WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 4, 16-30. Review Article ISSN 2277– 7105

ROLE OF GENERAL GYNECOLOGISTS IN THE PREVENTION OF INFERTILITY

Maysoon Abbood Majeed and Hind Saaran Hussein*

Ministry of Health, Baghdad, Iraq.

Article Received on
22 Jan. 2019,

Revised on 11 Feb. 2019,
Accepted on 03 Mar. 2019

DOI: 10.20959/wjpr20194-14417

***Corresponding Author**
Hind Saaran Hussein
Ministry of Health, Baghdad, Iraq.

ABSTRACT

General gynaecologists have a significant role to play in the prevention of infertility. Some of the causes of infertility are iatrogenic and secondary to pelvic surgery. Careful assessment of women with gynaecological conditions such as fibroids and ovarian cysts and identification of those who can be managed without surgery may avoid potentially eliminate fertility difficulties secondary to pelvic adhesions in these women. When surgery is clinically indicated, primary prevention of pelvic adhesions would be of paramount importance. The measures to avoid postoperative adhesions include the use of a reliable surgical technique and potential use of anti-adhesion agents. Ovarian surgery for endometriomas and other benign cysts should be performed in the hands of experienced surgeons or in 'centres of clinical expertise'; maximum efforts are exercised to preserve normal ovarian tissue as much as possible. General gynaecologists also have a role in the identification and early treatment of subclinical and overt STIs and pelvic infections; these efforts are likely to reduce the likelihood of tubal damage and subsequent infertility.

KEYWORDS: gynecologists, infertility.

INTRODUCTION

Infertility is a common clinical problem. It affects 13% to 15% of couples worldwide.[1] The prevalence varies widely, being less in developed countries and more in developing countries where limited resources for investigation and treatment are available[2], it is estimated that one in six couples would complaint of infertility.[3]

In addition, infertility is considered also a public problem. It does not affect the couples' life only, but it also affects the healthcare services and social environment.[4] The feelings

experienced by the infertile couples include depression, grief, guilt, shame, and inadequacy with social isolation.

Today, many patients do not receive the recommended medical care based on the best available evidence.[5]

Infertility is defined as the inability to conceive naturally after one year of regular unprotected intercourse. Most of the time, infertility is some degree of subfertility in which 1 in 7 couples need specialist help to conceive. Subfertility can be either primary or secondary.

Primary subfertility is a delay for a couple who have had no previous pregnancies; and, secondary subfertility is a delay for a couple who have conceived previously, although the pregnancy may not have been successful for example, miscarriage, and ectopic pregnancy.[6] The aim of this paper is to discuss the male and females causes of infertility, treatment modalities and role of gynecologists in dealing.

The chance to conceive depends on the length of sexual exposure, the frequency of coitus, and couple's age. The normal, young aged couples have a 25% chance to conceive after 1 month of unprotected intercourse; 70% of the couples conceive by 6 months, and 90% of the couples have a probability to conceive by 1 year.

Only 5% of the couples will conceive after one and a half year or two years.[7] Both males and females are equally responsible for the causes. Most of the infertile couples have one of these three major causes including a male factor, ovulatory dysfunction, or tubal-peritoneal diseas.[8] Literature shows that vaginismus and dyspareunia are more common in 20-24 years aged females.[9]

The sexual response cycle plays an important role to promote fertility, because it comprises of sequential physical and emotional changes that occur as a person becomes sexually aroused.[10] In normal physiology, the two gonadotropin hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH) are produced in the pituitary and their secretion is controlled by gonadotropin releasing hormone (GnRH) that is released by the hypothalamus. At the start of a new cycle, the hypothalamus begins to release GnRH that acts on the pituitary gland to release FSH and LH.

These two hormones stimulate the ovary and cause the follicles to develop. Every month about 30-40 follicles start to grow in response to FSH, but only a single mature egg is released every month. This involves messages transmission in the form of hormones from the ovary, the pituitary and the hypothalamus. When the egg is ripe, the mature follicle releases an increasing amount of estrogen, is produced by the granulosa cells lining the follicle. The estrogen produced by the dominant follicle progressively increases in quantity as the egg matures, until a surge of estrogen is released into the blood. The high level of estrogen stimulates the pituitary to release a large amount of LH, thus leading to the LH surge. This LH in turn acts on the mature follicle, causing it to rupture to release the mature egg (ovulation) in the ovary.[11]

Males born without testes or vas deferens can become infertile. Some men have both the testes but they are not able to produce sperm or may produce very few sperms also suffer from infertility. Moreover, stress can cause decreased libido and the couple can end up in having infertility.

Several studies have reported different causes of infertility.[12] Some causes are more common in some countries than others, such as pelvic inflammatory diseases (PID) and sexually transmitted infections (STI) in Africa.[13]

Some personal habits are considered risk factors for infertility, such as excess alcohol intake and cigarette smoking.[14]

According to the literature survey, the most common causes of infertility are: male factor such as sperm abnormalities[15], female factors[16] such as ovulation dysfunction and tubal pathology, combined male and female factors and unexplained infertility; where no obvious cause could be detected.[17]

As the rate of getting spontaneous pregnancy among infertile or subfertile couples is lower than that among the normal fertile population, it is recommended to carry out the following diagnostic, evidence-based, work-up to detect any hidden treatable cause.

Couples with infertility problem should be interviewed separately as well as together, to bring out important facts that one partner might not wish to disclose to the other. Full history taking of both partners usually denotes the underlying problem.[18]

Full clinical examination of both partners usually stands for the underlying physical problem.[19] By the end of this step, most healthcare professionals will be able to sketch out their provisional diagnosis. Investigations will be requested to prove the clinical diagnosis and to exclude other close possibilities.

BACKGROUND

infertility in the United States, and is even more prevalent in certain communities.[20] Paralleling the aforementioned global infertility disparity, TFI is disproportionately common in women in developing countries; for example, it has been shown to account for >85% of female infertility cases in regions of subSaharan Africa, compared to 33% of cases worldwide.[21]

Most cases of TFI are due to salpingitis, an inflammation of the epithelial surfaces of the fallopian tubes, and subsequent pelvic-peritoneal adhesions, both of which are most commonly caused by previous or persistent infections.[22]

Bacteria ascend along mucosal surfaces from the cervix to the endometrium and ultimately to the fallopian tubes. This causal pathway presents itself clinically as acute pelvic inflammatory disease (PID), which in turn is strongly associated with subsequent TFI. In fact, approximately 15% of women with PID develop TFI, and the number of episodes of PID a woman experiences is directly proportional to her risk of infertility.[23]

However, the majority of women with TFI do not have a history of clinically diagnosed acute PID, but rather develop asymptomatic or minimally symptomatic salpingitis as a result of upper genital tract infection.[24]

Examining the effect of those infections, particularly those that occur in the absence of clinically evident PID, is critical to understanding TFI. Several sexually transmitted diseases (STDs), including Chlamydia trachomatis and Neisseria gonorrhoeae, have been widely studied to understand their role in salpingitis and infertility. Additionally, several other pathogens such as Mycoplasma genitalium, Trichomonas vaginalis, and other microorganisms within the vaginal microbiome, may also play roles in tubal damage and other potential causes of infertility. Still, data suggest that not all infections yield the same long-term sequelae.

Tubal damage secondary to infection.

Tubal infertility is most commonly due to pelvic inflammatory disease (PID) secondary to sexually transmitted infections (STIs). Other causes of tubal damage are postsurgical adhesions, endometriosis and intra-abdominal infections secondary to inflammatory gastrointestinal disorders and perforated appendicitis. STIs mostly affects the young population. Infection due to Chlamydia trachomatis is the most common reportable disease in the USA and, together with that due to Neisseria gonorrhoeae, is a common cause of PID.[25]

Approximately 10e20% of women with untreated chlamydial infection develop PID, and up to 18% of women who develop PID eventually suffer from tubal infertility.[26] Even subclinical chlamydial and gonorrhoeal infections are associated with tubal infertility. Although detection and treatment of subclinical infection may not necessarily prevent subsequent infertility[27], it is well understood that women who delay seeking treatment have a high risk of infertility.[28]

Hence, the identification and treatment of these women in general gynaecology clinics are likely to reduce the risk of future infertility. This requires identification and screening of women at risk of STIs, low threshold for suspicion of subclinical or clinical PID, appropriate testing, early treatment and partner screening/ treatment.

Postsurgical adhesions

Postsurgical adhesions are one of the most frequent side effects of abdominal and pelvic surgery. Whilst the majority of women with postoperative adhesions may not suffer any adverse outcomes, a significant number will experience infertility by distorting the pelvic anatomy and interfering with gamete and embryo transfer.[29] High-risk gynaecological procedures for adhesion formation are myomectomy, endometriosis surgery, ovarian cystectomy and tubal surgery.[30] Both laparoscopic and open procedures may cause adhesions. Adhesion formation is an inherent process in endometriosis, but adhesions after ovarian cystectomy or myomectomy are usually de novo events. The first and most effective approach to the prevention of adhesions related to surgical procedures is to avoid unnecessary operations. In the absence of significant symptoms, functional cysts can be managed expectantly, as they almost always resolve spontaneously. Similarly, operations on small and asymptomatic benign ovarian cysts are usually avoidable, as long as there is no uncertainty about the nature of the cyst. Many women with fibroids are asymptomatic, and anxiety over future fertility may be the only reason why they seek their removal. Although the fibroids are

common, they are thought to be the only cause of infertility in only 1e3% of infertile patients.[31] Adhesions are found in up to 96% of women after laparoscopic or open myomectomy. For these reasons, gynaecologists should resist the temptation to agree to a myomectomy operation in asymptomatic women who have not tried to become pregnant. The second step of prevention is the use of a reliable surgical technique. Some of the surgical principles that may reduce adhesion formation include careful/atraumatic tissue handling, avoidance of starch-containing gloves and dry towels/sponges, diligent haemostasis, limiting use of diathermy and suture material, choosing a fine and non-reactive suture material, using frequent irrigation/aspiration to reduce drying of tissues, reducing pneumoperitoneum pressure for laparoscopic surgery and taking measures to reduce risk of infection.[32]

These measures reduce but do not eliminate adhesion formation altogether. Gynaecologists who perform pelvic surgery should adopt these approaches in all women to reduce adhesion formation, particularly in those who have future fertility plans.

Adhesion formation inside the uterine cavity is another cause of infertility. Intrauterine adhesions (IUA) may form following pregnancy-related complications or intrauterine surgery. Prolonged retention of products of conception or placental material after a delivery, termination of pregnancy or surgical management of miscarriage in the presence of inflammation/infection is a well-known predisposing factor for IUA. Intrauterine surgical procedures such as hysteroscopic myomectomy and division of septum (septoplasty or metroplasty) are the other common causes of IUA. Hysteroscopic surgery, which does not extend to the level of the myometrium, such as polyp removal, is less likely to cause adhesions.[33]

The best approach for the management of prolonged products of conception to prevent IUA is not clearly known. As expected, avoidance of leaving placental material in the uterine cavity after delivery or ensuring complete evacuation of the uterine cavity during termination of pregnancy or surgical management of miscarriage would be the most effective way of prevention by avoiding prolonged retention of products of conception and subsequent inflammation. Once prolonged retention occurs, the least traumatic elimination of the products of conception, use of ultrasound guidance and administration of intrauterine anti-adhesion agents may be helpful. The role of hysteroscopic tissue removal systems remains to be proven, but these systems are likely to be useful by targeted removal of the retained tissue

and due avoidance of unnecessary trauma to the unaffected part of the cavity. Hysteroscopic myomectomy is known to be associated with a significant risk of IUA.[34]

IUA formation was reported in 7.5% infertile women who underwent fibroid resection. The use of a reliable surgical technique, avoiding the use of excessive diathermy and preservation of endometrium as much as possible are important steps in reducing the risk. This risk is significantly high in the presence of multiple fibroids. Exposure of myometrium on opposing walls of the uterus is probably the main mechanism in this situation. Hence, resecting fibroids on opposing walls of the uterus in different sittings may be a favourable strategy to reduce the risk of IUA.[35]

Endometriosis

Women with endometriosis are more likely to experience infertility. A prospective study showed that women with laparoscopically diagnosed endometriosis are 1.78 times more likely to experience infertility in the future.[36] It is therefore important to manage endometriosis carefully in women who have not tried for pregnancy yet, particularly by paying attention to the preservation of ovarian reserve and prevention of adhesions. Some of these women may eventually require treatment with assisted reproductive technologies, and good ovarian reserve would probably optimise their chances of a successful outcome. A Joint Working Group of European Society for Gynaecological Endoscopy, European Society of Human Reproduction and Embryology and World Endometriosis Society published recommendations on the optimal surgical techniques for endometriomas.[37] and described approaches to preserve ovarian reserve. These approaches include assessment of the ovarian reserve before deciding on surgery, possible fertility preservation if the ovarian reserve is already compromised, use of the least traumatic technique, application of anti-adhesion agents and referring the woman to a centre of expertise where the necessary skills for surgery are available. Post-operatively, long-term use of combined oral contraceptives, either cyclically or continuously, has been demonstrated to reduce endometrioma recurrence, and these contraceptives should be offered to those women who do not plan to become pregnant.[38]

Ovarian cysts

Ovarian cysts in women are relatively common, and some of these cysts require surgical treatment because of either symptoms or anxiety on the nature of the tumour or future risk of ovarian torsion.

Sometimes, repeat operations are performed for recurrent cysts or ovaries are removed because of the inability to preserve healthy ovarian tissue or clinical suspicion of possible malignancy. These operations result in diminishing ovarian function and can compromise the woman's fertility or fertility treatment in the future, use of high-quality imaging and tumour markers, when required, are essential before deciding on surgical management. Operating on functional cysts should be avoided; relatively small asymptomatic benign cysts can usually be managed expectantly, whereas normal ovarian tissue can be preserved when surgery for benign cysts is required, even if the cyst is very large. Oophorectomy for benign cysts in young women or girls is usually unnecessary. The recommendations described for the management of endometriomas above would be applicable to the other benign ovarian cysts.[39]

Investigations The following investigations can be done to confirm the diagnosis in female.

Female Endocrine System Evaluation Basal Body Temperature Charting (BBT)

This is the simplest test for ovulatory evaluation. Elevated progesterone levels during the second half of the menstrual cycle cause the temperature of the body to rise 0.5-1.0 0F. A BBT chart which demonstrates a 12 to 14 day elevation in temperature after day 11-16 is considered to be normal. Approximately 90% of women can be expected to have ovulated two days before or after the lowest temperature recorded before a sustained rise.[40]

Endometrial Biopsy

An endometrial biopsy in the mid to late luteal phase (post-ovulatory day 7 to 12) can provide the confirmatory information to the BBT and serum progesterone testing, as well as diagnose endometritis. It is the gold standard for diagnosing luteal phase defect. Multiple endometrial biopsies are not necessary to monitor response to ovulatory drugs.

Urinary Luteinizing Hormone Detection

This predicts LH surge, the urinary LH surge usually occurs about one to two days prior to the rise in BBT and 12 to 60 hours before ovulation. A shorter range is 22 to 44 hours, with a mean of 30 hours. The most sensitive use of the test requires a woman to empty her bladder in the morning, restrict fluids, and then perform the test between 10 AM and 12 PM.[41]

Ultrasonography

It can be performed either trans-abdominally or, preferably, trans-vaginally, and is a very useful clinical tool to evaluate follicular development and ovulation. As discussed earlier, generally follicles mature and rupture between 17 to 22 mm in size. The loss of follicular size, the loss of clear follicles, and the appearance of fluid in the cul-de-sac are all suggestive of ovulation. The presence of multiple small follicles is indicative of PCO. Additionally, the endometrial thickness in the mid luteal phase greater than 8 mm reflects of normally developed post ovulatory endometrium. Follicle Stimulating Hormone (FSH) and Estradiol (E2) The normal upper range for this test is generally 10-13 mIU/ ml.

Levels below this range are normal, while levels approaching 20 mIU/ml are associated with markedly decreased pregnancy rates. E2 is almost always tested at the same time as the FSH level to prevent an inappropriate interpretation of the test results. Several studies have demonstrated that even one elevated cycle day 2-4 FSH level is associated with a poorer prognosis.[42]

Laparoscopy

This may be performed to identify ovarian follicles and irregularities related to normal ovulation. The finding of a follicular cyst on the ovary or corpus luteum is suggestive of ovulation. The presence of multiple small follicles confirms the presence of PCO. II. Pelvic Factor Investigation If a gynecologist and a midwife suspect a physical or anatomic problem within the women's pelvis, the following diagnostic tests can be conducted.

Hystero-salpingogram (HSG)

It is a procedure in which a small amount of radio-opaque fluid is injected into the uterus and fallopian tubes and then visualized with x-rays. It is useful to diagnose intrauterine structures and lesions and evaluate the status of the tubes in the proximal, distal, and intra-pelvic region. Additionally, data suggest that the HSG may be associated with increased rates following its use. Disadvantages of HSG include pain and discomfort, radiation exposure, infection, dye embolism and iodine hypersensitivity.[43]

Hysteroscopy

This is an operative procedure performed as a diagnostic procedure or as a therapeutic intervention used to do tubal catheterization to open the blocked tubes, and, visualize the internal structure of the tubes. This diagnostic test may be very useful in determining the

functional status of the fallopian tubes. Disadvantages of the procedure include adhesions and potential surgical and anesthetic complications. Scarce evidence on the effectiveness of hysteroscopic surgery in sub-fertile women with polyps, fibroids, septate/ bipartite uterus or intrauterine adhesions exist, therefore, it is suggested to conduct Randomized Control Trials (RCTs) to provide general recommendations.[44]

Magnetic Resonance Imaging

This can be useful for differentiating myomas, and complex congenital uterine and pelvic abnormalities as well as masses. Its high cost limits its general use, but it is helpful in selected situations.

Post-Coital Test

This is the standard test for evaluating cervical factor infertility. The test can help to identify difficulty in timing intercourse, sexual dysfunction, poor cervical mucus, cervical infection, low sperm count and/or motility, and the presence of antibodies; but this test is not very accurate. It must be carefully timed to be performed at ovulation or the results are not interpretable.[45]

Antisperm Antibody Tests

Antisperm antibody tests may be helpful in selected patients with shaking sperm motion on the semen analysis or post-coital test, or a history of testicular operation or injury.

Cervical Cultures

Cervical cultures can be assessed for E. coli, gonorrhea, chlamydia, and mycoplasma can be helpful in identifying infection in selected patients or in those undergoing intrauterine insemination or assisted reproductive technology procedures.

In Male

Male infertility is mostly related to deficiencies in sperm transport or spermatogenesis. Diagnosis can be confirmed by doing a detailed evaluation of semen analyses, gonadotropin and other assays.[46]

Semen Analyses

This should be done and the midwife should explain the procedure to collect the specimen. Semen should be produced by masturbation, after three days of abstinence from sexual

activity. The specimen should be kept warm and sent to a laboratory, within an hour from production.

Sperm function tests

These tests can be done to evaluate the function of the sperms. The Hamster Egg Penetration Assay (HEPA) and the Hemizona Assay (HZA) can help to assess the ability of sperm to penetrate the egg.

FSH and LH

The levels of FSH and LH can be raised in a condition called hyper gonadotrophic hypogonadism. In this condition, the high levels of FSH and LH occur due to impaired spermatogenesis as a result of testicular failure. Moreover, clients with cryptorchidism, Klinefelter's syndrome, orchitis, testicular torsion, testicular tumor, etc. can also have this problem and become infertile. Whereas, in hypo gonadotrophic hypogonadism, the levels of FSH and LH are decreased due to the pituitary gland or hypothalamus dysfunction. Clients with Kallmann's syndrome, malignant CNS tumors, pituitary adenoma, etc. can suffer from this condition and become infertile.[47]

Urine Analyses

Untreated urinary tract infections and sexually transmitted diseases can also cause infertility. It is important to evaluate such infections. These infections can also cause partial or complete obstruction of the ejaculatory ducts, prostate gland and seminal vesicles. Color Doppler Ultrasound.

To evaluate intra-scrotal defects, Doppler ultrasound can be done to detect varicocele, testicular tumors and testicular micro-calcifications.

Testicular biopsy

Testicular biopsy is often done in clients with azoospermia, but having normal testicular volume and FSH levels. This is performed in clients who decide to go for Intracytoplasmic Sperm Injection (ICSI).[48]

CONCLUSIONS

Infertility can have drastic effects on the couple's lives; hence, it is important to improve their reproductive health issue.

Among other health care professionals, gynecologists can be one of the care providers to whom the couples meet initially for history taking and initial assessment. As being involved in reproductive health, they can play a vital role in infertility care also by strengthening their knowledge and competencies.

They can use a number of assessment strategies, one of which is the application of nursing theories into care. They should build rapport and assess couples comfort level to share their highly personal and sensitive information. They should be knowledgeable about reproductive anatomy and physiology, and should have experience in dealing with such clients. They must have skills to help the couple to explore their fears, anxieties, feeling of hopelessness, loneliness and psychological and spiritual distress related to their sexual dysfunction, and assist in identifying coping strategies to maintain a healthy reproductive life. They can liaison between the infertile couple and the multidisciplinary health care team to identify treatment modalities to promote health as a whole with a special focus on reproductive health.

REFERENCES

1. Bhattacharya S, Johnson N, Tijani HA, Hart R, Pandey S, Gibreel AF. Female infertility. BMJ Clin Evid, 2010 Nov 11. 2010.
2. Tsevat DG, Wiesenfeld HC, Parks C, Peipert JF. Sexually transmitted diseases and infertility. Am J Obstet Gynecol, 2017 Jan; 216(1): 1e9.
3. Haggerty CL, Gottlieb SL, Taylor BD, Low N, Xu F, Ness RB. Risk of sequelae after Chlamydia trachomatis genital infection in women. J Infect Dis, 2010; 201(Suppl 2): S134e55.
4. [1]Wiesenfeld HC, Hillier SL, Meyn LA, Amortegui AJ, Sweet RL. Subclinical pelvic inflammatory disease and infertility. Obstet Gynecol, 2012 Jul; 120(1): 37e43.
5. De Wilde RL, Trew G. Postoperative abdominal adhesions and their prevention in gynaecological surgery. Gynecol Surg, 2007; 4: 161e8.
6. Whynott RM, Vaught KCC, Segars JH. The effect of uterine fibroids on infertility: a systematic review. Semin Reprod Med, 2017 Nov; 35(6): 523e32.
7. Buckley VA, Nesbitt-Hawes EM, Atkinson P, Won HR, Deans R, Burton A, et al. Laparoscopic myomectomy: clinical outcomes and comparative evidence. J Minim Invasive Gynecol, 2015 Jan; 22(1): 11e25.
8. Ahmad G, O'Flynn H, Hindocha A, Watson A. Barrier agents for adhesion prevention after gynaecological surgery. Cochrane Database Syst Rev, 2015; 4: CD000475.

9. Touboul C, Fernandez H, Deffieux X, Berry R, Frydman R, Gervaise A. Uterine synechiae after bipolar hysteroscopic resection of submucosal myomas in patients with infertility. Fertil Steril, 2009 Nov; 92(5): 1690e3.
10. Taskin O, Sadik S, Onoglu A, Gokdeniz R, Erturan E, Burak F, et al. Role of endometrial suppression on the frequency of intrauterine adhesions after resectoscopic surgery. J Am Assoc Gynecol Laparoscopists, 2000 Aug; 7(3): 351e4.
11. Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. Hum Reprod, 2016 Jul; 31(7): 1475e82.
12. Working group of ESGE, ESHRE, WES, Saridogan E, Becker CM, Feki A, Grimbizis GF, Hummelshoj L, Keckstein J, et al. Recommendations for the surgical treatment of endometriosis-part 1: ovarian endometrioma. Gynecol Surg, 2017; 14(1): 27
13. Seracchioli R, Mabrouk M, Frasca C, Manuzzi L, Montanari G, Keramyda A, et al. Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. Fertil Steril, 2010 Jan; 93(1): 52e6.
14. Poppe K, Velkeniers B. Thyroid and infertility. Verh K Acad Geneeskd Belg, 2002; 64(6): 389–399.
15. Razzak AH, Wais SA. The infertile couple: A cohort study in Duhok, Iraq. Est Mediterr Health J, 2002; 8(2-3): 234–238.
16. Ikechebula JI, Adinma JI, Orie EF, Ikegwuonu SO. High prevalence of male infertility in Southeastern Nigeria. J Obstet Gynecol, 2003; 23(6): 657–659.
17. Araoye MO. Epidemiology of infertility: Social problems of the infertile couples. West Afr J Med, 2003; 22(2): 109–106.
18. Tolstrup IS, Kjaer SK, Hoist C, Sharif H, Munk C, osier M. Alcohol use as predictor for infertility in a representative population of Danish women. Acta Obstet gynecol Scand, 2003; 82(8): 744–749.
19. Saleh RA, Agarwal A, Sharma RK, Nelson DR, Thomas AJ Jr. Effect of cigarette smoking on levels of seminal oxidative stress in infertile men: A prospective study. Fertil Steril, 2002; 78(3): 491–499.
20. Esimai OA, Orji EO, Lasisi AR. Male contribution to infertility in Nigeria. Niger Med, 2002; 11(2): 70–72.
21. Olatunji AO, Sule-odu AO. The pattern of infertility cases at a university hospital. West Afr J Med, 2003; 22(3): 205–207.

22. Bayasgalan G, Naranbat D, Tsedmaa B, Tsogmaa B, Sukhee D, Amarjargal O, Lhagvasuren T, Radnaabazar J, Rowe PJ. Clinical patterns and major causes of infertility in Mongolia. J Obstet Gynaecol Res, 2004; 30(5): 386–393.
23. Peroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility. 6. Lippincott Williams & Wilkins, Philadelphia, PA, USA; 1999. Female infertility.
24. Forti G, Krausz C. Evaluation and Treatment of the Infertile Couple. J Clin Endocrinol Metab, 1998; 83(12): 4177–4188.
25. Whitman-Elia GF, Baxley EG. A primary care approach to the infertile couple: Clinical review. J Am Board Fam Pract, 2001; 14: 33–45.
26. Case AM. Infertility evaluation and management: Strategies for family physicians. Canadian Family Physician, 2003; 49: 1465–1472.
27. Taylor A. ABC of subfertility: Making a diagnosis. BMJ, 2003; 327: 494–497.
28. National Institute for Clinical Excellence (NICE) guideline 11. Fertility: Assessment and treatment for people with fertility problems, Clinical Guideline.RCOG press, London, 2004.
29. The Practice Committee of the American Society for Reproductive Medicine. Vaccination guidelines for female infertility patients. Fertil Steril, 2008; 90: S169–171.
30. Macaluso M, Wright-Schnapp TJ, Chandra A, Johnson R, Satterwhite CL, Pulver A, Berman SM, Wang RY, Farr SL, Pollack LA. A public health focus on infertility prevention, detection, and management. Fertil Steril, 2010; 93(1): 16.
31. Hargreave TB, Mills JA. Investigating and managing infertility in general practice: Fortnightly review. BMJ, 1998; 316: 1438–1441.
32. Balasch J. Investigation of the infertile couple in the era of assisted reproductive technology: a time for reappraisal. Hum Reprod, 2000; 15: 2251–2257.
33. Rowe PJ, Comhaire FH, Hargreave TB, Mahmoud AMA. WHO Manual for the standardized Investigation, Diagnosis and Management of the Infertile Male.Cambridge University Press, Cambridge, 2000; 54.
34. Foresta C, Ferlin A, Gianaroli L, Dallapiccola B. Guidelines for the appropriate use of genetic tests in infertile couples. Euro J Hum Gene, 2002; 10:303–312.
35. Fatum M, Laufer N, Simon A. Investigation of the infertile couple: Should diagnostic laparoscopy be performed after normal hysterosalpingography in treating infertility suspected to be of unknown origin? Hum Reprod, 2002; 17(1): 1–3.
36. Oladokun A, Arulogun O, Oladokun R, Morhason-Bello I, Bamgboye E, Adewole I, Ojengbede OA. Acceptability of child adoption as management option for infertility in

Nigeria: Evidence from focus group discussions. Afr J Reprod Health, 2009; 13(1): 79–91.

37. Brinsden P, Hartshorne G, Hirsh A, Owen E. Reproductive Medicine: From A to Z. Oxford. Oxford University Press, UK, 1998.
38. Cahill DJ, Wardle PG. Management of infertility: Clinical review. BMJ, 2002; 325: 28–32.
39. Verkauf BS. The incidence and outcome of single factor, multifactorial, and unexplained infertility. Am J Obstet Gynecol, 1983; 147: 175–18.
40. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: A systematic analysis of 277 health surveys. PLoS Med, 2012; 9(12): e1001356.
41. Jungwirth A, Diemer T, Dohle GR, et al. Guidelines for the investigation and treatment of male infertility. Eur Urol, 2012; 61(1): 159-163.
42. Bosteels, Weyers S, Puttemans P, et al. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynecological symptoms: a systematic review. Hum Reprod Update, 2010; 16(1): 1-11.
43. Tayebi N, Ardakani SMY. Incidence and prevalence of the sexual dysfunctions in infertile women. European Journal of General Medicine, 2009; 6(2): 74-77.
44. Bosteels, Weyers S, Puttemans P, et al. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynecolog Kakarla N, Bradshaw K. Evaluation and Management of the Infertile. Glowm, 2008.
45. Jungwirth A, Diemer T, Dohle GR, et al. Guidelines for the investigation and treatment of male infertility. Eur Urol, 2012; 61(1):159-163.
46. Taylor A. Extent of the problem. ABC of subfertility, 2003; 327(7412):434-436.
47. Kamel RM. Management of the infertile couple: an evidence based protocol. Reprod Biol Endocrinol, 2010; 8: 21.