1979; Mallidis *et al.*, 1991)**, and many aspects of the profile are subjective, and have not traditionally been subjected to quality control, with disconcerting evidence of inconsistency between laboratories **(Neuwinger and Nieschlag, 1990; Cooper *et al*., 1992; Matson, 1995)**. Although WHO has promulgated a range of 'normal' values, these are not evidence-based, either in terms of their diagnostic value, nor in terms of their relationship to the normal fertile population. As a consequence, many couples with 'unexplained' infertility can be shown to have defective sperm function when appropriately sensitive assays are

used, and some couples with subnormal conventional semen parameters have normal sperm function **.**

(Irvine and Aitken, 1986; Glazener *et al*, 1987; Anonymous, 1996). It is perhaps more logical for individual laboratories to define their own normal ranges, with reference to their normal fertile population.

II.1.4. Possible causes of male infertility

Male infertility has many causes, which may be pre-testicular, testicular, and post-testicular. From the practical point of view, abnormalities that cause testicular failure and impaired spermatogenesis cannot be corrected while obstructive processes involving the sperm transport system are potentially correctable. Post-testicular causes include obstruction of the sperm delivery route (male factor obstructive infertility) anti-sperm antibodies and retrograde ejaculation **(Turek *et al*., 1996).** Obstruction can occur at any level either proximal, affecting the epididymis or distal, affecting the ejaculatory duct (Goluboff ***et al***., 1995 and Brugh ***et al***., 2007).

Seminal tract obstruction can be classified according to the level of obstruction, into proximal seminal tract obstruction, including epididymis and scrotal portions of the vas deferens and distal seminal tract obstruction including inguinal, pelvic and ampullary portions of the vas deferens, and ejaculatory ducts. Pathology from complete ejaculatory duct obstruction occurs in < 1% of infertile men, whereas the frequency of incomplete obstructive pathologies is reportedly 4.4% **(Schlegel 1997).** Using data taken from a WHO study of >8500 couples from 33 centres in 25 countries, 71% of whom reached the point of diagnosis **(Comhaire *et al*., 1987)**. It can be seen that the largest single male 'diagnostic' category was men with seminal

abnormalities of unknown cause. Beyond this, varicocele was a relatively common pathology, as was male accessory gland infection; however, systemic, iatrogenic and endocrine causes were very infrequent.

It is important to recognize that a number of general epidemiological factors will have a bearing on a couple's fertility. Examples of this include age, there being clear evidence that the age of the female partner is a major determinant of fertility **(Joffe and Li, 1994b; Templeton *et al.*, 1996)**, although the impact of male age is less certain. Smoking by both partners is highly relevant, there being evidence that smokers have lower sperm concentrations than non-smokers **(Joffe and Li, 1994b; Vine *et al.*, 1994, 1996)**. Occupational, environmental and genetic factors may also be highly relevant. There can be no doubt that recent advances in assisted conception technology have revolutionized the treatment of couples with male factor infertility **(Bonduelle *et al.*, 1996; Silber *et al.*, 1996)**, and have advanced our understanding of the aetiology of male infertility by drawing attention to the major contribution of genetic factors **(Reijo *et al.*, 1995; Najmabadi *et al.*, 1996; Vogt *et al.*, 1996)**.

II.1.4.1. History

II.1.4.1.1. Reproductive and sexual history

For the reproductive history, any prior conceptions for the male with present or past partners, details of any prior difficulty achieving conception, past evaluations and treatments for infertility, and previous use of contraception should all be recorded, along with the frequency and timing of intercourse with the man's current partner. Information about erectile and

ejaculatory function and frequency of masturbation should be requested, as well as the timing of first masturbation and intercourse.

II.1.4.1.2. Medical history

Diabetes may affect erectile and/or ejaculatory function **(Greene and Kelalis, 1967),** and any systemic illness accompanied by fever or viremia can lead to impaired testicular function, although the effects may not be measurable in the ejaculate for 1–4 months. A history of pyospermia or prostatitis should be noted, although both are uncommon and neither is proved to cause infertility **(Weidner *et al*., 1999)**. Primary ciliary dyskinesia (also known as immotile cilia syndrome), which should be suspected when there is a history of chronic upper respiratory infections, causes severe defects in sperm motility.

When this condition is associated with situs inversus, it is known as Kartagener syndrome, which is a rare cause ofmale infertility **(Wilton *et al*., 1986)**. Frequent respiratory infections associated with azoospermia raise the possibility of Young syndrome **(Wilton *et al*., 1991)**, in which epididymal obstruction is caused by the inspissation of secretions. Neurologic issues can lead to male infertility as a variety of hormonal abnormalities including thyroid disorders, hyperprolactinemia, and elevated estrogen levels. Finally, any history of urinary tract infections or sexually transmitted disease should be recorded, particularly if associated with epididymitis, as these conditions can lead to epididymal obstruction.

II.1.4.2 Environmental factors

There has long been debate over whether male reproductive ability is determined by environmental factors, such as those present in the workplace or area of residence. Having a major effect on this debate was the sensational report by **Whorton *et al*.,** published in **1977**, which found that of 25 male workers involved in producing the insecticide dibromo-3-chloropropane, 14 were diagnosed as azoospermic or oligospermic (**Whorton *et al*., 1977)**. In 1992, Carlsen et al. reported that the previous 50 years saw a marked decrease in

sperm count **(Carlsen *et al*., 1992).** That same year, Brake and Krause reported that during the period since 1970 in Scotland, sperm counts had decreased by approximately 25% compared with the period prior to 1959, a mean annual rate of 2.1% **(Brake and Krause, 1992).**

Many researchers and clinicians have asserted that societal progress in advanced countries and worsening of the natural environment have likely resulted in decreased male fertility. Long-reported risk factors include working in high temperatures **(Zorgniotti *et al*., 1982)**, noise associated with manufacturing **(Carosi and Calabr, 1968)**, exposure to radiation **(Sandeman, 1966)**, electromagnetic waves **(Lancranjan *et al*., 1975),** and a variety of chemical substances **(Kenkel *et al*., 2001).**

II.1.4.3. Varicocele

A varicocoele is an abnormal venous dilatation of the pampiniform plexus, which may lead to symptoms of pain and discomfort, failure of ipsilateral testicular growth and development, or infertility **(Beddy *et al*., 2005).** A varicocoele is a common finding in approximately 20% of adolescents and adult males, and in up to 40% of infertile patients **(Weidner *et al*., 2010).** The direct connection between varicocoele and infertility is not clear. It is well known that after operative therapies on a varicocoele an improvement in sperm quality is found **(Weidner *et al*., 2010).** A recent Cochrane review **(Evers *et al*., 2009)** found no evidence that treatment of varicocoeles in males from couples with otherwise unexplained subfertility improved pregnancy rates. However, of the eight studies in this review two included some males with normal semen analysis and three studies specifically addressed only males with subclinical varicocoeles. In a multicentre trial specifically looking at infertile males with moderate oligozoospermia and a clinically

apparent varicocoele with no other demonstrable cause for infertility, varicocoele correction improved sperm parameters and the fertility rate **(Madgar *et al*., 1995).** Thus there is still likely to be a place for varicocoele treatment in improving fertility when there is a clinically detectable varicocoele and abnormal sperm parameters. Diagnosis of a varicocoele is made on clinical examination and usually confirmed by ultrasound with high accuracy (sensitivity 97%, specificity 94%) **(Trum *et al*., 1996)**. On greyscale imaging a varicocoele is seen as serpiginous tubules posterior to the testis, and may extend to the inferior pole of the testis with at least two or three veins of the pampiniform plexus measuring .2–3mm in diameter. Colour Doppler ultrasound is a routine component of the examination as identification of flow reversal on Valsalva improves diagnostic accuracy. The degree of venous reflux during the Valsalva manoeuvre may be graded 1–3: Grade 1, reflux induced by the Valsalva manoeuvre; Grade 2, intermittent spontaneous reflux; and Grade 3, continuous spontaneous reflux **(Dogra *et al*., 2003, Beddy *et al*., 2005, Kocakoc *et al*., 2003).**

II.1.4.4. Male accessory gland infection

The second commonest diagnostic grouping in the WHO survey, this is also an area of considerable aetiological controversy. Whilst there is little doubt that overt sexually transmitted disease may damage male fertility, and should be appropriately man aged, there is much more doubt about the relevance of sub-clinical infection. Thus it is clear that gonorrhoea is implicated in the aetiology of obstructive azoospermia **(Jequier and Holmes, 1984)**, and that chlamydia infection in the male can lead to tubal infertility in his partner **(Westrom, 1996)**. It is much less clear whether subclinical infection in the male is causally associated with infertility (**BarChama *et al.*, 1994)** and there is no clear consensus on diagnostic criteria **(Purvis and Christiansen,**

1993). One possible consequence of infection is seminal leukocytosis **(Eggert-Kruse *et al.*, 1995)** and one consequence of seminal leukocytosis is the excessive generation of reactive oxygen species (ROS) by these cells **(Krausz *et al.*, 1992)**. There is good evidence linking the excessive generation of ROS with male infertility as an aetiological entity in its own right - prospective studies have shown that couples with elevated levels of ROS generation are less likely to conceive either spontaneously, or in the context of in-vitro fertilization **(Aitken *et al.*, 1991; Sukcharoen *et al.*, 1995)**. Excessive ROS can originate from both abnormal spermatozoa and from contaminating leukocytes **(Aitken *et al.*, 1994)** and the diagnostic and therapeutic implications of this pathology remain to be fully elucidated (**Irvine and Aitken, 1996)**.

II.1.4.5. Immunological causes

Suspected immunological infertility was found in some 3% of couples in a WHO survey on the basis of the finding of 10% of motile spermatozoa coated with antibody using assays such as the immunobead test (IBT) or the mixed antiglobulin reaction (MAR). Whilst antisperm antibodies are found in perhaps one in six of the male partners of infertile couples, a prevalence which is higher than that for fertile controls, their effect on fertility is hard to determine. Some studies suggest that 'antibody-positive' couples conceive at a lower rate than those without immunological problems **(Busacca *et al.*, 1989)**. Unfortunately, antibodies to sperm surface antigens are also found in fertile control populations, and it is unfortunate that these techniques do not permit the meaningful separation of cases with auto-immunity to biologically relevant epitopes **(Paradisi *et al.*, 1995)**. Given the consensus view that assisted conception is the treatment of choice, this may not now be a clinically relevant issue.

II.1.4.6. Ejaculatory duct obstruction

Ejaculatory duct obstruction **EDO** is relatively uncommon, with the incidence of complete bilateral EDO reported as less than 1% in infertile males **(Jarow *et al*., 1989).** The incidence of incomplete EDO is unknown because of variations in definitions between authors **(McIntyre and Fisch, 2010)**. Congenital causes of EDO include duct atresia or stenosis as well as compression by midline prostatic cystic lesions, e.g. cysts of the prostatic utricle (previously named Mu¨ llerian duct cysts), cystic dilatation of the prostatic utricle and ejaculatory duct cysts **(Galosi et *al*., 2009)**. Cystic obstruction of the ejaculatory tracts is usually congenital and acquired lesions are rare **(Sidhu, 2006).**

II.1.4.7. Sexually transmitted diseases

Sexually transmitted diseases STDs are, as outlined above, prominent risk factors for infertility in developing countries. The organisms most commonly involved are Chlamydia trachomatis and Neisseria gonorrhea **(Walker and Hofler, 1989; Mascie-Taylor, 1992; Mayaud *et al*., 1995; Sciarra, 1997)**. Pelvic tuberculosis can also result in tubal infertility, and high incidences have been reported in studies from the Indian subcontinent as well as from Ethiopia **(Mascie-Taylor, 1992; Parikh *et al*., 1997; Sekadde-Kigondu and Machoki, 2002; Shaheen *et al*., 2006).**

Another sexually transmitted organism associated with infertility is HIV-1. Several studies have documented reduced fecundity in HIV-infected individuals **(Brocklehurst and French, 1998; Glynn *et al*., 2000; Sekadde-Kigondu and Machoki, 2002).** Mechanisms involved include tubal factor infertility through the greater susceptibility to other STDs, male hypogonadism, altered spermatogenesis, increased risk of miscarriages as well as

behavioural factors **(Lyerly and Anderson 2001; Gilling-Smith *et al*., 2006).** On the other hand, marital instability and polygamy secondary to infertility may in turn increase the spread of HIV-1 infection **(Nabaitu *et al*., 1994).** The high prevalence of infections is commonly compounded by a delayed or a complete lack of diagnosis together with incomplete, inappropriate or no intervention at all **(Adler, 1996; Giwa-Osagie, 2002a,b).** Related risk factors include, among others, poor education, poverty, negative cultural attitudes to women, early age at first marriage, polygamy, lack of access to contraception and the adverse effects of migrant labour **(Bambra, 1999).** Effective and appropriate educational, preventive and curative sexual and reproductive health programmes are urgently required **(Leke *et al*., 1993; Temmerman, 1994).**

II.1.4.8. Genetic causes

Perhaps the most striking advances in our understanding of the aetiology of male infertility in the past has been in the area of genetics. Many of the 'systemic' disorders mentioned above are now understood to have a genetic basis, and as our knowledge of the aetiology of disease expands, this will be increasingly the case. Traditionally, genetic causes of male infertility have been sought at the level of chromosomal abnormalities, with chromosomal abnormalities being detected in between 2.1 and 8.9% of men attending infertility clinics. Chandley, in a study of 2372 men attending an infertility clinic in Edinburgh, found significant abnormalities in 21.5 per 1000 men, significantly different from the rate of 7 per 1000 newborn males in the same city **(Chandley, 1994)**. Of these the majority were sex chromosome abnormalities, most commonly being associated with azoospermia. However, it has been recognized for some time that structural anomalies of the Y chromosome, resulting in deletion of the

distal fluorescent heterochromatin in the long arm, are associated with severe abnormalities of spermatogenesis **(Chandley *et al.*, 1986, 1989)**. Other studies have defined a family of genes on the Y chromosome involved in spermatogenesis **(Ma *et al.*, 1993; Reijo *et al.*, 1995)**, and it has become clear that a little >10% of cases of non-- obstructive azoospermia may be due to deletions affecting these genes **(Reijo *et al.*, 1996)**. A proportion of cases of very severe oligozoospermia may have a similar aetiology **(Najmabadi *et al.*, 1996; Reijo *et al.*, 1996)**.

II.1.5. Possible causes of female infertility

II.1.5.1. 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.

II.1.5.2. 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**. (Gunn,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.1.5.3. 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.1.5.4. 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.1.5.5. 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.

II.1.5.6. 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.

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. **Mokhtar *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.1.5.7. 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.1.5.8. 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.1.5.9.Infection

In the last 30 years, sub clinical infection due to several microorganism have been implicated in infertility. Two types of mycoplasma, *Mycoplasma 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.

The detailed possible risk factors associated with infertility related to female in Gaza was studied by other researchers at Al-Azhar University, faculty of science **(Sirdah *et al.,* 2013).**

CHAPTER III

Materials and Methods

III. Materials and Methods

III.1. Study design

The present work was designed as a descriptive study aiming at the investigation of the possible risk factors associated with infertility among Palestinian men at the Gaza strip.

III.2. Target population and sample size

Seven hundred and two subjects suffering from infertility and referring to Al Basma fertility center in Gaza, covering the period from January 2006 to December 2012 were selected randomly and their were studied comprehensively to identify the major risk factors.

The subjects were divided into 3 groups:. The characteristics of each group as follows:

Group 1: If the cause of infertility is related to woman (this case was addressed in another study **(Sirdah *et al.*, 2013).**

Group 2: If the cause of infertility is related to man

Group 3: if the cause of infertility is referred to both man and woman.

The causes of infertility related to man were studied comprehensively and the major risk factors associated with infertility among men were identified.

III.3. Study tools

III.3.1. Questionnaire interview

A closed-ended questionnaire was used to collect the important data and was constructed and conducted in Arabic. A copy of the questionnaire is included in Annex (page 64). The questionnaire was designed to include major issues: socio-demographic and general characteristics; urology information, other health characteristics, health complains and medical history of the subjects. The items and components of the questionnaire were arbitrated and validated at two 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 objectives of the study were attached with the questionnaire. Some of the items were added, some modified and some were excluded. The questionnaire was checked by scientists and gynecologists.

III.3.2. Urology diagnosis

After classifying the cases, the men were clinically investigated by the Urologist for the status of the reproductive system. The Urologist provided an evaluation about the morphological characteristics of men testes. The main points of interest were: anatomical and size of both testes; abnormalities of seminal tubes (damage or blockage); examination of the prostate gland and presence of fibroids and the presents of varicocele.

III.3.3. Reproductive and urinary infections examination

The Urologist also examined the ejaculated semen for any causative microorganisms using sterile cup and executed culture technique to identify the presence of any microorganisms. Urine sample was also collected in a sterile cup and investigated microscopically for microbiological infection and culture technique.

III.3.4. Hormonal analysis

Venous blood from the subjects was tested for the following hormones using the commercially available kits as indicated : Prolactin ST AIA-PACK PRL (the male normal range 2.0 - 18.0 ng/ml); Follicle Stimulating Hormone (FSH) ST AIA-PACK FSH (the male normal range 1.5 - 12.4 mIU/ml); Luteinizing Hormone (LH) ST AIA-PACK LH II (the male normal range 5.0 - 25 IU/L); Testosterone ST AIA-PACK TESTOSTERONE (the male normal range 300 - 1,000 ng/dL) ; and Thyroid Stimulating Hormone (TSH) ST AIA-PACK TSH (the normal range 0.4 - 4.0 mIU/L). All the reference value according to **Clemmons (2011).**

III.3.5. Ultrasound or sonography

The subjects were clinically investigated by the Urologist 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 the morphological characteristics of men testes. The main points of interest were the presence of varicocele and condition of the prostate gland

III.4. Statistical analysis

- The results obtained from the medical files of the cases were tabulated, encoded and statistically analyzed using the Statistical Package for the Social Science (SPSS) version 17. The following statistical tests and comparisons were performed.
- Frequency table for all the study variables
- Profile is rated for patients within several variables, place of residence, age, and education degree
- The causes of infertility were divided into four variables, namely hormonal problems, physical problems, physiological problems and finally combined problems (it the cause of infertility is related to more than one variable).
- The numbers of cases were calculated and their percentage within each group was determined separately and distributed in illustrative tables

CHAPTER IV

Results

IV. Results

The present study focused on the cases were the cause of infertility is related to man. The cases of men infertility was classified into two factors: the first factor is a social factor that depend on the case education level, age, place of residence and the second factor is a clinical factor that depends on the reason that may caused infertility such as hormonal problems, physicals problems and psychological problems.

IV.1. The different groups of the overall study

The present study is a part of an overall study comprised 702 subjects referring to Al Basma fertility center in Gaza. As indicated in Table 1 and Figure 1, the number of cases where infertility is related to woman, to man and to both woman and man were 374 (53.2 %), 293 (41.7 %) and 35 (5.0 %) respectively. The woman related infertility risk factors were identified and published in a separate study (**Sirdah *et al.*, 2013**). The present study focused on the cases were the cause of infertility is related to men.

Table (1): The different groups of the overall study

Group	definition	No.	%
Group 1	Cases where infertility is related to woman	374	53.2 %
Group 2	Cases where infertility is related to man	293	41.7 %
Group 3	Cases where infertility is related to both woman and man	35	5.0 %
	Total	**702**	**100**

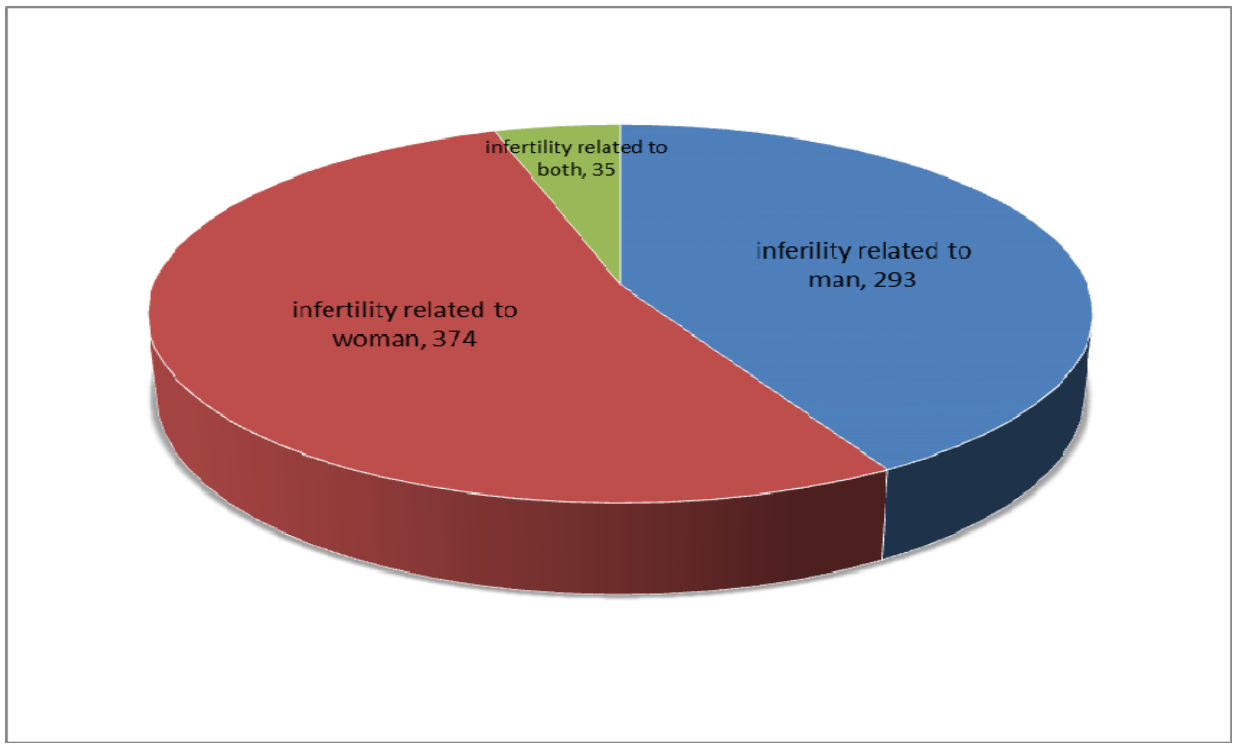

Figure (1): Groups of the overall study

IV.2. Distribution and general characteristics of the study population

IV.2.1. Distribution according to Governorate

The distribution of the cases according to governorate is shown in Table 2 and Figure 2. The highest number of cases (42.3%) were from the Gaza Governorate, followed by the Northern Governorate (28.6%), Mid-zone (10.6%), Rafah (9.5%) , and the lowest number of cases (8.9 %) was from Khanyounis Governorate.

Table (2): Distribution of the cases according to Governorate

Governorate	Infertility N= 328	
	number	%
North	94	28.6%
Gaza	139	42.3%
Mid-zone	35	10.6%
Khanyounis	29	8.9%
Rafah	31	9.5%
Total	**328**	**100**

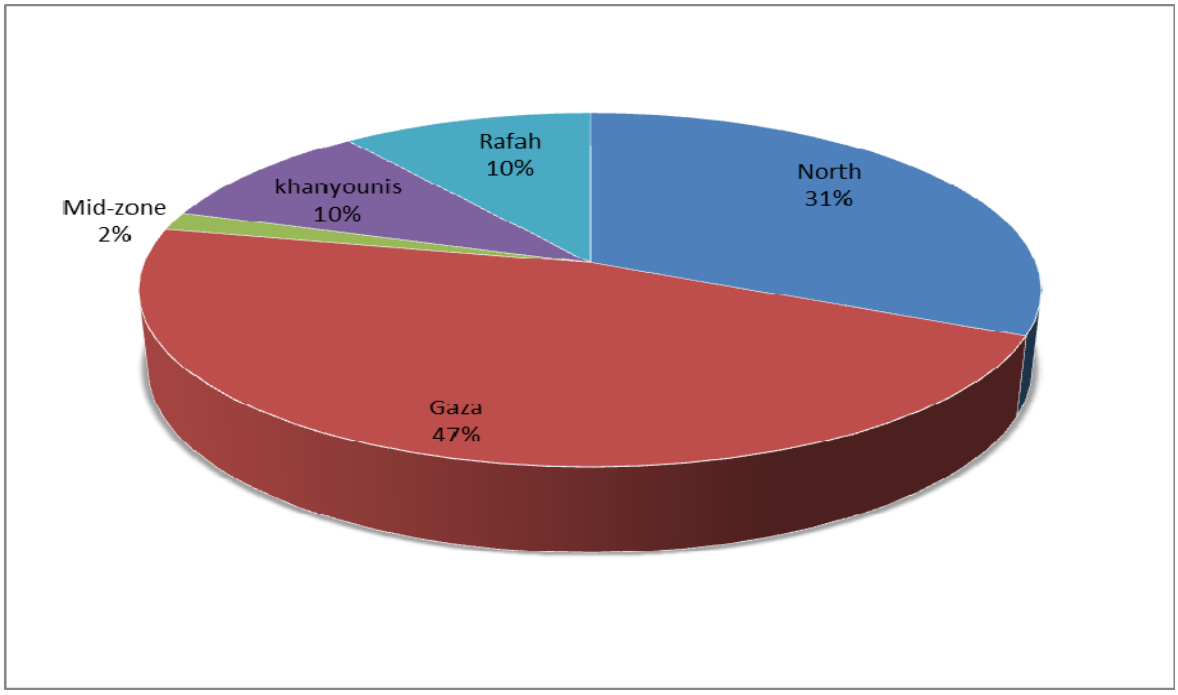

Figure (2): Distribution of the cases according to Governorate

IV.2.2. Age characteristics of the study population

The age characteristics of the study population are shown in Table 3 and Figure 3. The subjects suffering from infertility who were younger than 30 years old constituted 72.2%, while those older than 30 years old constituted 27.7%.

Table (3): Age characteristics of the study population

Age	Infertility N= 328	
	number	%
< 30 years	237	72. 2%
>30 years	91	27.7%

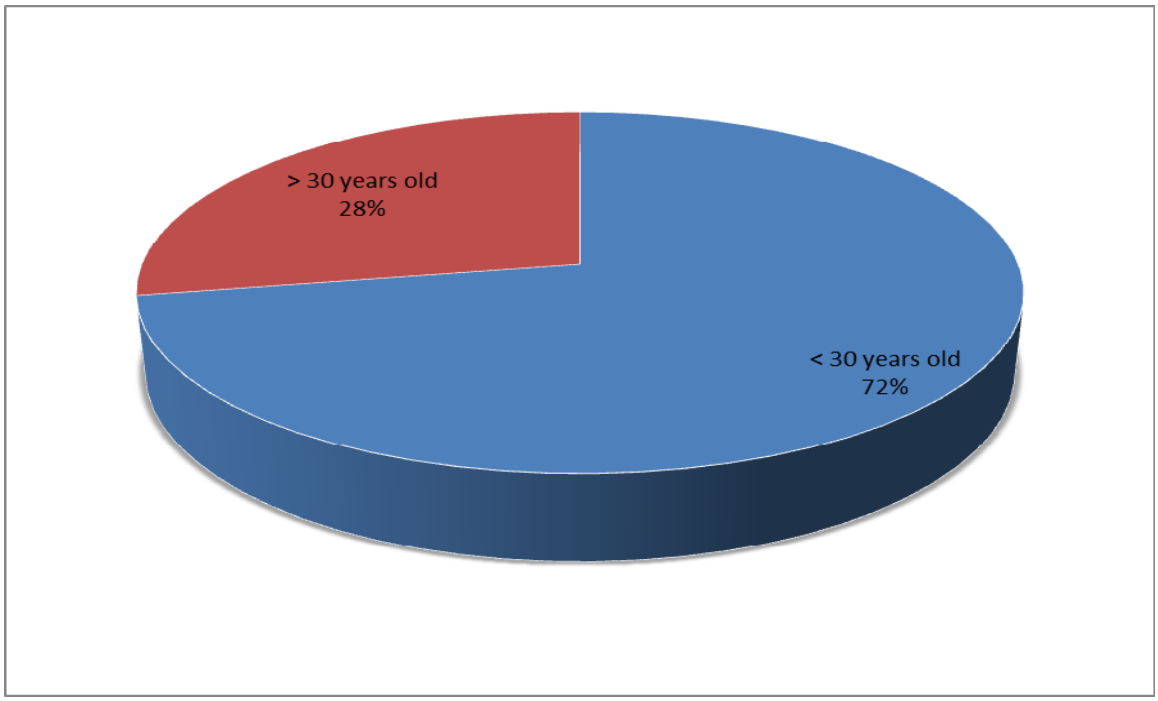

Figure (3): Age characteristics of the study population

IV.2.3. Level of education of the study population

The education level of the subjects of the study is illustrated in Table 4 and Figure 4. Two hundred and nine subjects 63.7%, finished their high school, while 119 subjects 36.2% did not finish their high school.

Table (4): Level of education of the study population

Level of Education	Infertility N= 328	
	Number	%
< high School	119	36.2%
> high School	209	63.7%

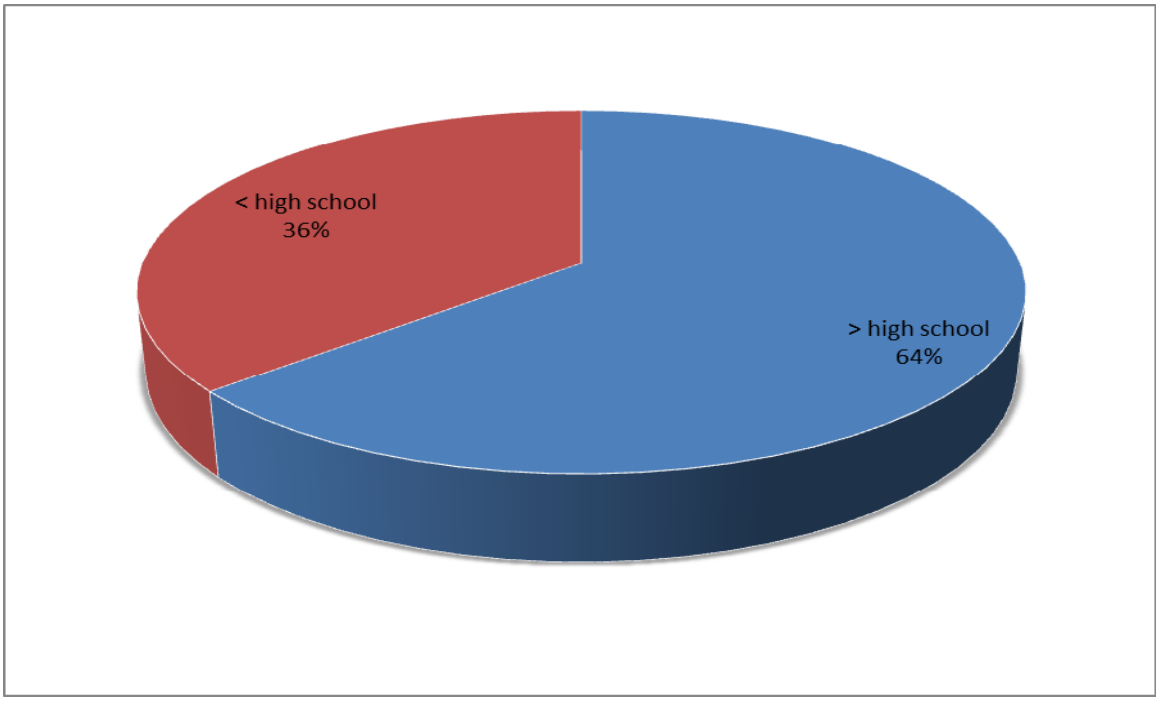

Figure (4): level of education of the study population

IV.3. Medical and clinical characteristics of the study population

Medical and clinical characteristics of the subjects were divided into 4 categories: hormonal problems, physical problems, psychological problems and combined problems.

IV.3.1. Hormonal problems

The hormonal problems of the study population are mentioned in Table 5. Twenty three subjects suffered from hormonal problem which represent 23 subjects 7% of the total cases; it is subdivided into two causes hyperprolactinemia 14 subjects 4.2% and hypogonadotropic hypopituitarism 9 subjects 2.7% of the cases.

IV.3.2. Seminal problems

The seminal problems of the study population are summarized in Table 6. One hundred and seventy four subjects suffered from seminal problem, which represent 174 subjects 53% of the total cases. The subjects are classified into five groups as shown below. The highest percentage infertile men caused by physical aspects were from azoospermia 83 subjects 25.3%, 58 subjects 17.6% suffered from oligospermia, 16 subjects 4.8% suffered from semen OTA, 11 subjects 3.35% that suffered from asthenospermia, 6 subject 1.8 % suffered from damage sperm ducts.

IV.3.3. Psychological problems

Psychological problems among study population are shown in Table 7. Fourteen subjects suffered from psychological problem which represent 14 subjects 4.3 % of the total cases. Twelve subjects 3.6% suffered from premature ejaculation, one subject 0.3% suffered from retrograde ejaculation and one subject 0.3% suffered from ejaculatory incompetence

IV.3.4. Other common reasons that may cause infertility

Table 8 shows that some subjects suffer from infertility due to the presence of varicocele 32 subjects 9.7%, or due to infection 25 subjects 7.6%. The cause of infertility of others 60 subjects 18.2% is due to several factors (compound infertility).

The compound cause of infertility (where more than one cause of infertility is present) is shown in Table 9 the factors were classified into 4 categories; the first one was hormonal and physical problems 9 subjects 15%, the second category was infection and seminal problems 16 subjects 26.6%, the third category was the infertility due multiple seminal problems 22 subjects 36.6% and the last category was varicocele and seminal problems 13 subjects 21.6%.

Table (5): Hormonal problems of the study population

Hormonal problems	Infertility N= 328	
	number	%
Hyperprolactinemia	**14**	4.2 %
Hypogonadotropic Hypopituitarism	**9**	2.7 %
Subtotal	**23**	7.0 %

Table (6): Seminal problems of the study population

Seminal problems	Infertility N= 328	
	Number	%
semen OTA *	**16**	4.8 %
Asthenospermia	**11**	3.4 %
Azoospermia	**83**	25.3 %
Oligospermia	**58**	17.6 %
Damaged sperm ducts	**6**	1.8 %
Subtotal	**174**	53.0 %

*** OTA:** Oligoteratoasthenozoospermia

Table (7): Psychological problems of the study population

Psychological problems	Infertility N= 328	
	number	%
Premature ejaculation	**12**	3.6 %
Retrograde ejaculation	**1**	0.3 %
Ejaculatory incompetence	**1**	0.3 %
Subtotal	**14**	4.3 %

Table (8): Other common reasons that may cause infertility among the study population

Other common reasons to cause infertility	Infertility N= 328	
	number	%
Varicocele	32	9.7 %
Infection	25	7.6 %
Compound infertility (due to more than one cause)	60	18.2 %
Subtotal	117	35.6 %

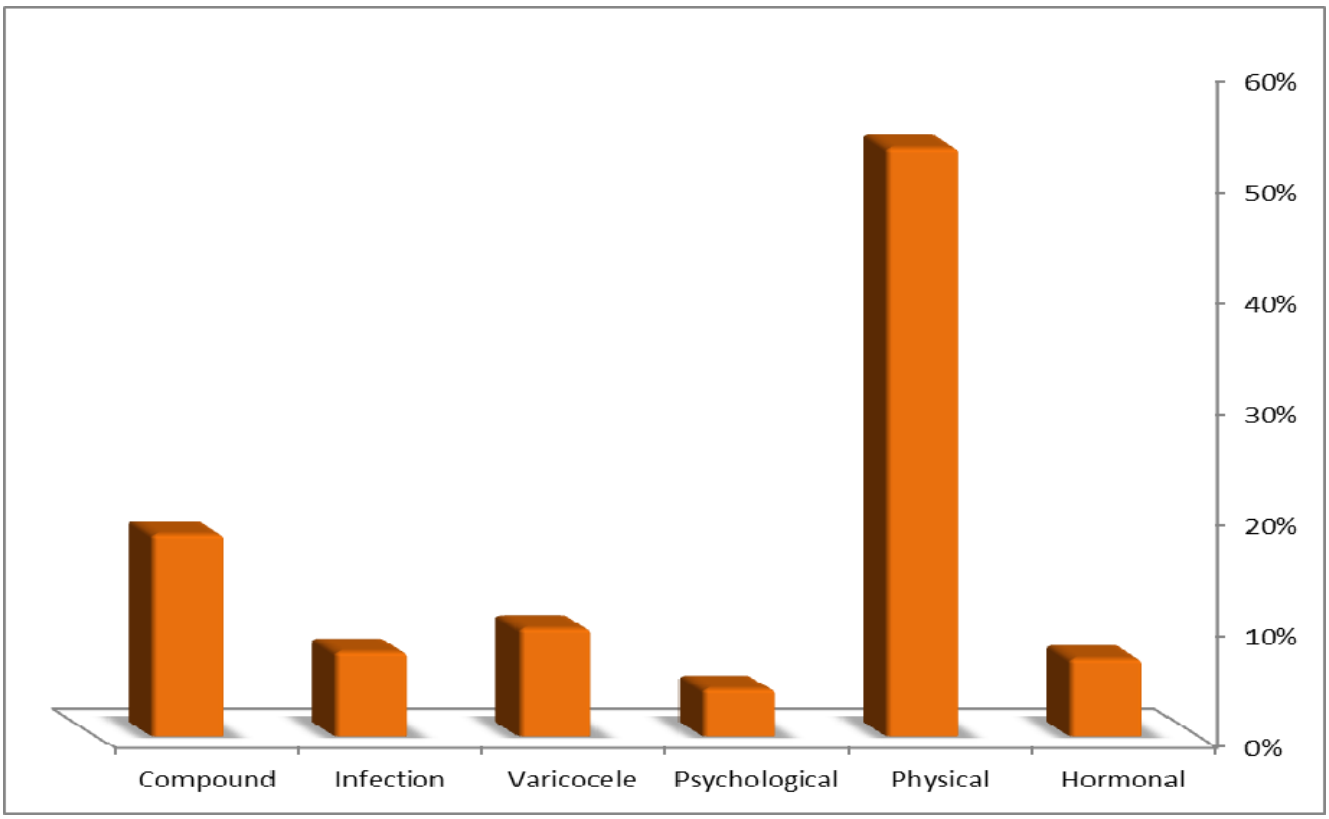

Figure (5): Medical and clinical characteristics of the study population

Table (9): Distribution of risk factors among compound infertility

Compound infertility	number	%
Hormonal and seminal problems	**9**	15%
Infection and seminal problems	**16**	26.6%
Multiple seminal problems	**22**	36.6%
Varicocele and seminal problems	**13**	21.6%
Subtotal	**60**	100%

CHAPTER V

Discussion

V. Discussion

Infertility 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).** The inability to have children is considered a personal tragedy and a bother for the couple, affecting the entire family and even the whole community, which may lead to negative psychosocial severe consequences **(Daar and Merali, 2002; Dyer, 2005)**. In the Arabic oriental culture and in their oriental cultures, 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, then isolated, disregarded, and disrespected **(Gerrits, 1997; Papreen *et al*., 2000; Richards, 2002; Wiersema *et al.,* 2006).**

The world health organization estimated 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 work that investigated the magnitude and risk factors associated with men infertility.

The worldwide prevalence of childless is considerably high and specially in the developing countries, however identification of the possible causative factors is key of successful treatment and problem solving for a considerable high number of cases.

The present work was aimed at identifying the risk factors associated with infertility among Palestinian men in Gaza strip.

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

The majority 42 % of the cases (infertile men) in this work were from the Gaza Governorate (Table 2). Although this is concomitant with the population distribution at the different Governorates of Gaza strip.

Table 3 showed that the rate of infertility among those men who are younger than 30 years old was 72% of the cases, while the rate of those infertile men who are older than 30 years old was 28%.

Consequently the age of the subjects is considered as significant factor in our study, the analysis of the significant rate of infertility among those who are younger than 30 years old is due to the fact that the younger marriage age of Palestinian men in Gaza is between 23-25 years, and due to fact that the society expect that 9 month after marriage the couple should have their first baby, and couples consult Gynecologist or fertility center if pregnancy did not take place after few months of regular unprotected sexual intercourse.

There is no scientific study or scientific reports considered the educational level of men in Gaza strip among the risk factors for infertility. Our results for Palestinian residents confirmed that the level of education may be considered an influential factor for infertility, (Table 4) shows that the high percentage of the people who suffered from infertility have completed higher levels of education 63.7%. These percentages show that the level of education of the couple have a role in diagnosis or in treatment of infertility. Those subjects who finish high school or higher are not impressed or ashamed from admitting of the presence of a problem to conceive, consonantly the consult a specialist and this explain the high percentage 63.7% of the subjects.

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

As has been shown in the present results, hormones abnormality can be considered as a major risk factor causing infertility among men in Gaza, Table 5 showed that the increase in prolactin hormones value above normal value (2.0 - 18.0 ng/ml), is the highest hormone abnormality that may cause infertility (4.2%) from the subjects suffering from hormones abnormality **(Zargar *et al.,* 1997 ; Biller, 1999)**showed that hyperprolactinemia is associated with an increased production of prolactin, and often leading to reproductive dysfunction.

Prolactinoma is a benign tumor of the pituitary gland that produces a hormone called prolactin and it consider as the most common cause of hyperprolactinemia, which is a common cause of infertility in males and females **(Buvat *et al.,* 2003 and Ciccarelli**

***et al.,* 2005).** Hyperprolactinemia causes infertility in around 11% of oligospermic males **(Masud *et al.,* 2007).** Hyperprolactinemia inhibits the pulsatile secretion of the gonadotrophin releasing hormone, which causes decreased pulsatile release of follicle stimulating hormone(FSH), luteinizing hormone(L H), and Testosterone, which in turn causes spermatogenic arrest, impaired sperm motility, and altered sperm quality **(Masud *et al.,* 2007).** Hyperprolactinemia is a common cause of infertility in males but the latest European guidelines published in European Urology 2005 and revised in 2010 for evaluation of male infertility has not included the hormonal assessment of the serum prolactin level during evaluation of male infertility **(Dohle *et al.,* 2005).**

Hypopituitarism is a condition in which the pituitary gland is not producing one or more of its hormones (TSH, FSH, LH, PRL, Growth hormone GH), or is producing them at lower than normal levels. These hormones stimulate other endocrine glands to produce their hormones. For example, if the pituitary gland doesn't make thyroid stimulating hormone (TSH), the thyroid gland doesn't work correctly. In our study about 2.7 % of infertile men have hypopituitarism.

On the other hand the azoospermia, is defined as complete absence of sperms from the ejaculate, about 1% of the world population are suffering from Azoospermia, , 10% to 15% among of infertile men are suffering from azoospermia. Although azoospermia has many causes, but about 40% of the cases are resulted from obstruction in the ductal system (**Jarow *et al.,* 1989).** Our study showed that 25.3 % of the infertile men are

suffering from azoospermia.

Oligospermia if define as low sperm count less than 20 million sperm/mL . As defined by the World Health Organization **(WHO, 1999)**. about 17.6 % of infertile men in our study were suffering from oligospermia. In addition it was found that 3.6% of infertile men were suffering from premature ejaculation. Premature ejaculation is defined as persistent or recurrent ejaculation with minimal sexual stimulation before, upon, or shortly after penetration and before it is wished by the man or his partner. It is considered the most commonly experienced male sexual dysfunction, affecting tens of millions of American men and causing infertility to many American men **(Laumann *et al.*, 1999)**.

From the study of **(McMahon *et al*., 2012)** it was concluded that self-reported premature ejaculation is more prevalent 13% than self-reported erectile dysfunction 8%. An online survey of 804 Arabic-speaking internet user men in the middle east revealed that a total of 82.6% reported various degrees of premature ejaculation, despite a median Intravaginal Ejaculatory Latency Time (IELT) of 5 min **(Shaeer and Shaeer 2012).**

Another recent cross-sectional study conducted at a primary care clinic in Malaysia applied the Premature Ejaculation Diagnostic Tool (PEDT) questionnaire and found an extremely high prevalence (40.6%) among patients with various medical conditions **(Tang, and Khoo, 2011).**

Our study showed that 9.7 % of the cases were suffering from varicocele which

affects sperm concentration leading to oligospermia or azoosperima of the subjects.

In WHO study **(WHO, 1992a)** it was shown that 11% of the men who are attending infertility clinics are suffering from varicocele while 25% are suffering from abnormal semen. Some evidence suggests that the presence of varicocele may even reduce the ability of the haploid male gamete to generate embryos when used for micro-assisted fertilization **(Sofikitis *et al.,* 1996)**. Varicocele is identified in 7% and 10%–25% of prepubertal and postpubertal men respectively **(Akbay *et al.,* 2000 and Callam, 1994)**. The higher frequency in elderly males and in men with secondary infertility suggests that it is a progressive disease **(Canales *et al.,* 2005 and Raman *et al.,* 2005).** Recent studies showed that varicocele occurrence is inversely correlated with body mass index **(Nielsen *et al*. 2006 and Chen *et al*. 2010).** A higher prevalence in first-degree relatives has also suggested an inherited pattern **(Raman *et al.,* 2005).**

Epidemiologic studies suggest that approximately 15% of all men in the general population have a clinical varicocele. In contrast, between 19–41% of men evaluated for infertility are found to have varicoceles **(Naughton *et al*., 2001)**. Interestingly, the rate of varicocele is increased in men with secondary infertility to approximately 70%, suggesting that varicoceles may cause a progressive decline in fertility potential **(Witt, and Lipshultz, 1993).**

Infections such mumps, tuberculosis, brucellosis, gonorrhea, typhoid, influenza, smallpox, and syphilis can cause testicular atrophy. Some sexual transmitted diseases like gonorrhea and chlamydia can cause infertility by blocking the epididymis or tubes. **(http://www.stanford.edu , 2013).** All types of infection can affect male fertility,

about 7.6 % of infertile men in this study have at least one type of infection. Other types of infection can play an indirect role in causing men infertility.

Seminal tract infections may play a considerable role in causing men infertility. Infections impair fertility by different mechanisms, including damaging spermatogenesis, impairing sperms function, and obstructing seminal tract **(Bar-Chama *et al.* 1993 and Purvis *et al.* 1996).** There is increasing evidence that viral infections play a role in the pathogenesis of male infertility **(Lai *et al.*, 1997 and Dejucq *et al.* 2001).** Viral infections impair male fertility, either by directly invading the male genital tract cells, or by indirectly causing local inflammatory or immunological responses that could deteriorate reproductive functions **(Keck *et al.*, 1998).** In addition, pro-inflammatory cytokines and ROS may play an important role in causing infertility **(Comhaire *et al.*, 1999).** ROS may damage fertility by decreasing polyunsaturated fatty acid on sperm membrane, including DNA damage and impairing a chromosomal reaction **(Comhaire *et al.*, 1999 and Agarwal *et al.*, 2008)**.

In conclusion, our results showed that the cause of infertility in 53.2% of the studied cases is related to female reasons, while 41.7% is related to male reasons, and 5.0% is related to both. Seminal problems 53.0%, vaicocele 9.7%, hormonal problems 7.0 %, infection7.6 %, and ejection problem 4.26 % are the five major risk factors associated with infertility among men in Gaza. We suggest that in the course of treatment plan of the infertile couple and when the cause of infertility is related to man, doctors should concentrate on obtaining clear picture about semen quality and count, the presence of vaicocele, hormonal analysis, genital and urinary tract infection, and erection and

ejection status, these finding account for almost all risk factors associated with infertility among men in Gaza. Studying these issues will give clear picture about each single case and help shortening the period of treatment. Infertility and its therapy with accompanying psychological disturbances may also significantly affect the partners relationships and cause hormonal disturbance and poor quality semen **(Zorn *et al* 2002, Esiocak, 2005)**.

We recommend that psychological evaluation and consequently psychotherapy should be included in management of infertility.

CHAPTER VI

Conclusion and Recommendations

VI.1. Conclusions

From our study about the risk factors associated with infertility among Palestinian men in Gaza we concluded that:

- The percentage of woman related and men related infertility in Gaza is (53.2% and 41.7 %) and 5.0% related to both.

- The age and the educational level of the men are considered as important risk factors for men infertility in Gaza and must be taken in account by urologist when treating.

- Abnormalities in sex and thyroid hormones are considered among the high risk factors for infertility among Palestinian men in the Gaza.

- Also azoospermia and oligospermia are considered as risk factors for infertility among Palestinian men.

- The premature ejaculation play an important role as a factor of infertility and considered here as one of the risk factors.

- Varicocele affects sperm concentration that leading to infertility, and it's the most effective risk factor for infertility.

- Infections and infection transmitted sexually disease can play direct role in infertility.

- Infertility among Palestinian men in the Gaza, could be prevented or avoided if men have ability to understand and seek medical treatment at the fertilization infertility clinics.

VI.2. Recommendations

- The family history is great importance and must be taken in account when dealing with infertility related to man.

- Palestinian men in the Gaza strip must review fertilization centers and reproductive clinics and conduct all the necessary tests if the pregnancy did not occur after one year of unprotected sexual intercourse.

- Avoiding any family and community pressures on the couples when the pregnancy delays since this will affect the hormonal system and causes farther complication.

- Minimizing, managing, and preventing the causes of sexual transmitted disease, and acute infections.

- Focusing on sex hormones testing, and using the results in identifying patients with endocrine abnormality.

CHAPTER VII

References

VII. References

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Risk factors associated with infertility among Palestinian men in Gaza

عوامل الخطورة المصاحبة للعقم لدى الرجال في قطاع غزة

الجزء الأول: المقابلة الشخصية

الجنس	☐ ذكر			☐ أنثى	
هل هناك عقم	☐ نعم			☐ لا	
نوع العقم	☐ أولي			☐ ثانوي	
عدد الأطفال إن وجد	.....				
المحافظة	☐ الشمال	☐ غزة	☐ الوسطى	☐ خان يونس	☐ رفح
العمر	.....				
المستوى التعليمي	☐ جامعي	☐ ثانوية عامة		☐ أقل من ثانوية عامة	
الرجل يعمل	☐ نعم			☐ لا	
السيدة تعمل	☐ نعم			☐ لا	
نوع العمل	.....				
هل هناك مشاكل وحالات عقم في العائلة	☐ نعم			☐ لا	
هل هناك عمليات جراحية سابقة في منطقة البطن	☐ نعم			☐ لا	
هل هناك اعتلال في الغدة الدرقية	☐ نعم			☐ لا	
هل تعاني من أمراض ضغط الدم	☐ نعم			☐ لا	
هل تعاني من السكري	☐ نعم			☐ لا	
هل هناك مشاكل وضغوطات حياتية واجتماعية	☐ نعم			☐ لا	

الجزء الثاني: الفحص الطبي والمخبري

وضع الخصيتين	☐ طبيعي			☐ غير طبيعي	
هل تعاني من دوالي الخصيتين أو دوالي الحبل المنوي	☐ نعم			☐ لا	
هل تعاني من سرعة القذف	☐ نعم			☐ لا	
هل هناك انسداد أو تعطل في القنوات المنوية	☐ نعم			☐ لا	
هل تعاني من مشاكل في الانتصاب	☐ نعم			☐ لا	
هل هناك خلل هرموني	☐ طبيعي			☐ غير طبيعي	
فحص الهرمونات	☐ Testosterone	☐ LH	☐ FSH	☐ Prolactin	☐ TSH
هل تعاني من أمراض منقولة جنسياً	☐ نعم			☐ لا	
هل هناك التهابات في مجرى البول	☐ نعم			☐ لا	