INTRODUCTION

Infertility is a common condition with important psychologic, economic, demographic, and medical implications ***(Practice Committee of the American Society for Reproductive Medicine, 2008)***.

It is inability of a couple to conceive after 12 months of regular intercourse without use of contraception in women younger than 35 years of age; and after 6 months of regular intercourse without use of contraception in women 35 years and older ***(Habbema et al., 2004)*.**

Clinicians using the term of subfertility to explain this failure to conceive unless the couple has been proven to be sterile ***(Thoma et al., 2013)*.**

The term of (fecundability) is the probability of achieving a pregnancy in one menstrual cycle. This term is more accurate descriptor because it shows varying degrees of infertility ***(Zinaman et al., 1996)*.**

Researches show that 80 - 90 % of apparently normal and healthy couples will conceive during the first year of attempted conception ***(Slama et al., 2012)*.**

Patients that had not achieved pregnancy after 12 months had lower fecundability ***(Habbema et al., 2004)*.**

In 2010, 1.9 % of women worldwide who aged 20 - 44 years wanted to have children were not be able to have their first live birth and 10.5 % of women with a previous live birth were not be able to have another live birth ***(Chandra et al., 2013)***.

Infertility causes may be due to either male factor like oligozospermia athenzospermia and teratozospermia or due to female factors like ovulatory dysfunction, tubal occlusion uterine abnormalities or idiopathic causes. Frequency of these factors in infertility is the same whether infertility is primary or secondary, and has not changed over the last 25 years in developed countries ***(Bhattacharya et al., 2009).***

Ovulatory function assessment is a key component of the evaluation of the female partner as ovulatory dysfunction is one of the most common causes of infertility. The treatment of ovulatory dysfunction is aimed at improving or inducing ovulatory function ***(Cousineau et al., 2009).***

Diminished ovarian reserve is one of the most important causes of ovulatory failure which means diminished oocyte quantity, oocyte quality, or reproductive potential. The identification of diminished ovarian reserve is an important item of the initial infertility evaluation as patients are

presenting for diagnostic evaluation later in their reproductive lifespan ***(Practice Committee of the American Society for Reproductive Medicine, 2015)***.

There is no ideal test for detecting ovarian reserve. Although, a lot of screening tests are utilized, but no single test is highly reliable for predicting pregnancy potential. Therefore, coordination of tests provides the best assessment. Many have moved to using anti-müllerian hormone (AMH) level as main test for ovarian reserve ***(Broekmans et al., 2006)***.

Women above 35 years of age and younger women with risk factors for premature ovarian failure, we suggest investigating ovarian reserve with a day 3 FSH level. Other tests such as antral follicle count, AMH level, and the clomiphene citrate challenge test (CCCT) are used by some physicians and in special circumstances. These tests have good specificity for predicting a poor response in vitro fertilization (IVF) cycles, but have limited value for predicting IVF outcome ***(Hendriks et al., 2009)***.

Poor ovarian reserve: (also known as impaired ovarian reserve, premature ovarian aging or declining ovarian reserve**)** is a state of decreasing fertility characterized by low numbers of remaining oocytes in the ovaries, or impaired preantral oocyte development or recruitment. Recent studies show that premature ovarian aging usually accompanied by high FSH (follicle stimulating hormone) levels ***(Gleicher et al., 2009)*.**

Incidence of poor ovarian reserve is (**1%)** of women below 40 years, **(0.1%)** of patients younger than 30 years and **(0.01%)** of patients under the age of 20 years ***(Luborsky et al., 2003)***.

FSH and AMH are two different hormones predict ovarian reserve at two different stages of follicular development. FSH levels reflect antral and postantral follicular development while AMH values are representative of postprimordial preantral follicular pool ***(Gleicher et al., 2010)***.

Thus correct assessment of ovarian reserve and prediction of ovarian response to gonadotropin stimulation are important for patients undergoing assisted reproduction treatment (ART) and are a core issue in modern fertility management ***(Broekmans et al., 2006)***.

In fact, Diminished ovarian reserve results in a poor response to gonadotropins, and could be related to advanced age, previous ovarian surgery or endometriosis. Poor responders need more gonadotropins to increase the number of oocytes retrieved and the fertilization rate, but increasing gonadotropins above a threshold dose may be useless ***(De Placido et al., 2001)***.

Dehydroepiandrosterone (DHEA) is a steroid secreted from zona reticularis and ovarian theca cells ***(Burger, 2002)*** that play an important role in the biosynthesis of testosterone

and oestradiol. There are conflicting data regarding the effect of DHEA on IVF-ICSI outcomes. **Casson et al** reported that DHEA enhanced ovarian function in poor responders ***(Casson et al., 2000).*** Barad and Gleicher found that DHEA supplementation could increase the number of oocytes and embryos ***(Barad et al., 2006)***. **Kara et al** reported that DHEA supplementation led to improved IVF-ICSI outcomes ***(Kara et al., 2011)*** and another study showed that DHEA supplementation enhanced the IVF-ICSI outcome in women with diminished ovarian reserve ***(Hyman et al., 2013)***.

It is difficult to choose the correct fertility treatment in women with poor ovarian reserve although various methods have been used; the management of controlled ovarian hyperstimulation is not easy in poor responders ***(Kara et al., 2011).***

AIM OF WORK

Research hypothesis:

In women with poor ovarian reserve, supplementation of DHEA for three months may improve ICSI/IVF outcome.

Research question:

In women with poor ovarian reserve, Dose DHEA supplementation for three months will improve ICSI/IVF outcome?

The aim of this study is to assess the effect of dehydroepiandrosterone supplementation on women with poor ovarian reserve undergoing assisted reproductive technique (IVF-ICSI).

Chapter 1

INFERTILITY

Introduction:

Infertility is a common medical condition associated with important psychological, demographic, economic, and medical implications ***(Practice committe of american society for reproductive medicine 2008)***.

Definitions:

Infertility is considered as unique medical condition because it involves a couple, rather than a single individual.

Infertility is failure of a couple to conceive after 12 months with regular intercourse and without use of contraception in women less than 35 years of age; and after six months of regular intercourse without use of contraception in women 35 years and older. Clinicians are using the term subfertility to explain this failure to conceive unless the couple has been proven to be sterile.

Fecundability is ability to achieve pregnancy in one menstrual cycle. It is more accurate descriptor because it shows varying degrees of infertility ***(Practice committee of American society for reproductive medicine 2008).***

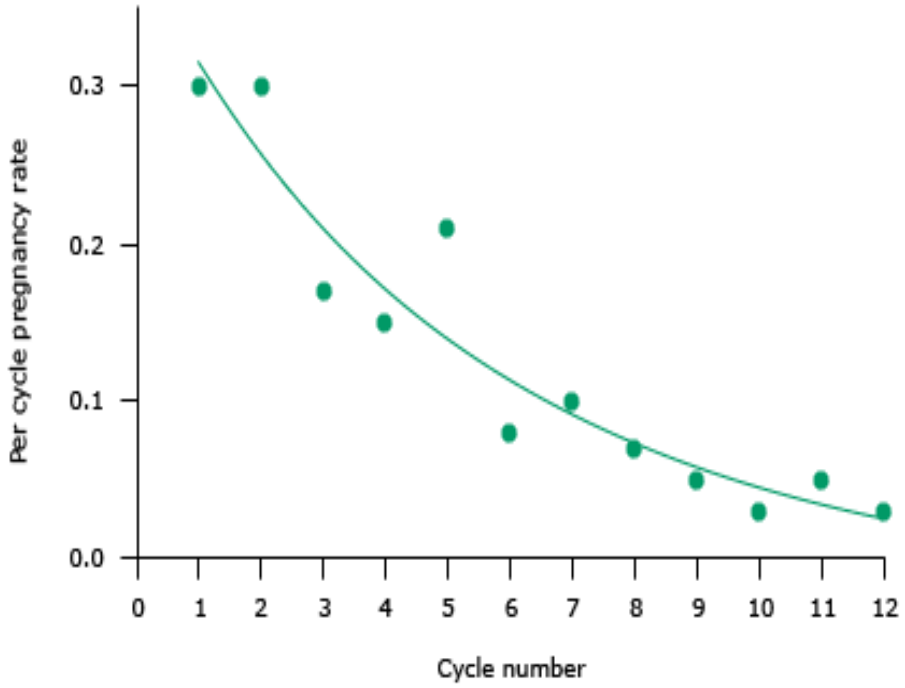

Figure (1): Fecundability in a cohort of healthy couples attempting to conceive Zinaman, MJ, Clegg, ED, Brown, CC, et al., Estimates of human fertility and pregnancy loss ***(Fertil Steril 1996)***.

Multiple studies explain that the big number of apparently normal couples (80 to 90 %) will get pregnant within the first year of attempted conception, studies also document that the fecundability of the cohort decreases by time and by increasing age of the female partner. Thus, the possibility of infertility may be suspected after 6 months of unprotected intercourse without conception. Patients who did not get pregnant after 12 months have even lower fecundability.

5 to 15% of healthy couples will get pregnant in the second 12 months of attempted conception so that after 24

months of trying to get pregnant, 95 % of couples will have conceived ***(Habbema et al., 2004)***.

Prevalence of infertility:

(NSFG) The National Survey of Family Growth making interview with 12,279 women aged 15 to 44 years to evaluate the prevalence of infertility in the U.S.A A woman was considered infertile if she and her husband were continuously married or cohabiting during the previous 12 months or more, were sexually active each month, had not used contraception, and had not become pregnant ***(Chandra et al., 2013)***.

The percentage of women from 1982 to 2006-2010, meeting these criteria for infertility fell from 6.0 to 8.5 %. This figure is lower than the incidence of infertility estimated from prospective studies in the United States, which ranges from 12 to 18 % ***(Thoma et al., 2013)***.

It is also lower than the rate in nulliparous married women that represent primary infertility. Primary infertility frequency in married women by age groups was: women 15 to 34 years (7.3 to 9.1%), 35 to 39 years (25%), and 40 to 44 years (30%) ***(Chandra et al., 2013)***.

Prevalence of infertility is highest in Eastern Europe, Oceania, North Africa/Middle East, and Sub-Saharan Africa In 2010, 1.9 % of women worldwide their age between 20 to 44 years who wanted to get pregnant were unable to have their

first live birth and 10.5 % of women with a previous live birth were unable to have another live birth ***(Mascarenhas et al., 2012)*.**

Causes of infertility:

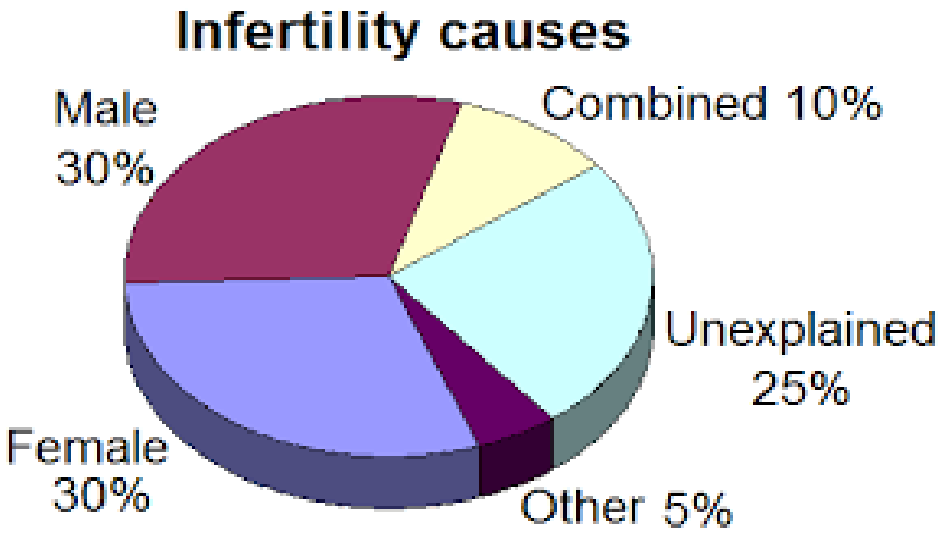

Figure (2): infertility causes from regulated fertility services: a commissioning aid - June 2009, from the Department of Health UK.

The World Health Organization **(WHO)** does a great effort in Diagnosis and management of Infertility. Study of 8500 infertile couples was performed and standard diagnostic criteria were used to determine the medical conditions contributing to infertility ***(WHO Technical Report, 1992)***.

Infertility due to female factor in developed countries was reported in 30% of infertile couples, Infertility due to male factor in 30 %, and both male and female factor infertility in 10 %. 25% of these couples had unexplained infertility and 15 % got pregnant at the time of the study. This study demonstrated

that infertility should not be assumed to result primarily from any problems in the female partner.

Male factor:

(Hypogonadism, post-testicular defects, seminiferous tubule dysfunction) **26%.**

Female factors:

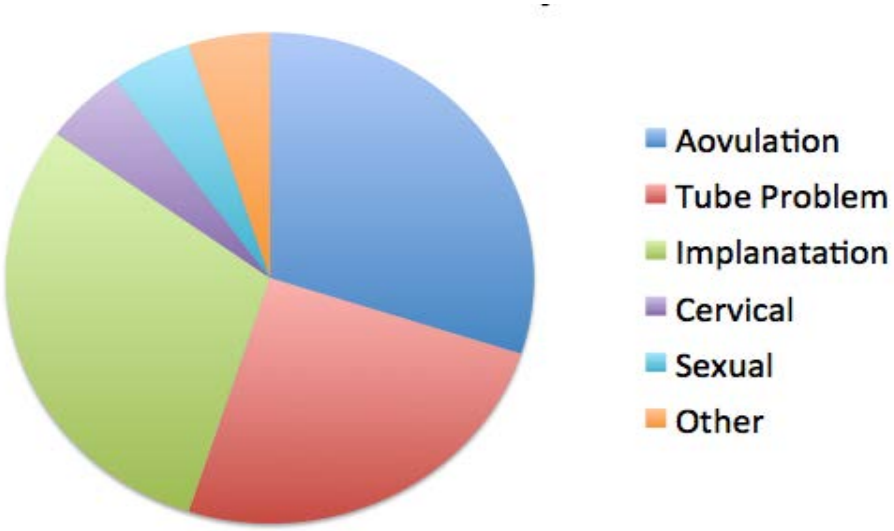

Figure (3): Causes of female infertility; www.almostadoctor.co.uk

- Ovulatory dysfunction 21 %
- Tubal damage 14 %
- Endometriosis 6 %
- Coital problems 6 %
- Cervical factor 3 %
- Idiopathic 28 %

These factors in infertility is similar in its incidence

whether infertility is primary or secondary, and has not changed significantly over the past 25 years in developed countries ***(Bhattacharya et al., 2009)*.**

Timing of infertility evaluation:

Fertility physicians or specialists with a great experience in the evaluation and treatment of infertility should do infertility evaluation. Less experienced physicians may start the infertility evaluation system, and couples with abnormal test results must be referred to a specialist ***(Ceballo R, et al. 2010).***

Infertility evaluation scheme should be performed for partners who have not been able to get pregnant after 12 months of frequent unprotected intercourse, but earlier evaluation should be done according to medical history, surgical history, past history and physical findings, and in women over 35 years of age ***(American College of Obstetrics and Gynecology, 2014)***.

Some researchers have proposed starting an infertility scheme work-up after 6 months of fertility-oriented intercourse without pregnancy since prospective cohort studies have demonstrated that a significant decrease in fecundity occurs by this time ***(Brosens et al., 2004)***.

Delaying the time of assessment and management of an infertile woman in her mid-thirties will decrease the success rate once therapy is initiated. For these reasons in women between 35 and 40 years of age we should initiate the infertility evaluation work-up after 6 months of frequent unprotected sexual intercourse without pregnancy and we start the

assessment after less than 6 months in women above 40 years of age ***(American College of Obstetrics and Gynecology, 2012)***.

A.C.O.G (The American College of Obstetricians and Gynecologists) and **A.S.R.M** (The American Society for Reproductive Medicine) advise the women above 35 years receive an expedited infertility evaluation and start treatment after 6 months of failed attempts to get pregnant or earlier, if clinically indicated ***(American College of Obstetrics and Gynecology, 2012)***.

Assessment is started immediately if the female partner has one of the risk factors for ***premature ovarian failure*** (previous extensive ovarian surgery, exposure to cytotoxic drugs or pelvic radiation therapy, smoking, autoimmune disease, strong family history of premature ovarian failure/ early menopause, advanced stage endometriosis, or known or suspected tubal/uterine disease). Male factors are indications for starting early assessment of the male partner. These factors include a history of adult mumps, testicular trauma requiring treatment, impotence or other sexual dysfunction, radiation and/or chemotherapy, or past history of infertility with another partner. Evaluation or assessment should be initiated as soon as possible if the female partner has a history of amenorrhea /oligomenorrhea, radiation and/or chemotherapy , or endometriosis, known or suspected tubal disease, or if male risk factors are present ***(Practice Committee of American society for Reproductive Medicine 2012)***.

Table (1): Initial evaluation of infertility ***(Lesser, 2014).***

Male	Female
Duration of infertility	Duration of infertility
Fertility in other relationships	Number and outcome of any prior pregnancies (including ectopic and miscarriages) with the same or a different partner
Medical and surgical history, including testicular surgery and history of mumps	Gynecologic history, including history of pelvic inflammatory disease, fibroids, endometriosis, cervical dysplasia; surgery of the cervix, ovary, uterus, fallopian tube, pelvis, or abdomen; intrauterine device use, other prior contraceptive use, diethylstilbestrol exposure in utero, uterine anomalies.
	Menstrual history (age at menarche, cycle length, and regularity), presence of molimina or vasomotor symptoms (hot flashes), dysmenorrhea
	Changes in hair growth, body weight, or breast discharge
	Other medical and surgical history
Medications	Medications
History of chemotherapy or radiation	History of chemotherapy or radiation
Cigarette smoking, alcohol, marijuana and other drug use; environmental and occupational exposures	Cigarette smoking, alcohol, marijuana and other drug use; environmental and occupational exposures
Sexual dysfunction or impotence	Exercise and dietary history
Frequency of intercourse, use of lubricants(which may be toxic to sperm)	Frequency of intercourse, use of lubricants (which may be toxic to sperm). presence of deep dyspareunia suggestive of endometriosis
Previous infertility testing and therapies	Previous infertility testing and therapies
Family history of mental retardation, birth defects, or reproductive failure	Family history of mental retardation, birth defects, or reproductive failure
	Abdominal or pelvic pain, symptoms of thyroid disease

Infertility Evaluation:

We should take in consider that the couple may have multiple factors sharing in their infertility; therefore, initial evaluation, including a complete history and physical examination, should be started. This will detect the most common causes of infertility, if present. Evaluation of both partners is performed concurrently. The same approach is used for both primary and secondary infertility ***(Practice Committee of American society for Reproductive Medicine, 2012)***.

The following tests are used in most couples complaining of infertility:

- Semen analysis for male factors
- Menstrual history, assessment of LH surge in urine prior to ovulation, and/or luteal phase progesterone level to assess ovulatory function
- Hysterosalpingography (HSG) to assess tubal patency and the uterine cavity.
- Estradiol (E2) and Day 3 serum FSH levels.

In select couples, the following additional tests may be warranted:

- Laparoscopy to identify endometriosis or pelvic pathology.