International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Brief Overview on Female Infertility, It's Causes and Diagnostic Approaches

Krishna Takankhar[1], Diksha Gupta[2], Rajesh Oswal[3]

[1]Research Student, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, India.
[2]Assistant Professor, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, India.
[3]Principal, Genba Sopanrao Moze College of Pharmacy, Wagholi, Pune, India.

ABSTRACT

Female infertility is the major disorder which has altered the man kind foe lack of conception and reproducibility, stressful world, excess radiation, lack of biological food, genetically disorder ,changing life style, increased electronic discharge have resulted the female infertility. Infertility/ childlessness cause great personal suffering & distress. Most of this agony & misery is hidden from the public gaze. That is the reason this topic is not discussed about openly. The dismal ignorance & neglect about the causes of childlessness and its treatment are main reason for the lack of public support for childless couple. Female fertility can be limited or diminished or destroyed in a number of ways. Women have a finite number of germs cells and follicles that are available for a limited period, from menarche to menopause, during their lifetimes. The process of ovulation is mediated by the interactions of hypothalamic, pituitary and ovarian hormones. Interference with ovulation can occur at any one or combinations of these sites. The oviducts can be distorted or blocked by the consequences of endometriosis or infection. The quality of the ova and spontaneous pregnancy decreases steadily with age. Drugs are available that stimulate ovulation and donor eggs can be used. The cryopreservation of ova or ovarian tissue is technique now receiving research attention. Diagnosis is straightforward when causes are severe and laparoscopy is still the preferred method for assessing for tubal factor infertility and endometriosis. IVF remains the dominant treatment, although traditional measures still have a major role. Internationally, IVF opportunities are limited in view of cost. About 10-15% of couples experience some difficulty with fertility. Remedies range from a visit to a primary physician, education and adjustments in timing attempts to conceive, to placing the entire reproductive process in the hands of specialist.The purpose of the study is to evaluate existing literature for possible associations between female infertility, infertility-associated diagnoses, and the following areas of disease: infertility and mental health significance of the study common factors ,diagnosis methods artificial fertility treatment methods ethical issues about

Keywords- Infertility, IVF, ART, Endoscopy, Miscarriage

INTRODUCTION

Infertility is a medical condition that can cause psychological, physical, mental, spiritual, and medical detriments to the patient. The unique quality of this medical condition involves affecting both the patient and the patient's partner as a couple. Although male infertility is an important part of any infertility

discussion, this paper will review the evaluation, management, and treatment of female infertility. One must understand normal fecundability, the probability of achieving pregnancy in one menstrual cycle, to understand infertility. This basic understanding will help the healthcare team properly counsel the patient on referrals and provide basic education and understanding of this medical condition.

The research community has established a fecundability rate multiple times, which hashelped establish normal pregnancy rates to assist in diagnosing infertility. The largest study identified that 85% of women would conceive within 12 months. Based on this study's findings, fecund ability is 25% in the first three months of unprotected intercourse and then decreased to 15% for the remaining nine months.[1]This research has helped the American Society of Reproductive Medicine (ASRM) establish when a couple should undergo an infertility evaluation. The ASRM recommends initiating an evaluation for infertility after failing to achieve pregnancy within 12 months of unprotected intercourse or therapeutic donor insemination in women younger than 35 years or within 6 months in women older than35.[2]

INFERTILITY AND MENTAL HEALTH

Six studies included in this review evaluated the impact of infertility on mental health. Universally, authors concluded that women with a history of infertility or an infertility- related diagnosis, specifically PCOS, were at increased risk to develop mental health disorders [3]. Four out of the six studies that found correlations with mental health issues used women with PCOS as their primary population [4] Depression risk was found to be elevated in four out of the six studies based on scores from validated scales such as the Edinburgh Depression Scale [5]. Five of the six studies noted significant increases in diagnoses of anxietyor psychosocial distress in the specific study populations [6]

The sole study which did not find an increase in anxiety was by Baldur-Felskov et al. This study was a retrospective cohort study published in 2013 that included 98,320 Danish women who were evaluated for infertility between 1973 and 2008, with a median follow up of
11.3 years. Women who sought infertility treatment were tracked through medical registries to determine rates of subsequent psychiatric hospitalizations. While there was no statistically significant increase in hospitalizations related to anxiety in the PCOS/infertile population, it is difficult to assess whether actual levels of anxiety were elevated but simply did not lead to subsequent hospitalizations. A main drawback of the Baldur-Felskov study was the fact that only inpatient hospitalizations were tracked, likely underestimating the true correlation between infertility and psychiatric disease. Importantly, the Baldur-Felskov study did note a significant increase in hospitalizations related to alcohol and drug abuse in the PCOS/infertilepopulation [7]

EPIDIMIOLOGY

Infertility is a complex disorder with significant medical, psychosocial, and economic problems [8]. Data from population - based studies suggest that 10-15 % of couples in the world experience infertility [9]. In Africa, its prevalence is particularly high in sub-Sahara ranging from 20% to 60% of couples

[10]. It is estimated that female factors and unexplained infertility accounts for 50-80% while the male factor accounts for 20-50% of the cause of infertility in different parts of Nigeria [11]. Available evidence suggests that the social consequences of infertility are particularly profound for African women as compared to men[12]. Community based data suggest that up to 30 per cent of couples in some parts of Nigeria may have proven difficulties in achieving a desired conception after two years of marriage without the use of contraceptives [13]

SIGNIFICANCE OF THE STUDY

Infertile women should seek counseling and consider natural at home options for feelings of sadness, and depression. Not doing anything about it and keeping it to her isn't going to help. Cruel feelings of loss, depression and trauma are so stressful emotionally and psychologically that they can lead to physical manifestations in the body; actually affect physical functions of the body. Once psychological health affects the physical body, the situation gets worse than physical symptoms feed the depression.[14] Infertility is a very real part of millions of people's lives, and all of those going through these deserve to be heard and guided to psychological health support on this cruel journey. In fact, the psychological health aspect of infertility needs to be part of every couple's health plan. Whether a couple decides to continue to pursue parenthood or not, a psychological health plan must be part of the overall picture.[15] Akker (2005) mentioned that, investigations on infertility are voluminous and have shown that involuntary childlessness can be devastating, and it is associated with psychological distress.[16] Infertility seem to have comprehensive effects in woman's life, it is not only restricted to sexual or reproductive areas of life but also impact burden on several psychosocial areas of human existence.[16,17,18,19] Impairments have been reported regarding distinct aspects, such as relationship abilities, psychopathology, family life, marital life, and economic terms.[20 21 22] Beauty of life for children and we do not have a happy life without them. Deprivation from the grace of reproduction is meaningless life and the couple's relationship getting in the deterioration and lacks stability. If infertility period is prolonged, it put a childless woman in severe pressure on herself, may become depressed and concern for her married life, and sometimes because they have lost themost important role of her creation, moreover her marriage became threatens. These increase Psychological disorders and depression symptoms, especially if the husband isn't a concerted.

OPERATIONAL DEFINATIONS

Infertility: Infertility, as defined by the World Health Organization, is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse, without the use of contraception.[23]

Primary infertility: Couples who have been no prior conception after at least one year, having sex without usage birth control methods.[24]

Secondary infertility: Couples who have been able to get pregnant at least once, but now are unable to conceive.[24]

Psychological distress: A state of emotional suffering that may impact on social functioning and day to day living of individuals characterized by symptoms of depression, anxiety, stress and tension.[25, 26]

THE MOST COMMON IDENTIFIABLE FACTORS OF FEMALE INFERTILITY

- Ovulatory disorders - 25%
- Hyperprolactinemia-7%
- Pelvic adhesions-12%
- Tubal blockage-11%
- Other tubal/congenital uterian anomalies-11%
- Endometriosis-15%

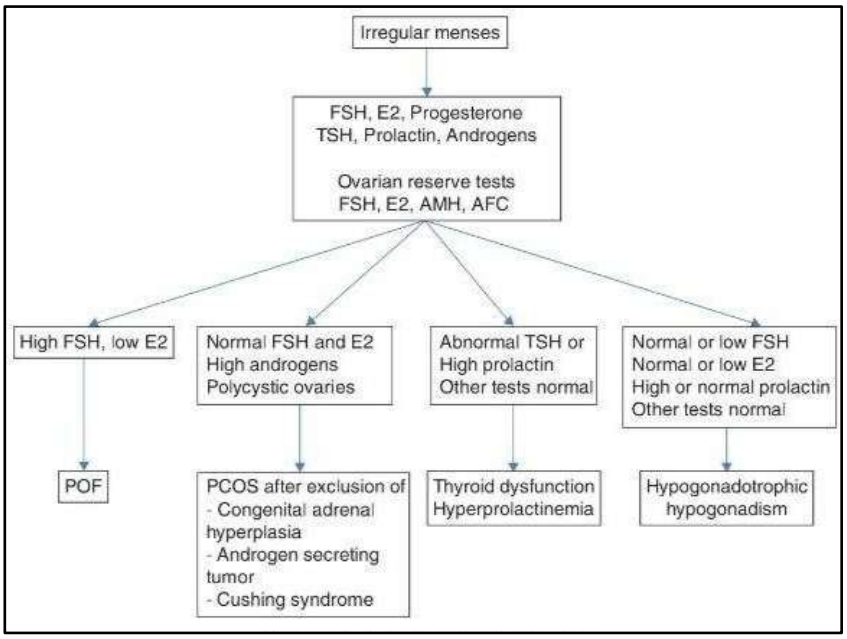

Fig no.1:- *Tests for ovulation function.*

Each of these causes will be further investigated in later portions of this paper. Male and unknown factors are outside the scope of this paper and will be discussed elsewhere. Even though these factors are not discussed here, it is important to realize that male factor infertility represents a substantial portion of the identifiable factors causing infertility.

ANOVULATION

Disorders of anovulation account for about 30% of infertility and often present with irregular periods (oligomenorrhoea) or an absence of periods (amenorrhoea). Many of the treatments are simple and effective, so couples may need only limited contact with doctors. This makesit easier for a couple to maintain a private loving relationship than in the stressful, more technological environment of assisted conception. However, not all causes of anovulation are amenable to treatment by ovulation induction. Anovulation can sometimes be treated with medical or surgical induction, but it is the cause of the anovulation that will determine whether ovulation induction is possible[27]

HYPOTHALAMIC-PITUITARY CAUSES:-

Hypogonadotropic hypogonadism is characterized by a selective failure of the pituitary gland to produce FSH and LH. The commonest cause is excessive exercise, being underweight, or both. Women who have a low body mass index (BMI), for example <18Kg/m2 or who exercise excessively, for example gymnasts, marathon runners, ballerinas, may develop amenorrhoea because of a physiological reduction in the hypothalamic production of gonadotropin releasing hormone. Women who are underweight for their height when they get pregnant are more likely to have .small for dates. babies; and children of women who have eating disorders are more likely to be admitted to hospital with failure to thrive. Sheehan.s syndrome (panhypopituitarism), caused by infarction of the anterior pituitary venous complex (usually after massive postpartum haemorrhage or trauma), and Kallman.s syndrome (amenorrhoea with anosmia caused by congenital lack of hypothalamic production of gonadotropin releasing hormone) are rare. Children treated for a craniopharyngioma or some forms of leukaemia may have hypogonadotropic hypogonadism secondary to cerebral irradiation, which may affect the hypothalamus or the pituitary[27]

OVARIAN CAUSES:-

Polycystic ovary syndrome is the commonest cause (70%) of anovulatory infertility[28-32] The primary abnormality seems to be an excess of androgen production within the ovary[33,34] that leads to the recruitment of large numbers of small preovulatory follicles, which fail to respond to normal concentrations of follicle stimulating hormone[35]. Thus, a dominant follicle is rarely produced. Women with polycystic ovary syndrome commonly present their late teens or early 20s with hirsutism, acne, or irregular periods (cycle length > 35days). Even if they ovulate, the chance of conception for these women is reduced because fewer ovulatory events occur in a given time frame. Obesity is present in varying degrees (30% to 70%) in women with the syndrome and is usually of the central type[36-38]. Central obesity, being a prominent feature of the so-called metabolic syndrome, is directly linked to increased peripheral insulin resistance (IR)[39]. Furthermore, PCOS itself has been shown to confer a risk for insulin resistance, beyond that caused by obesity alone[40]

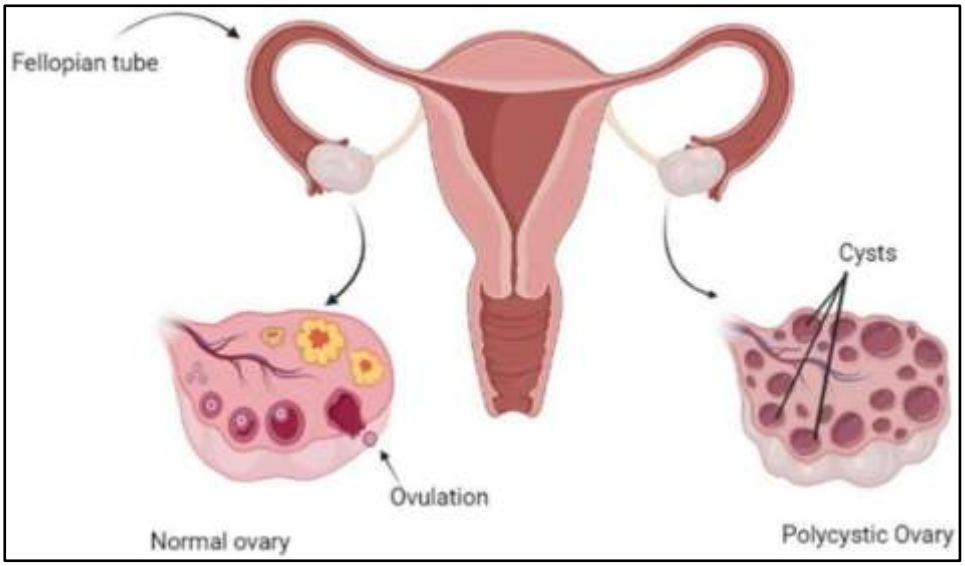

fig no.2:-*normal ovary and polycystic ovary*

CAUSES UNSUITABLE FOR OVULATION INDUCTION

Premature ovarian failure:-Premature ovarian failure (POF) is the cessation of ovarianfunction before 40 years of age. The term refers to the condition when the ovaries have lost their germinative and hormonal functions because of the exhaustion of the number of ovarian follicles prior to the typical age for physiological menopause, which in Poland averages 51 years [41].

The physician may encounter this condition when examining a young female patient who is struggling to get pregnant or is experiencing secondary amenorrhoea. In order to make a diagnosis in the case of a young female, it might be helpful to determine if there are any menopausal symptoms. The medical history of patients with POF usually reveals a normal age of menarche [42 43] and regular menstrual cycles, followed by oligomenorrhoea or sudden amenorrhoea. In some cases, secondary loss of menses is diagnosed after stopping contraceptive pills [44-46]. Most frequently, women suffer from hot flushes, excessive sweating, hair loss, as well as skin and mucous membrane dryness

Genetic abnormality -The commonest genetic abnormality is Turner.s syndromeTurner syndrome was first reported as a clinical syndrome (prior to the availability of karyotyping) in seven women with short stature, sexual immaturity, neck webbing, and cubitus valgus in a paper published in 1938 by Henri Turner, an Oklahoma physician [47]. However, Otto Ulrich had already described an eight-year-old girl with a similar phenotype several years earlier [48].

Turner syndrome is the most common sex chromosome abnormality in females and occurs in approximately 1 in 2000 to 1 in 2500 live female births, based on epidemiological and newborn genetic screening data from Europe, Japan, and the United States [49-51]. The true prevalence of Turner syndrome remains difficult to ascertain because patients with a milder phenotype may remain undiagnosed. Some individuals are not diagnosed until late adulthood if their phenotype is mild [52]. Turner syndrome occurs with more or less the same prevalence in all ethnic groups and in different countries. However, the prevalence at birth may be declining in some countries. This is related to the increased use of ultrasonographic screening prenatally and the fact that some mothers carrying fetuses with Turner syndrome choose to terminate the pregnancy [53 54]. On the other hand, most gestations (likely more than 99 percent) affected by X chromosome monosomy (45,X) do not survive to birth. The 45,X genotype is found in at least 10 percent of all spontaneous abortions [55-59]The diagnosis of TS could be obtained prior to birth using prenatal diagnostic testing such as chorionic villus sampling or amniocentesis. Using those tests, an analysisof the fetal chromosomal structure would defiantly confirm the diagnosis. TS should be clinically suspected in thepresence of prodromal symptoms. For example, thepresence of fetal hydrops, cystic hygroma, or cardiac defects on a prenatal ultrasound would raise the suspicionof TS [60 61]. Post-delivery karyotype testing is often required to confirmthe diagnosis. In cases where the TS is a result ofmosaicism, karyotype can come back normal. If a high suspicion of TS remains despite a normal karyotype,fluorescence in situ hybridization analysis can offer an additional modality to the karyotype [60].Later in life, patients with TS who went undiscovered might present with developmental abnormalities such asthe delayed onset of puberty or amenorrhea. A high concentration of the follicle- stimulating hormone is highlyindicative of TS. Anti-Mullerian hormone offers a highlysensitive marker for ovarian failure prediction [62 63].

OVULATION INDUCTION

Treating specific causes

Waight change-Weight reduction through dietary modification and exercise is recommended for overweight PCOS patient [64]. Some studies show that over 10% of women with PCOS will regain spontaneous ovulation when placed on low calorie, low-fat diet, and exercise or with surgery. The aim of dietary restriction and exercise is toward losing about 5–10% of their body weight. This form of treatment alone or in combination with pharmacologic agents would reduce insulin resistance and is advocated for overweight to obese women of BMI > 24 [64]. The drawbacks of this method of treatment are that such women lack the motivation toremain on diet and exercise, and may not be able to achieve the desired weight loss to trigger spontaneous ovulation, and most times pharmacologic agents are added to assist ovulation. The duration it takes to achieve the desired body weight to bring about ovulation is not defined, but differs among patients. Other drawbacks are that it may not treat anovulation in normal-weight women even though they also have insulin resistance as well. The advantageis that it is cost-effective and will not produce any form of drug reactions. It will also reduce the high level of luteinizing hormone and reduce early pregnancy loss. A combination of lifestyle modification with weight loss before pharmacologic ovulation-inducing agents improved ovulation and live birth in women with PCOS in a USA study [65] and in addition, required lower doses of pharmacologic agent for ovulation induction.

HYPERPROLACTINEMIA

The prevalence of hyperprolactinemia ranges from 0.4% in unselected normal adult femalesto as high as 9%–17% in 1,2 females with reproductive health disorders. Its prevalence was found to be 5% in a family planning clinic, 9% in women with adult-onset amenorrhea, and 17% among women with 1 polycystic ovary syndrome.[66]

Diagnostic evaluation-For the correct identification of the etiology of hyperprolactinemia, some parameters must be taken into account: medical history, physical examination, clinical features, laboratory findings (especially PRL serum levels), as well as imaging studies of the pituitary and sella turcica. Furthermore, the screening for macroprolactinemia should often beconsidered.

In addition to PRL determination, TSH, free T 4 , and creatinine levels should be obtained to rule out secondary causes of hyperprolactinemia[67 68 69]. Moreover, acromegaly must be investigated by means of IGF-1 measurement in all patients with a macroadenomas, even though there are no manifestations of this disease[70]. Finally, b-hCG measurement is mandatory in any childbearing woman with amenorrhea[67 68]

Hypothyroidism-WHO estimates the overall prevalence of primary infertility in India to be 3.5-16.8%.2 Both hyperthyroidism and hypothyroidism have profound effects on estrogen and androgen metabolism, menstrual function and fertility[71] They may cause delayed onset of puberty, menstrual abnormalities, anovulatory cycles, miscarriages and infertility.[72]Hypothyroidism can be easily

detected by assessing serum thyroid stimulating hormone (TSH) levels. A slight increase in TSH levels with normal T3 and T4 indicates subclinical

hypothyroidism whereas high TSH levels accompanied by low T3 and T4 levels indicate clinical hypothyroidism. Elevated thyrotropin- releasing hormone levels due to hypothyroidism are often associated with increased prolactin (PRL) levels and a delayed LH response to GnRH.[73] Thyroid dysfunction is implicated in abroad spectrum of reproductive disorders, ranging from abnormal sexual development to menstrual irregularities and infertility.[74] It has been proved that for normal sexual function, thyroid secretion of T3, T4 need to be approximately normal. We had conducted this study to collect some specific information regarding hypothyroidism in infertile women and to assess their responses in treatment procedures. Diagnostic evaluation-Thyroid dysfunction is a common cause of infertility which can be easily managed by correcting the appropriate levels of thyroid hormones.[75 76] It has been recommended that in the presence of raised TSH along with raised PRL levels, the treatment should be first to correct the hypothyroidism before evaluating further causes of hyperprolactinemia. Hormone therapy with thyroxine is the choice of treatment in established hypothyroidism. It normalizes the menstrual cycle, PRL levels and improves the fertility rate. Therefore, with simple oral treatment for hypothyroidism, 76.6% infertile women with hypothyroidism conceived after 6 weeks to 1 year of therapy. We tried to maintain normal TSH levels; compliance and adequacy of hypothyroid drug dose were checked by TSH measurement after 6 to 8 weeks interval.

Therefore, the normal TSH levels are the pre-requisite requirements for fertilization. The decision to initiate thyroid replacement therapy in subclinical hypothyroidism at early stage is justified in infertile women. Our data also indicate that variations in TSH levels in the narrower range or borderline cases, i.e. 4–5, 5–6, and >6.0 μIU/ml, should not be ignored in infertile women which are otherwise asymptomatic for clinical hypothyroidism. This group of infertile women, if only carefully diagnosed and treated for hypothyroidism, can benefit a lot rather than going for unnecessary battery of hormone assays and costly invasive procedures. For better management of infertility cause, we should plan further studies with the large sample size and long-term follow-up which are necessary to validate the variation in TSH and PRL levels.

PELVIC ADHESION

In the case of pelvic inflammatory disease, or any other infection of the reproductive tract, the fallopian tubes can become inflamed. The inflamed surfaces can develop scar tissue or adhesions within the tubes. These adhesions prevent egg and sperm from coming together.[77] Adhesions caused by endometriosis usually occur in the pelvic cavity. They may be present near the fallopian tubes or ovaries. Endometrial adhesions may interfere with ovulation.[78] Sometimes, endometrial adhesions prevent the fallopian tube from moving naturally. The ovary is not attached directly to the fallopian tubes. During ovulation, when an egg is released from the ovary, it must find its way into the fallopian tube If adhesions interfere with the fallopian tubes natural movement, an egg may not make it into the fallopian tube.[79] This decreases fertility.

***Diagnosis*-**If the adhesions are within the fallopian tubes, surgical repair may be possible.[80]However,IVF treatment may be more successful and cost-effective.If Asherman's syndrome is the cause of infertility, the adhesions may be removed during an operative hysteroscopy. You may be able to conceive naturally afterward, or you may require fertility treatment in addition to surgery.[81]In the case of pelvic adhesions or endometriosis, removal of the adhesions may reduce pain and may improve the odds of pregnancy success. However, depending on the situation, you may still need IVF or fertility treatment after surgery.[82]

TUBAL BLOCKAGE-Blocked fallopian tubes are a common cause of infertility. Sperm and an egg meet in the fallopian tube for fertilization. A blocked tube can prevent them from joining.If both tubes are fully blocked, pregnancy without treatment will be impossible. If the fallopian tubes are partially blocked, you can potentially get pregnant. However, the risk ofan ectopic pregnancy increases.This is because it's harder for a fertilized egg to movethrough a blockage to the uterus. In these cases, your doctor might recommend in vitro fertilization (IVF), depending on whether treatment is possible.If only one fallopian tube is blocked, the blockage most likely won't affect fertility because an egg can still travel throughthe unaffected fallopian tube. Fertility drugs can help increase your chance of ovulating onthe open side

HYSTEROSALPINGOGRAPHY (HSG):

The diagnosis of tubal patency based on radiologica lfindings is not considered a complete or an absolute diagnosis. X-ray gives an idea about the size and shapeof the uterine cavity, the isthmus and the cervical canalwhen viewing anteroposterior or profile films.[83] HSG iswidely used and has some advantages, including thelack of need for anesthesia, relative speed with which the procedure is completed, and a potential therapeutic effect with oil soluble contrast media.[84] The therapeutic impact of HSG is, in part, due to the flushing of tubal debris. In addition, in-vitro studies have shown that oil-based flushing media prevents peritoneal mast cell phagocytosis of spermatozoa and increases fecundity in subfertile mice. A pathognomonic finding on HSG is seen with SIN, in which the contrast filled diverticular projections result in a radiographically honeycombed appearance.[85]Hydrosalpinx also has a characteristic appearance; however, transvaginal ultrasound better evaluates the volume of the dilated tubes.[86] HSG findings can be used to stage tubal disease and the appearance of the intraluminal mucosal architecture as a rugal pattern isa good prognostic factor forsubsequent pregnancy.[87 88] A potential limitation of HSG is tubal spasm, especially with elevated contrast injection pressure. Based on hysteroscopic tubalcannulation, it has been estimated that HSG may give a false positive diagnosis of proximal tubal obstruction 50 % of the time.[89] Lower pressure, the use of spasmolytic agents, such as glucagon, diazepam and terbutaline and follow-up imaging to assess contrast spillage following resolution of spasm have been proposed.[90,91,92]. However, intermittent tubalobstruction during HSG may suggest underlying tubal pathology, especially in the setting of low injection pressures, and thus the value of spasmolytic agents may be limited.[90] Furthermore, the efficacy of these agents with respect to reversal of tubal spasm remainsto be established.[93 94] A recent study suggested thatunilateral cornual obstruction may be resolved in

morethan 50% of patients by rotating the patient so that theobstructed tube is in a more inferior position.[95]

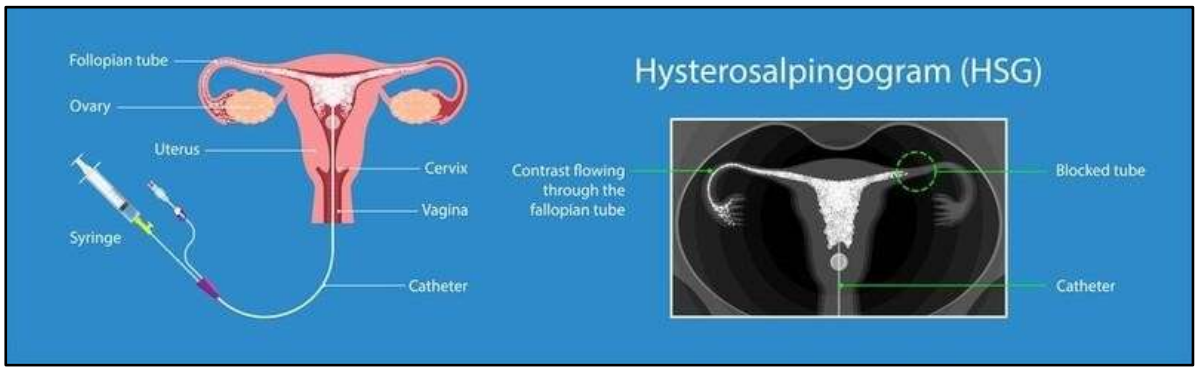

Fig no.3:-*hysterosalpingogram*

ENDOSCOPIC EVALUATION

When managing a woman with infertility, it is important to avoid missing the correct diagnosis and treating a woman empirically for having an unexplained infertility, while existent tubal pathology might benefit of surgery. HSG has been considered as a screening test for tubal pathology, making only abnormal results an indication for laparoscopy to confirm the diagnosis, exclude artifacts resulting from transient tubal contractions and undergo a fertility-enhancing surgical intervention. However, many authors have stressed on the relative low sensitivity and the false negative rates when using HSG alone. Compared to laparoscopy, HSG has a sensitivity of 40 to 70% in the detection of bilateral tubal occlusion[96]Contrast intravasation into uterine and ovarian veins can be mistaken for tubal filling, with a false negative rate reaching 50% in proximal tubal occlusion, and 60% in distal tubal occlusion[97]Laparoscopy with direct visual examination of the pelvic anatomy is the ideal method available to diagnose tubal and peritoneal abnormalities that may impair fertility, in contrast with HSG which can miss pelvic adhesions and endometriotic implants[98] When it was first implemented, laparoscopy was suggested as a mandatory step to rule out the existence of eendometriosis and peritubal adhesions as a cause of infertility, even when tubal patency with free spillage of injected dye has been demonstrated by HSG [99]great difference in the rate of abnormal findings was noted at that time between laparoscopy and the other noninvasive tests. In 1975, the first published paper concluded that laparoscopy frequently identifies a possible cause of infertility in women whose failure to conceive has remained unexplained by other methods of investigation[100]The majority of these lesions are endometriotic ones, with accompanying tubal adhesions found in 20% of cases. Unilateral or bilateral tubal occlusion could still be found as well in a minority of cases[96]Fallopian tubes can be patent under high pressures but dysfunctional physiologically [101]such abnormalities can be corrected during laparoscopy using neosalpingostomy, increasing therefore the pregnancy rates both spontaneously and with IVF [102]

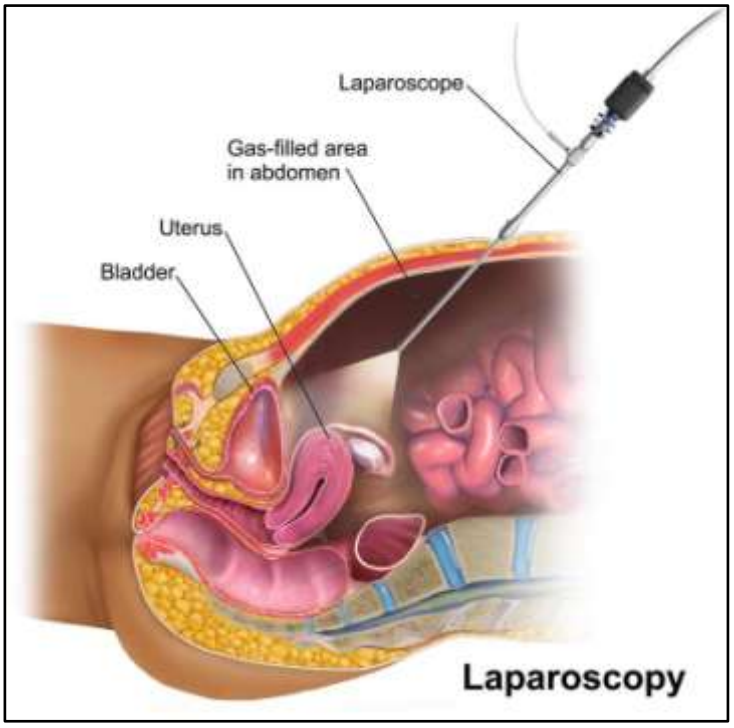

Fig no 4:-*laproscopy*

CONGENITAL UTERINE ANOMALIES

Congenital uterine anomalies result from the abnormal differentiation, migration, fusion, and subsequent canalization of Mullerian ducts during embryogenesis [103]. They have been reported to be implicated as a potential cause of reduced fertility and miscarriages [104-106]. Basing on anomalies in the embryological development process, the uterine malformations can be divided in unification defects of the Mullerian ducts (unicornuate, bicornuate or didelphys uterus), canalization defects for incomplete resorption of the midline septum (sub- septate or septate uterus), Mullerian agenesis and arcuate uterus [107]. Data from literature, demonstrated that the aforementioned anomalies are present in 1-10% of unselected population, 2-8% of infertile women and 5-30% of women with a history of miscarriage [108]; however, the prevalence rate is uncertain due to the application of several diagnostic methods such as hysterosalpingography, hysteroscopy, laparoscopy, magnetic resonance imaging and three-dimensional sonography. In the same view, the use of three different classification systems developed by the American Society of Reproductive Medicine (ASRM, 2006) [109], the European Society of Human Reproduction and Embryology (ESHRE, 2013) and the European Society for Gynecological Endoscopy (ESGE, 2013) does not permit to establish a unique consensus about the prevalence of these malformations [104]. Moreover, uterine anomalies are often asymptomatic and accidentally diagnosed during ultrasounds for other gynecological pathologies, assessment of tubal patency or pregnancy [110 111]. Moreover, they may also be recognized at delivery during spontaneous or cesarean section [112]. The presence of congenital uterine alterations represents a potential cause of infertility, recurrent pregnancyloss, preterm delivery, fetal malpresentation as well as small-for-gestational age infants, with greater effects being evident in women with more profound defects [113]

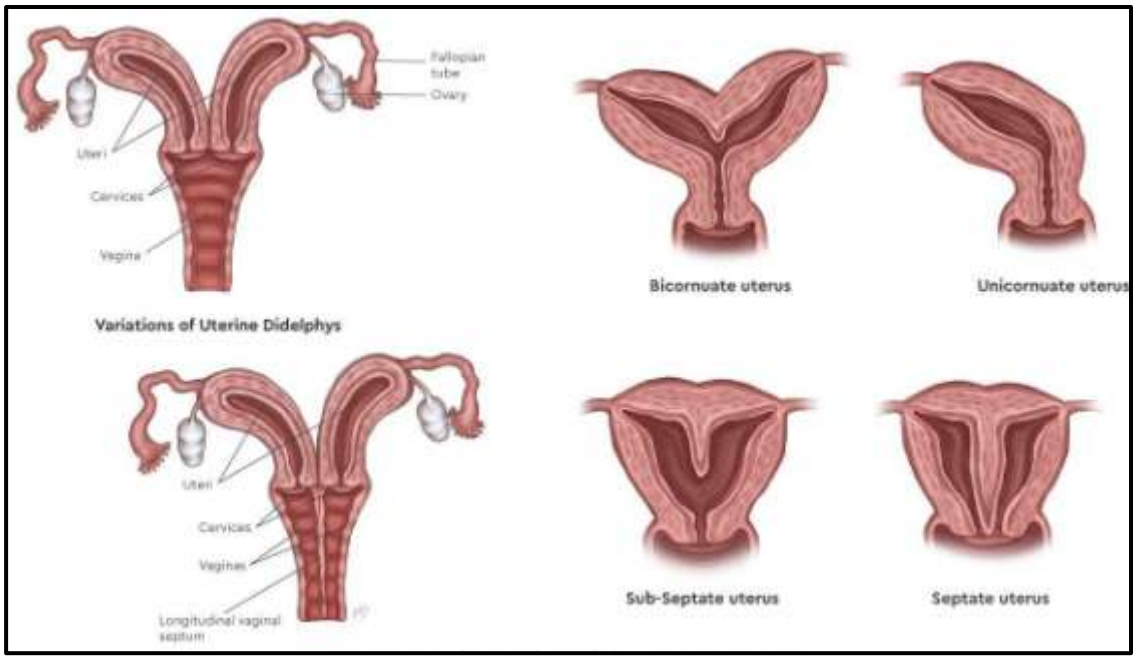

Fig no 5:-*uterian anomalies*

Diagnosis-As most CUAs are asymptomatic, the majority of them are detected incidentally. A significant proportion of anomalies are diagnosed during fertility investigations. Accurate diagnosis and correct classification help in the appropriate counselling of women about their potential reproductive prognosis and risks and for planning any intervention with a view to improve the reproductive outcome. Evaluation of the internal and external fundal contours of the uterus is the key in making a diagnosis and correctly classifying a uterine anomaly. Considering this, the gold standard test has been the combined laparoscopy and hysteroscopy, albeit invasive, in the past. Imaging modalities such as ultrasonography, hysterosalpingogram (HSG), sonohysterogram and magnetic resonance imaging (MRI) are less invasive modes of screening and classifying various uterine anomalies[113]. While conventional 2D transvaginal ultrasound (TVS) and HSG are considered as good screening modalities, 3D TVS and MRI can accurately diagnose and classify the types of CUAs[114 115], as they can define both external and internal uterine contours.

ENDOMETRIOSIS:-

Endometriosis is defined as the presence of endometrial glands and stroma like lesions outside of the uterus[116]. The lesions can be peritoneal lesions, superficial implants or cysts on the ovary, or deep infiltrating disease[117]. While there is no definitive etiology of endometriosis, there are several hypotheses regarding how endometriotic lesions develop. One possible mechanism is retrograde menstruation, a feature of the menstrual cycle in women and non-human primates, which is an outflow of the endometrial lining through the patent fallopian tubes into the pelvic space. This retrograde flow, along with potential hematogenous or lymphatic circulation, may result in the seeding of endometrial tissue in ectopic sites. However, retrograde menstruation is common (perhaps universal among menstruating women) while endometriosis is much less common. Therefore, other factors, such as hormonal, inflammatory, or immunologic milieu may determine whether lesions deposited in the pelvic

cavity implant and persist[118–121]. Alternatively, endometriosis lesions may arise from Müllerian remnants that did not properly differentiate or migrate during fetal development or from circulating blood cells that transdifferentiate into endometriosis [122–124]. Similarly, the characteristics of the local environment would influence the maintenance of these endometriotic lesions. When considering these etiologic hypotheses, it is important to recognize that endometriotic lesions are antigenically similar to eutopic endometrium but not necessarily endometrium.

Endometriosis affects 10–15% of all women of reproductive age[116] and 70% of women with chronic pelvic pain[125]. Unfortunately, for many of these women there is often a delay in diagnosis of endometriosis resulting in unnecessary suffering and reduced quality of life. In patients aged 18–45 years, the average delay is 6.7 years[126]. As most women with endometriosis report the onset of symptoms during adolescence, early referral, diagnosis, identification of disease and treatment may mitigate pain, prevent disease progression and thus preserve fertility[127–129]. Barriers to early diagnosis include the high cost of diagnosis and treatment in adolescent patients and presentation of confounding symptoms such as cyclic and acyclic pain. Thus, a non-invasive tool to diagnose endometriosis could facilitate earlier diagnosis and intervention that could ultimately improve quality of life and preserve fertility

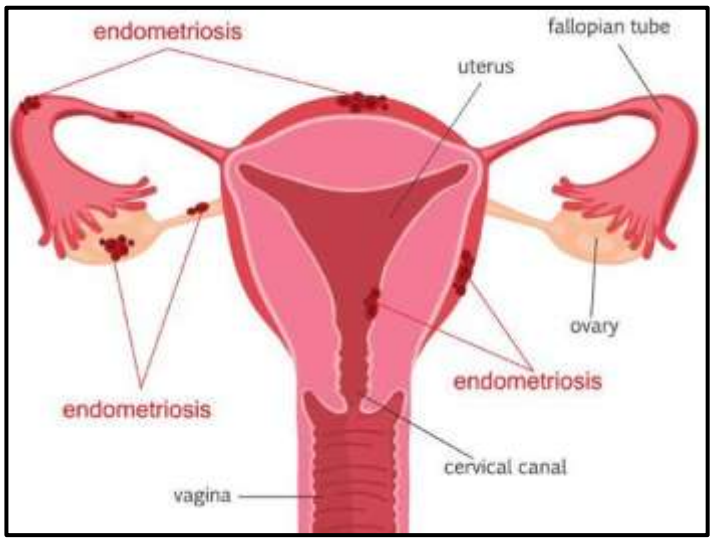

Fig no.6-*Endometriosis*

MEDICAL INDUCTION

Pulsatile gonadotropin releasing hormone:-The pulsatile release of GnRH and LH plays an important role in the development of sex function and in the normal regulation of the menstrual cycle. In 1970, Dierschke et al. first observed LH pulses in the ovariectomized monkey[130]. Later studies also showed this phenomenon in the human and rat. This LH pulse is produced by a corresponding GnRH pulse from the hypothalamus[131]. Both the frequency and amplitude of the GnRH pulse are critical for normal gonadotropin release[132]. One reason for the GnRH secretion in a pulsatile manner is to avoid the down-regulation of the GnRH receptor in the pituitary. In rhesus monkeys with hypothalamic lesions that abolish pituitary gonadotropin release, the constant infusion of exogenous GnRH fails to restore

sustained gonadotropin secration but intermittent administration of GnRH once per hour reestablishes gonadotropin secretion[133]. Westel et al. showed that intrinsic pulsatile secretory activity was seen in immortalized GnRH neurons indicating that the pulse generator is cell autonomous[134]. Furthermore, it is known that the activity of each GnRH neuron is synchronized in vivo and immortalized GnRH neurons will spontaneously synchronize in perfusion culture[135] Even though pulsatility of GnRH is recognized as a major determinant for differential gonadotropin subunit gene expression and gonadotropin secretion, very little is yet known about the signaling circuits governing GnRH action at the pituitary level. In this article, we review the current knowledge of the role of pulsatile GnRH on pituitary function and reproduction

Antiestrogen treatment: clomiphene citrate-Two or 3 days after starting clomiphene administration in the follicular phase of the ovarian cycle, the pulse frequency of LH increases, suggesting that the main action of the drug is to increase pulsatile secretion of gonadotrophin-releasing hormone (GnRH) by the hypothalamus (Sir et al., 1989).Clomiphene could also have a direct oestrogenic effect on the gonadotrophs, enhancing sensitivity to GnRH. As a consequence of the effects mentioned above, there is an increase in plasma concentration of gonadotrophins and in the number of follicles recruited. There is a resulting increase in plasma concentrations of oestradiol before ovulation and of progesterone during the luteal phase. Between 30 and 35% of patients who ovulate with clomiphene do so with a follicular rupture diameter that is larger than expected, as compared with spontaneous cycles. Moreover, clomiphene has a direct oestrogenic effect on the ovary, resembling that described for the pituitary gland. It sensitizes granulosa cells in the follicle to the action of gonadotrophins and up-regulates aromatase activity. Its effects on the cervix and endometrium are mainly anti-oestrogenic The different modulating effects (agonistic or antagonistic) shown by clomiphene on the effectors of the genital tract might be due to the different populations of α- or β-oestrogen receptors in those tissues[136] Clomiphene citrate induces ovulation in the majority of women. The ovulation rate ranges between 70% and 92%; however, the pregnancy rate is much lower. The discrepancy between the high ovulation rates and relatively low pregnancy rates may be due to the following factors:

1. Antiestrogen effects on the endometrium
2. Antiestrogen effects on the cervical mucus
3. Decrease of uterine blood flow
4. Impaired placental protein 14 synthesis
5. Subclinical pregnancy loss6.Effect on tubal transport
6. Detrimental effects on the oocytes[199]

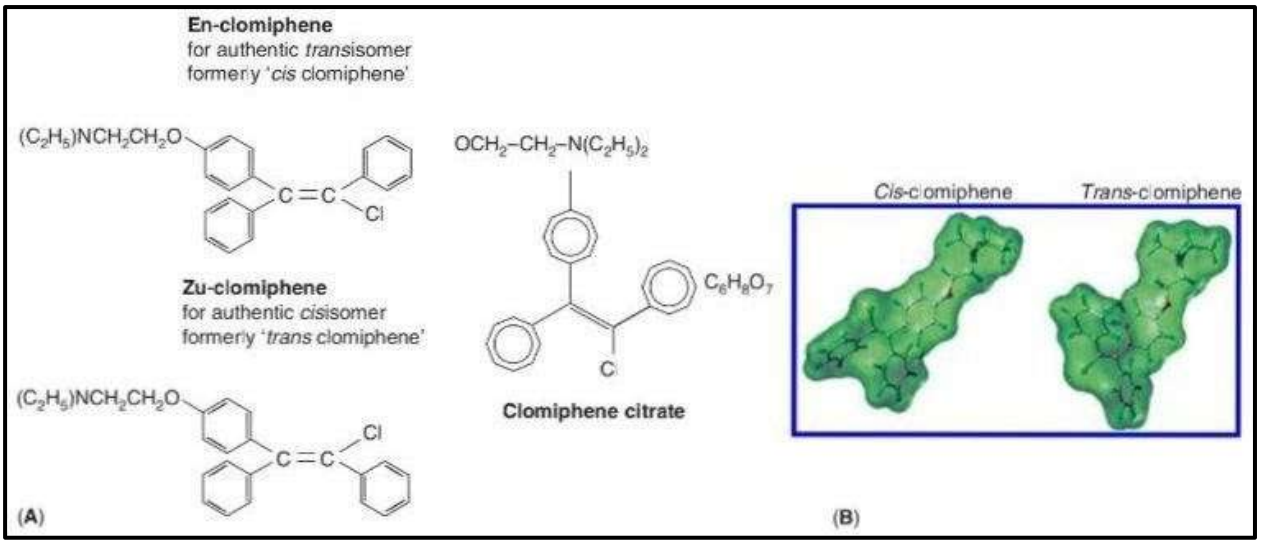

Fig.no:7*(A)** *Clomiphene citrate is available as a racemic mixture of two stereochemical isomers referred to as (cis) Zu-clomiphene or the (trans) En-clomiphene configuration, the former being signifi cantly more potent. In the preparations commercially available, the isomers are in the ratio of 38% Zu- and 62% En-clomiphene.* ***7(B) *Theisomeric models in a different confi guration.*

Gonadotropins:- Patients remaining anovulatory [CC-resistant anovulation (CRA)] and patients failing to conceive during CC treatment [CC failure to conceive (CCF)] are generally treated with exogenous gonadotropins[137]. Recently, it has become more accepted to treat CRA patients with a combination of CC and an insulin sensitizer before treatment with exogenous gonadotropins is started. Individual differences in the daily amount of FSH required to induce ongoing follicle growth and ovulation (the FSH response dose) have been suggested to be the main factor of hyper-responsiveness and severe complications during FSH ovulation induction[138]. This individual variation resulted in two different approaches in ovulation induction with gonadotropins. The 'step-up' protocol aims at slowly and prudently surpassing the FSH-threshold to reduce the chances of these complications. However, this approach might result in a prolonged treatment period and late follicular phase FSH accumulation, increasing the risk of multifollicular growth. In an attempt to overcome these problems, the 'step-down' protocol has been developed, which mimics the physiological FSH profile more closely[139]. The FSH starting dose is presumed to be the response dose; hence, dominant follicle growth is established more quickly. Thereafter, the FSH doses can be reduced slowly, resulting in the development of a single dominant follicle[139]. Frequent monitoring of the ovarian response is especially important during the step-down protocol, because the duration of FSH threshold being suppressed determines whether there will be mono-or multifollicular growth[140] . Stimulation is cancelled when multifollicular growth is apparent and more than three follicles >12mm in diameter are present.

Metformin:-This drug is used when insulin resistance is a known or suspected cause of infertility, usually in women with a diagnosis of PCOS. Metformin (Fortamet) helps improve insulin resistance, which can improve the likelihood of ovulation.Metformin is administered orally and has an absolute bioavailability of 50–60%, and gastrointestinal absorption is

apparently complete within six hours of ingestion. Metformin is rapidly distributed following absorption and does not bind to plasma proteins. No metabolites or conjugates of metformin have been identifi ed. Metformin undergoes renal excretion and has a mean plasma elimination half-life after oral administration of between four and 8.7 hours. Food decreases the extent of and slightly delays the absorption of metformin

Letrozole:-Letrozole (Femara) belongs to a class of drugs known as aromatase inhibitors and works in a similar fashion to clomiphene. Letrozole is usually used for woman younger than 39 who have PCOS.

Bromocriptine:-Bromocriptine (Cycloset, Parlodel), a dopamine agonist, might be used when ovulation problems are caused by excess production of prolactin (hyperprolactinemia) by the pituitary gland[141]

METHODS OF REPRODUCTIVE ASSISTANCE

Intrauterine insemination (IUI) and ovarian stimulation are part of the initial management of couples with infertility, known as low-complexity assisted reproductive technologies (ART). IUI requires basic supplies and simple training, constituting a low-cost technique, accessible for the majority of couples. However, its effectiveness has not been fully researched. Both, patients and the public in our country, believe IUI is very effective. Some researchers consider IUI as a trivial procedure for certain indications and recommend patients to go directly to high complexity ART[142]Others, point to it as a procedure with potential complications, specifically associated with multiple pregnancies[143]

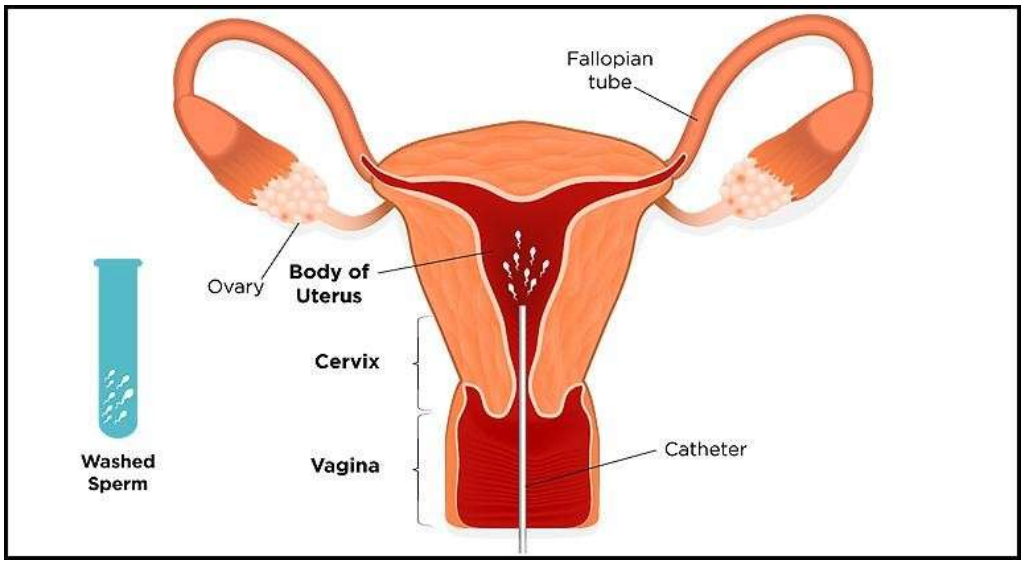

Fig no.8:-*intrauterine insemination*

Intrauterine insemination involves careful coordination before the actual procedure

Preparing the semen sample:-Your partner provides a semen sample at the doctor's office, or a vial of frozen donor sperm can be thawed and prepared. Because nonsperm elements in semen can cause reactions in the woman's body that interfere with fertilization, the sample will be washed in a way that separates the highly active, normal sperm from lower quality sperm and other elements. The likelihood

of achieving pregnancy increases by using asmall, highly concentrated sample of healthy sperm.

Monitoring for ovulation:-Because the timing of IUI is crucial, monitoring for signs of impending ovulation is critical. To do this, you might use an at-home urine ovulation predictor kit that detects when your body produces a surge or release of luteinizing hormone (LH). Or, an imaging method that lets your doctor visualize your ovaries and egg growth (transvaginal ultrasound) can be done. You also may be given an injection of human chorionic gonadotropin (HCG) or medications to make you ovulate one or more eggs at the right time.

Determining optimal timing:-Most IUIs are done a day or two after detecting ovulation. Your doctor or other care provider will have a plan spelled out for the timing of your procedure and what to expect.

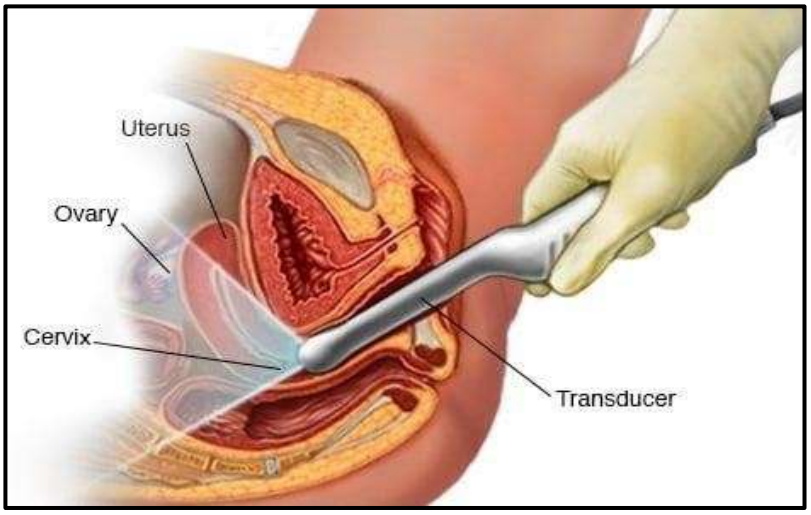

Fig no.9:-*transvaginal ultrasound*

INTRA UTERIAN INSEMINATION PROCEDURE:-

Once collected, the semen sample is then "washed" in the laboratory to concentrate the sperm and remove the seminal fluid (seminal fluid can cause severe cramping in the woman). This process can take up to 2 hours to complete.IUI is performed near the time that the woman is ovulating. The IUI procedure is relatively simple and only takes a few minutes once the semen sample is ready. The woman lies on an examining table and the clinician inserts a speculum into her vagina to see her cervix. A catheter (narrow tube) is inserted through the cervix into the uterus and the washed semen sample is slowly injected. Usually this procedure is painless, but some women have mild cramps. Some women may experience spotting for a day or two after the IUI.

IN VITRO FERTILIZATION

Techniques that involve manipulation of oocytes outside the body are termed assisted reproductive technology (ART) with in vitro fertilization (IVF) as the most common form. The term 'in vitro' means outside a living organism as oocytes mature in vivo in the ovary and embryos develop into pregnancy in the uterus, but the oocytes are fertilized in a petri dish. Robert Edwards, Ph.D., and Patrick Steptoe, MD, reported the first live birth from IVF in July 1978 in England. This achievement would later earn Dr. Edwards the Nobel Prize in Medicine in 2010.[144]

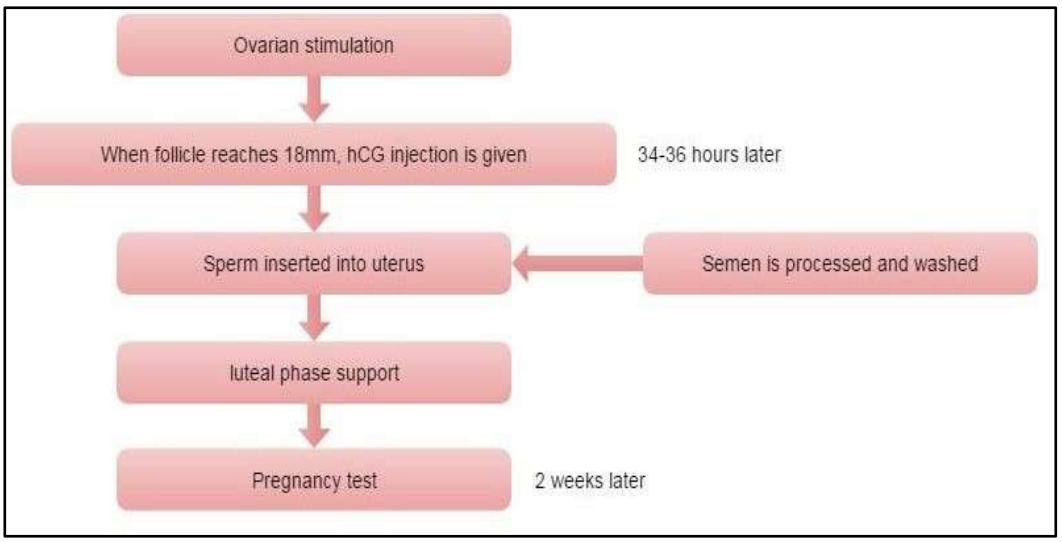

Fig.10:-*IUI procedure*

Since this major breakthrough in the treatment of infertility, the field of reproductive endocrinology/infertility (REI) has progressed rapidly, and IVF now accounts for 1.6% and 4.5% of all live births in the United States and Europe, respectively.[145] Initially developed as a way to bypass irreparable tubal disease, IVF is now widely applied for the treatment of infertility due to a variety of causes, including endometriosis, male factor, and unexplained infertility. Women who cannot use their own oocytes due to primary ovarian insufficiency (POI) or age-related decline in oocyte number can now become successfully pregnant utilizing donor oocyte IVF.

TECHNIQUE

Controlled Ovarian Stimulation:-Complex endocrine changes happen while a woman undergoes ovarian stimulation as part of IVF treatment. The two main aims of COS are: (a) to create a cohort of developing follicles; and (b) to prevent premature spontaneous ovulation.

GnRH agonists are administered intramuscularly, subcutaneously or intranasally. In the 'long protocol', the initial flare effect of the GnRH agonists is followed by desensitisation and down- regulation of the pituitary gland with an internalisation of the GnRH receptors. This protocol is associated with a higher oocyte number and clinical pregnancy rates, but there is evidence of an increase in the requirement of gonadotrophins compared to a 'short protocol[146]GnRH antagonists act by binding to the GnRH receptors and prevent endogenous release of GnRH from the pituitary gland. GnRH antagonist protocols are associated with immediate LH suppression and decreased gonadotrophin use. As a result, antagonist protocols are associated with a significant reduction in ovarian hyperstimulation syndrome (OHSS) without reducing significantly the live birth rate[147]

Oocyte Retrieval:-A needle is passed through the top of the vagina under ultrasound guidance to get to the ovary and follicles.

The fluid in the follicles is aspirated through the needle and the eggs detach from the follicle wall and are sucked out of the ovary (see video above).

The oocyte-cumulus complex is pulled from the follicle wall when we aspirate the fluid through the needle. The procedure usually takes about 10 minutes at our clinic The fluid with the eggs is passed to the IVF lab where the eggs are identified, rinsed in culture media, and placed in small drops in plastic culture dishes. The dishes with the eggs are then kept in specialized IVF incubators under carefully controlled environmental conditions.

Embryo Fertilization:-When the fertilized egg divides, it becomes an embryo. Laboratory staff will regularly check the embryo to make sure it is growing properly. Within about 5 days, a normal embryo has several cells that are actively dividing.

Couples who have a high risk of passing a genetic (hereditary) disorder to a child may consider pre-implantation genetic diagnosis (PGD). The procedure is most often done 3 to 5 days after fertilization. Laboratory scientists remove a single cell or cells from each embryo and screen the material for specific genetic disorders.

According to the American Society for Reproductive Medicine, PGD can help parents decide which embryos to implant. This decreases the chance of passing a disorder onto a child. The technique is controversial and not offered at all centers.

Embryo transfer-Embryos are placed into the woman's womb 3 to 5 days after egg retrieval and fertilization.The procedure is done in the doctor's office while the woman is awake. The doctor inserts a thin tube (catheter) containing the embryos into the woman's vagina, through the cervix, and up into the womb. If an embryo sticks to (implants) in the lining of the womb and grows, pregnancy results.More than one embryo may be placed into the womb at the same time, which can lead to twins, triplets, or more. The exact number of embryos transferred is a complex issue that depends on many factors, especially the woman's age.Unused embryos may be frozen and implanted or donated at a later date.

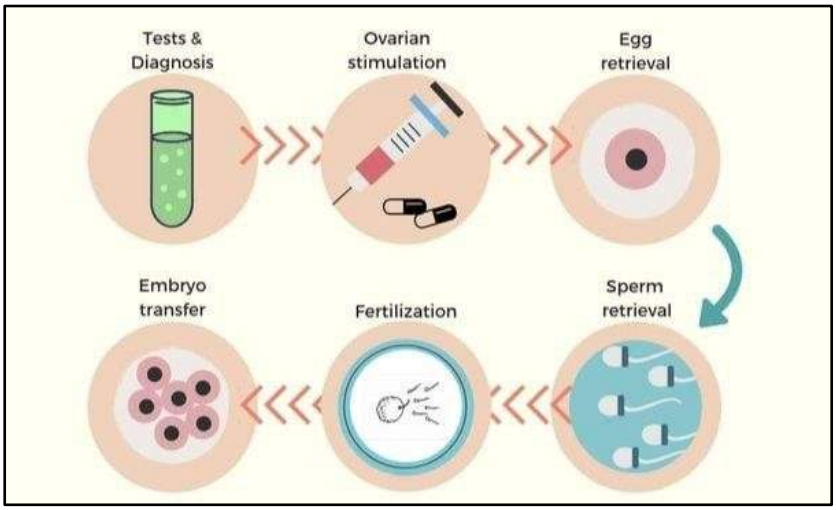

Fig no.11:-*ivf process*

INTRACYTOPLASMIC SPERM INJECTION(ICSI)

intracytoplasmic sperm injection(ICSI) was introduced in 1992 to improve fertilization in couples with male factor infertility undergoing in vitro fertilization (IVF) or in couples with fertilization failure in a prior IVF cycle without detectable abnormalities of semen parameters [148-150]. Although the diagnostic criteria used to identify male factor infertility fail to predict with perfect accuracy poor or absent fertilization in assisted reproductive technology (ART) [151–154], studies to date support the safety and efficacy of ICSI to treat various male factor conditions. The use of ICSI for patients with borderline or even normal semen parameters hasbecome more common[155 156]

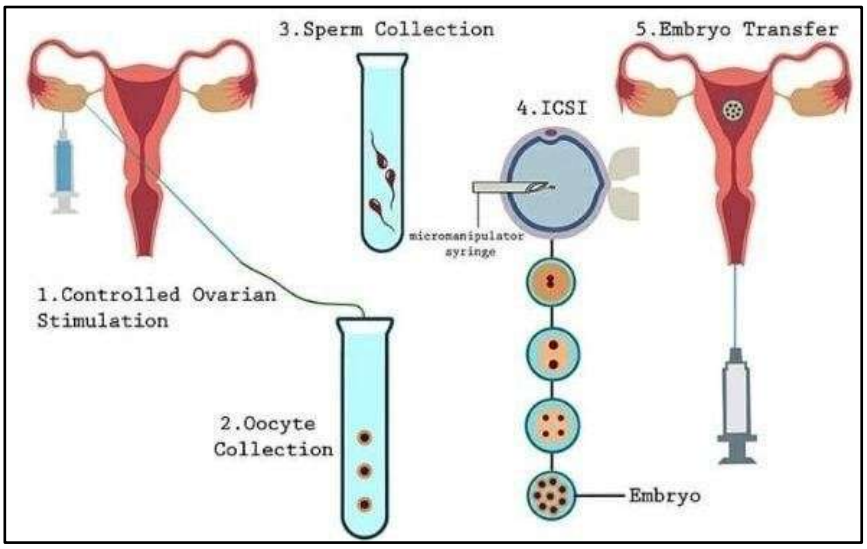

Fig no.12:-*intracytoplasmic sperm injection*

ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

When couples do not achieve pregnancy from infertility treatments or traditional ART, they may choose to use a third party–assisted ART method to get pregnant.[157]

ASSISTANCE CAN CONSIST OF:

- Sperm Donation
- Egg Donation
- Surrogates and Gestational Carriers
- Embryo Donation

SPERM DONATION:-Assisted reproductive technology (ART) has become increasingly popular over the past several decades. The advances in human sperm cryopreservation in the past 50 years and the creation of sperm banks have facilitated the increase in artificial insemination with donor sperm (AID) [158 159]. In cases of severe male infertility, the use of donor sperm is the only approach to infertility treatment[160]Sperm donation is used for the artificial insemination with a third party donor (AID). The donor becomes the biological father of the child, but he will not be considered the legal or social father. As a consequence, the child will have three parents, two fathers and a mother

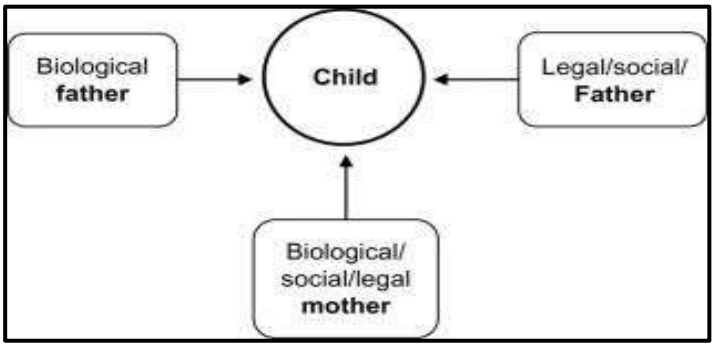

Fig no 13:-*biological and legal relation of mother and father to child*

EGG DONATION:-The procedure typically involves a doctor removing an egg or eggs from the donor, fertilizing them in a laboratory, and then transferring the resulting embryos into the recipient's uterus. Doctors do this using an implantation procedure, such as in vitro fertilization (IVF).Sometimes, specialists at the facility may freeze some or all of the embryos for later use or implantation in different women.Egg donation frequently benefits women who cannot use their own eggs for various reasons, including ovarian failure, avoiding congenital anomalies in the fetus egg donation follows the steps of IVF treatment (till egg retrieval). The main difference between IVF and egg donation is the role of donor and the recipient. In the entire procedure of egg donation India, egg donor plays a vital role to achieve success.Without nourished and healthy eggs, the step of fertilization can't take place, and this is the main reason, why donor is tested in a comprehensive route. The entire procedure of egg donation India majorly depends upon egg donor.Fertility veterans of Egg Donation Clinic in India start giving fertility medication and hormonal injections to the donor. The duration of this medication goes usually 12-14 days. Fertility medication is given to the donor so that she will come up with multiple eggs at the time of egg retrieval or egg collection phase. Once the eggs become fully matured, then with the help of hollow thin needle the eggs are picked up by the fertility veterans of Egg Donation Clinic in India.Once the eggs are taken out from the donor, the semen sample is collected from the recipient's male duo. Now eggs and sperms are kept on the culture dish for fertilization, where motile sperm self penetrates with the egg's wall and goes into the cytoplasm of the egg, resulting from cell division or fusion. Once the cells beginto divide successfully, fertilization happens.After 3-4 days of fertilization, the healthiest embryo is chosen by the experts and then transferred into the uterus of the infertile female for implantation. Now from here, recipient, that means infertile woman's role starts. Embryo transfer hardly takes 35-45 minutes for the completion and once the embryo is placed, a recipient can go back her home on the same day[161]

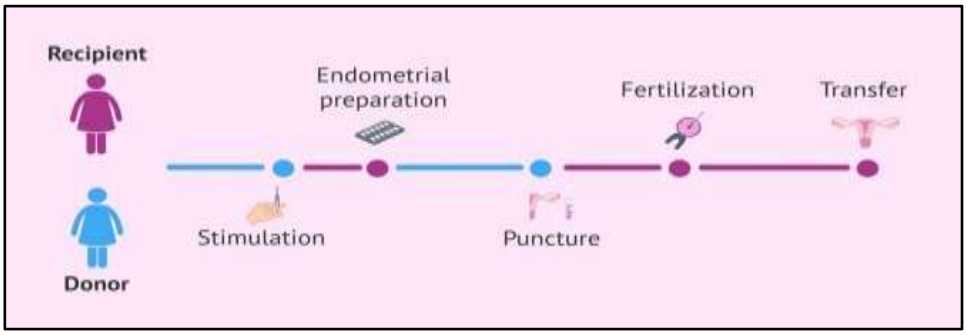

Fig no.14:-*Egg donation process*

SURROGATES AND GESTATIONAL CARRIERS:-

The word "surrogate" is rooted in Latin "Subrogare" (to substitute), which means "appointed to act in the place of." It means a substitute, especially a person deputizing for another in a specific role, so the surrogate mother implies a woman who becomes pregnant and gives birthto a child with the intention of giving away this child to another person or couple, commonly referred to as the "intended" or "commissioning" parents[162]

The surrogate embryo transfer could be fresh or frozen transfer and subject to availability of the gestational carrier. With advent of excellent vitrification techniques, surrogacy cycles have become less difficult for assisted reproductive technology (ART) clinic with good embryology laboratory and freezing facility.For a fresh surrogate transfer, the surrogate and the intended mother cycle may be synchronized with oral contraceptive pills or progesterone pills or surrogate may be put on agonist injection for flexibility of transfer dates.The surrogate is started on estrogen tablets from the 3rd day of her cycle for around 10 days. On reaching of minimum 8 mm, she is then put on progesterone supplementation for 3 days/5 days before a planned cleavage stage/blastocyst transfer, respectively

CARE OF SURROGATE

Once a pregnancy is confirmed in the gestational carrier depending on the facility of the ART clinic, she either stays in the surrogate house or at her home. The concept of surrogate house has recently caught a lot of attention for various reasons. Surrogate house is a place where surrogate stays for her entire antenatal period till the date of delivery and all her medical and pers

onal requirements are taken care of. The obstetrics care of surrogate is extensive due to the preciousness of the pregnancy. She stays under the supervision of 24-h nursing staff along with dietician, physiotherapist, counselors, and gynecologist for her medical care. It is due to this care and available facilities that intended couples have taken up more liking towards the concept of surrogate house. Although staying at surrogate house is preferred practice these days, considering the other side of coin, it could be emotionally taxing for surrogate and her entire family as she has to live away from her own child/children and family; however, during their stay at surrogate house, surrogate can go home for few weeks during pregnancy and her family members can also visit her at surrogate house. Staying at surrogate house should be optional and not compulsion for surrogate mother and she should be given a choice.

Surrogates undergo obstetrics assessment every 20 days till the date of delivery, obstetrics scans at 6–8 weeks, anomaly scan at 11–13 weeks, anomaly scan and 3D-4D at 20–22 weeks,and growth scan at 28 weeks and 34–36 weeks. Any additional scan is subject to the obstetricneed.

The intended couple is sent regular update regarding the surrogate's pregnancy in the form of her weight gain, vitals, fetal growth, and antenatal investigation reports and scans. Postdelivery, the surrogate is kept under observation for a minimum of 15 days before discharge

RISKS ASSOCIATED WITH SURROGACY

The major risk associated with surrogacy is that of obstetrics complication and multiple orderpregnancy being the most common. Recently, lot of recommendations are being made by American Society for Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology committees for single embryo transfer, but yet only 15%–20%of clinics follow single embryo transfer norms.[163] Pregnancy, birth, and the postpartum period includes complications such as preeclampsia and eclampsia, urinary tract infections, stress incontinence, and gestational diabetes and rare complications such as amniotic fluid embolism and possibility of postpartum hemorrhage, but these risks are associated with pregnancy in general and not specific to surrogacy.

Apart from physical risk, surrogacy may be reason for emotional trauma as the study by Foster (1987) states that many surrogate mothers face emotional problems after having to relinquish the child. However, a study by Jadva et al.[164] indicates that although some women experience emotional problems in handing over the baby, these feelings appeared to lessen during the weeks following the birth.[164]

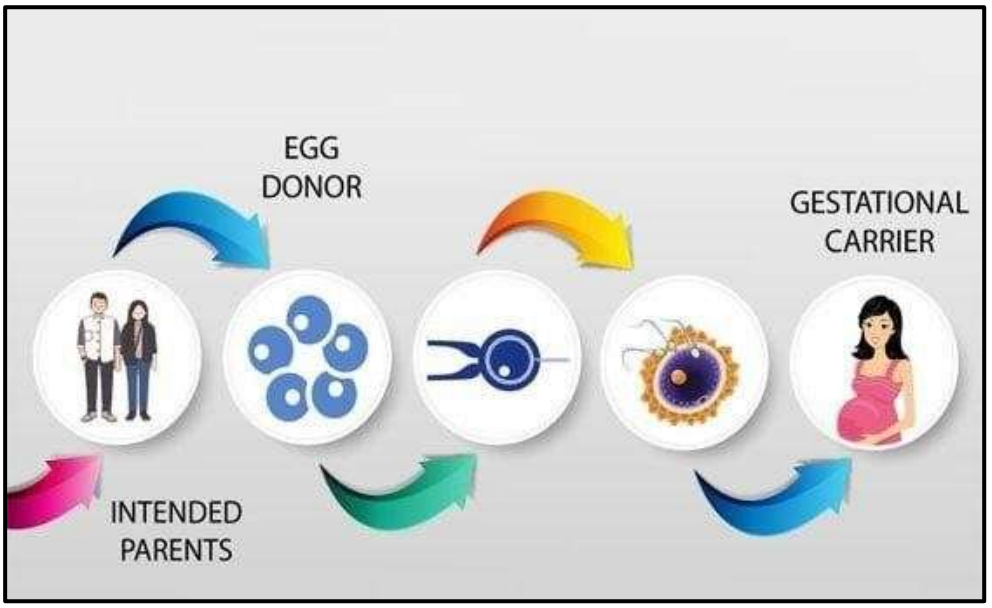

Fig no.15:-*Timeline of surrogacy process*

EMBRYO DONATION

In the current practice of in vitro fertilization (IVF), some patients may create more embryos (fertilized eggs) than they need. The extra embryos may be cryopreserved (frozen) so that they can be transferred later. However, sometimes these embryos may not be used. These patients have the option to have their embryos discarded, donated to research or donated to another woman to achieve pregnancy.[165]

MISCARRIAGE AFTER FERTILITY TREATMENT

Miscarriage is common, with a rate of between 10% and 30% of all spontaneous pregnancies[174]Infertility is also common, affecting about 15% of couples.[175] The causes of infertility are multiple and diverse yet some, for example endometriosis and the polycystic ovary syndrome (PCOS) may also affect successful implantation and pregnancy outcome. With the development of assisted conception it is now possible to overcome or circumvent many of the problems presented by the subfertile couple. The main questions arising from the various therapies available are: do they increase the rate of miscarriage or fetal malformations? by examining both the influence on miscarriage of the drugs used in ovulation induction and the effect of the different techniques employed in assisted conception. First it is important to consider special factors that pertain to miscarriage in the infertile couple.

THE INFLUENCE ON MISCARRIAGE OF THE DRUGS USED INFERTILITY THERAPY

Ovulatory failure accounts for about a fifth of cases of infertility. Over the last 30 years drug regimens of increasing complexity have evolved to induce ovulation. The drugs prescribed to anovulatory women are also used to induce multifollicular growth in women who ovulate normally. These women benefit from superovulation as the production of several oocytes increases the success of assisted conception therapies. The most commonly used preparations are the anti-estrogens (e.g. clomifene citrate), the gonadotropins and gonadotropin-releasing hormone analogs . Information about the sequelae of the use of fertility drugs therefore chiefly refers to these three groups

ANTI-ESTROGENS

The most widely prescribed anti-estrogen is clomifene citrate. Its use in ovulation induction was first reported by Greenblatt et al[176] at a time when human pituitary and menopausal urinary gonadotropins were also beginning to be extracted and standardized. In an earlyreport of pregnancy outcome in a small number of women, Greenblatt et al found theincidence of spontaneous abortion to be 22%.[177] Karow and Payne[178] reported on a heterogeneous group of 410 infertile women, in whom a pregnancy rate of 39.8% was achieved. The spontaneous abortion rate was 19%, similar to that seen in infertility patients prior to the advent of the drug. The incidence of twins was 8.6%, contributing to a premature delivery rate of 12%. There was no confirmation of an earlier theory that conception in the first treatment cycle resulted in an increased chance of miscarriage or multiple pregnancy. Also in 1968, a series of 2196 clomifene-induced pregnancies was reported,[179] in which the miscarriage rate was 17.6%, the multiple pregnancy rate 10.2%, and the incidence of congenital anomalies 2.5%. Although clomifene was found to induce ovulation in about 90% of infertile women and pregnancy in 50%, the multiple pregnancy rate was sometimes as highas 50%. In general the miscarriage rate after clomifene treatment has been reported to be between 20% and 27%, the rate of multiple pregnancy 10–15%, and the incidence of congenital abnormalities about 2–3%.[180-182] One series reported an overall miscarriage rateof 9.3%, 28.1% if conception occurred during the first cycle of treatment, and as high as 70% if conception resulted after seven cycles. It was thought that prolonged usage of clomifene might have a deleterious effect on the endometrium, causing atrophy and implantation failure. The relatively

high miscarriage rate during the first cycle of treatment that was seen in this study was postulated as being secondary to the release of "overripe" oocytes after a prolonged period of anovulation. Interpreting data from the early use of clomifene is complicated by the lack of uniformityin presenting details of maternal age and the cause of infertility. Monitoring was limited to measurement of urinary estrogens or vaginal cytology and often omitted. Pregnancy diagnosis was not as advanced as at present and so it is inappropriate to compare miscarriage data between the different series. Most women who require clomifene to induce ovulation have PCOS and are likely to have a tendency to hypersecrete LH. Clomifene achieves its action through stimulation of both follicle stimulating hormone (FSH) and LH secretion by the pituitary and women with PCOS can respond with an exaggerated release of LH and a resultant reduction in the chance of conception and increase in the risk of miscarriage.[183]

CONGENITAL ABNORMALITIES WITH CLOMIFENE CITRATE

The risk of congenital abnormalities and the physical development of infants born to mothers who have received clomifene has not been found to be different to that of the general population, yet concern was expressed about the finding of an increased frequency of chromosomal abnormalities after induced ovulation,[184] an effect that appeared to persist during the subsequent, non-stimulated cycle. Following the report of two cases of neural tube defects after clomifene therapy,[185] other isolated cases of congenital abnormalities appeared in the literature. Most have felt that factors related to infertility itself may be to blame, rather than ovulation induction, and that babies born after ovulation induction are no more at risk of being malformed than if they were conceived spontaneously.[186]Whereas there continue to be reports that suggest a more than coincidental association between ovulation induction, specifically using clomifene, and neural tube defects,[187] other reports are reassuring and suggest no evidence for this·[188] Shoham et al reviewed 3751 births after clomifene therapy and found an overall incidence of major and minor malformations of 32.5 per 1000 births,1 this figure being within the range found among the normal population.[186]

OVULATION INDUCTION WITH GONADOTROPINS

Women who do not respond to oral therapy may succeed in having ovulation induced with gonadotropin therapy. The preparations available either contain both LH and FSH or contain FSH alone. It was thought that the use of FSH alone would benefit women with the PCOS byminimizing circulating LH levels. However, these women are usually very sensitive to both forms of treatment and the use of FSH alone confers no advantage as serum concentrations ofLH are still within the normal range when human menopausal gonadotropin (hMG) is used. The amount of LH in hMG preparations is small compared with the amount secreted by the pituitary and so is rapidly diluted after administration; furthermore, with unifollicular ovulation induction the developing follicle secretes hormones that feed back to the hypothalamus and pituitary and suppress endogenous LH secretion. Studies to date indicate that miscarriage rates are similar irrespective of the gonadotropin used.

As for the actual reported miscarriage rate after gonadotropin-induced ovulation, this varies between 11.3% and 27.5%. Lunenfeld et al also reported an analysis of the abortion rates in both the first and subsequent treatment cycles and the first and subsequent pregnancies·[189]Miscarriage after fertility treatment In this study it was found that whereas theabortion rate was 28.8% in a first pregnancy, it was

only 12.8% in a second pregnancy. This figure is similar to the 13% of women who aborted after a spontaneous conception that followed a successful gonadotropininduced pregnancy. There was no difference in the abortion rates of patients who became pregnant after the first or subsequent treatment cycles. This goes against a commonly proposed theory that anovulatory women release eggs of "poor quality" in their first ovulation induction cycle.[190]Other groups have also found a higher miscarriage rate in the first gonadotropin-induced pregnancy. One series reported a reduction in miscarriage rate from 28.5% in first hMGpregnancies to 11.9% in those conceiving for a second time;[190]another series found these figures to be 33% and 9.8%, respectively.[191] In contrast to these studies, a more recent paper reported an overall spontaneous abortion rate in 350 pregnancies after first treatment cycles of 24.2%, yet a 48% abortion rate in a subsequentpregnancy in women whose first hMG pregnancy ended in a spontaneous abortion; this compared to an incidence of abortion of 6.7% if the first hMG-induced pregnancy was normal.[192]These data are in keeping with the notion that the risk of miscarriage following a natural conception is directly related to a woman's past obstetric history. We reported a retrospective analysis of all patients treated in the ovulation induction clinic at the Middlesex Hospital, London, from May 1982 to January 1993.[193] A total of 200 anovulatory patients were included in the analysis, 103 with clomifene citrate-resistant PCOS, 77 with hypogonadotropic hypogonadism (HH), and 20 with weight-related amenorrhea (WRA). There was no difference in the mean age of the three groups. The cumulative conception rates (CCR) and cumulative live birth rates (CLBR) of the three groups in the first course of therapy and after 12 cycles of treatment are illustrated in The miscarriage rates were 16.5% inPCOS patients, 22.9% in HH patients, and 32.3% in WRA patients and, while not statistically significantly different, this resulted in comparable CLBRs between the three groups. Patients with amenorrhea secondary to weight loss respond well to ovulation induction therapy with normal or supranormal cumulative conception rates.[194-196]The miscarriage rate in these patients, however, was 32% and this resulted in a cumulative live birth rate that was similar to that of patients with PCOS and HH. Furthermore, women who conceived spontaneously and had a body mass index (BMI) of less than 19.1 kg/m2 had twice the risk of delivering a low birthweight infant compared with women of normal weight ($p < 0.005$)[197] and they also had a higher incidence of preterm deliveries ($p < 0.01$). We have also reported previously that patients with WRA who conceive after treatment with pulsatile gonadotropin releasing hormone (GnRH) are more likely to deliver lighter babies than of normal weight ($p < 0.001$).[198] Our current approach is therefore to encourage weight gain and not to induce ovulation in women with a BMI of less than 19.5 kg/m2.

VIRAL DISEASE AND ASSISTED REPRODUCTIVE TECHNIQUES

HIV-positive women need to address a number of issues when planning to conceive. The HIV physician is best placed to provide pre-conceptual advice on HAART, self-insemination methods, and measures that will need to be put in place during pregnancy to reduce MTCT risk, as well as advising on any long-term health issues related to viral illness, which might be a contraindication to pregnancy. Relatively few antiretroviral medications (e.g., Efavirenz) are contraindicated during pregnancy due to potential teratogenic effects on the fetus[200]but it should be borne in mind that the evidence on the safety of most antiretrovirals duringpregnancy is still incomplete. Folic acid should be given antenatally to minimize the risk of neural tube defects as antiretrovirals are known to have a folate antagonist

effect.There is increasing evidence to suggest that HIV-positive women have reduced fertility[201-202]There are no data to suggest an increased incidence of cycle irregularity in positive women, but studies on positive women undergoing IVF suggest that HIV-positive women have lower IVF success rates than HIV-negative controls and require higher doses of gonadotropin stimulation [203-205]. IVF outcome does not appear to be affected in HIV-positive women undergoing ovum donation, pointing toward an effect of HIV and/or immunosuppression on ovarian response and ovarian reserve rather than on implantation [206]. Retrospective data from Sub-Saharan Africa [207-208] and prospective data from the United Kingdom indicate an increased incidence of tubal infertility in positive women [201-202] of at least twice that of HIV-negative controls. On the basis of increased risk of low ovarian reserve and increased tubal infertility, HIV-positive women trying to conceive should be referred sooner rather than later for fertility evaluation and certainly if they have not conceived within six to 12 months of self-insemination. Referral should be early if there is a history of pelvic infl ammatory disease or in women over 35 years of age to assess tubal function and ovarian reserve.

REDUCING RISK DURING ART IN POSITIVE WOMEN

Minimizing risk in HIV-positive women lies primarily in reducing MTCT. There are no additional specific measures that can be taken during fertility treatment to further reduce this risk. There has been concern that invasive procedures such as IVF could increase the chances of the embryo becoming infected. The number of women treated so far is small and prospective data limited. A study of 10 women undergoing IVF or ICSI demonstrated that HIV was detectable in follicular fluid removed during vaginal egg collection in all patients with a detectable serum VL and in 60% of those with an undetectable serum VL [209]. This raises the theoretical possibility of the embryo becoming infected at the laboratory stage of ART even before embryo transfer, although the likelihood is that viral infection would lead to embryo death. Longitudinal studies are needed to monitor outcome of ART cyclesin positive women to identify if any such risk increases the chance of MTCT.Management of HIV- positive women should involve a multidisciplinary team comprising HIV physician, fertility specialist, and obstetrician with a special interest in HIV. The couple should have a sexual health screen for the same reasons as couples undergoing sperm washing. Likewise they should have a fertility screen in a similar way to HIV-negative couples (early follicular phase endocrine profile and pelvic scan, mid-luteal progesterone, and test of tubal function) and the male partner should have a semen analysis[210]. Couples concordant for HIV should beadvised to conceive using sperm washing to prevent the risk of superinfection.

MANAGING PATIENTS WITH HEPATITIS

Hepatitis B (HBV) and Hepatitis C (HCV) viruses are major causes of chronic hepatitis, cirrhosis, and hepatocellular cancer. In cases where fertility treatment is required and one or both partners are HBV or HCV positive, samples should be treated as infectious and handled according to clinical and laboratory guidelines set out below.In the case of hepatitis B, vertical transmission accounts for over 40% of cases of chronic infection and the sexual transmission risk is twofold higher than for HIV and sixfold higher than for HCV. Unlike HIV or HCV, an effective vaccine is available for HBV and all healthcare workers and partners of known infected individuals should be vaccinated. Uninfected women should

only consider conception post-vaccination. Sperm washing should not be required as a means of reducing horizontal transmission risk unless a woman fails to develop adequate immunity through vaccination. If ART is required in HBV positive couples for fertility issues, similar clinical protocols to non-infected patients should be used. The Dutch view, as with HIV samples, is that if ART is required in a couple where the male is HBV positive, ICSI should be avoided due to the risk of introducing HBV into the oocyte [211]. There are no substantive data to support this view.Vertical transmission risk for an HBV positive woman during pregnancy is 2–15% if she is only HBsAgpositive, and 80–90% if she is also positive for HBeAg or is HBV DNA positive. Infection in the neonate can be minimized if immunoprophylaxis (HBV vaccination and one dose of Hepatitis B immunoglobulins) is given within 24 hours of birth with a further dose at one and six months. Breastfeeding does not appear to play a role in perinatal transmission.HCV infection is primarily transmitted by parenteral spread (blood products, shared needles, needlestick injury). Sexual transmission risk is very low unless the patient is co-infected with HIV[212]. There is no vaccine for HCV and sperm washing should be offered to HCVdiscordant couples where the male is infected. The principles of treatment are the same as in HIV-infected discordant couples[213,214] and sperm washing is as effective in reducing transmission risk to the female partner as in discordant cases of HIV. Patients who have expressed a desire to become parents, but who are in a high-risk group for infertility based on their age, should have a basic fertility evaluation and be referred to a specialist in a timely manner in order to maximize their fertility potentiaInfertility may work as a painful emotional experience[166 167]. It can cause a lot of psychological issues including stress, anxiety, depression, diminished self-esteem, declined sexual satisfaction, and reduced quality of life[168,169,170]. The resulted psychosocial issues affect the female gender adversely more than her spouse [171], especially in societies where there are prejudices against women[169 170 172]. As such, an infertile woman may show a relatively high level of frustration and anger which affect her relationship with family, friends and even her spouse. Likewise, infertile women are more likely to develop mental illnesses, marital dissatisfaction, and impaired quality of life compared to the individuals of fertile group[169, 172 173].

CONCLUSION

Many women have reported finding treatment for infertility stressful and a cause of relationship difficulties with their partners. The fear of failure was the most important barrier to treatment. The psychological support is fundamental to limit the possibility to drop-out from infertility treatment and reduce the distress level which is strongly associated with lower pregnancy rates. In addition some medications used in the treatment have several side effectswhich may be an important risk factor for the development of depression Many infertile women tend to cope with immense stress and social stigma behind their condition, which can lead to considerable mental distress.The long-term stress involved in attempting to conceive achild and the social pressures behind giving birth can lead to emotional distress that may manifest as mental disease.Women with infertility might deal with psychological stressors such as denial, anger, grief, guilt, and depression.There can be considerable social shaming that can lead to intense feelings of sadness and frustration that potentially contribute to depression and suicide.The implications behind infertility bear huge consequences for the mental health of an infertile woman because of the social pressures and personal grief behind being unable to bear children

ACKNOWLEDGEMENT

I express heartfelt gratitude to Dr. Rajesh Oswal and Prof Diksha Gupta, of Genba Sopanrao Moze College of Pharmacy , Wagholi for their full guidance and also for providing digital library.

REFERENCES

1. GUTTMACHER AF. Factors affecting normal expectancy of conception. J Am Med Assoc. 1956 Jun 30;161(9):855-60.
2. Infertility Workup for the Women's Health Specialist: ACOG Committee Opinion, Number 781. Obstet Gynecol. 2019 Jun;133(6):e377-e384.
3. Valoriani VFL, Lari D, Miccinesi G, Vaiani S, Vanni C, Coccia ME, et al. Differences in psychophysical well-being and signs of depression in couples undergoing their first consultation for assisted reproduction technology (ART): an Italian pilot study. Europ J Obstet Gynecol Reprod Biol. 2016;197:179–185.
4. Veltman-Verhulst S. Emotional distress is a common risk in women with polycystic ovarian syndrome: a systematic review and meta-analysis of 28 studies. Hum Reprod Update. 2012;18(6):638–651. doi: 10.1093/humupd/dms029.
5. Gokhan A. Level of anxiety, depression, self esteem, social anxiety, and quality of life among women with polycystic ovarian syndrome. Sci World J. 2013;2013:7.
6. Jedel E. Anxiety and depression symptoms in women with polycystic ovarian syndrome compared with controls matched for body mass index. Hum Reprod. 2009;25(2):450–
7. 456. doi: 10.1093/humrep/dep384.
8. Baldur-Felskov P. disorders in women with fertility problems: results from a large Danish register-based cohort study. Hum Reprod. 2013;28(3):683–690. doi: 10.1093/humrep/des422.
9. Wendy Kuohung, Mark, D. Hornstein, Robert, L. Barbieri, Vanessa, A. Barss. (2009): Evaluation of female Infertility; 2009, version 17.3
10. JLH Evers, JA Collins. Lancet, 2003, 361: 1849-52
11. SO Ogunniyi, OO Makinde, and FO Dare. African Journal of Medicine and Medical Science, 1999, 19(4): 271 – 274..
12. OA Esimai, EO Orji, AR Lasisi. Niger J Med., 2002, 11:70-72
13. MC Inhorn. Social Science and Medicine, 1994a, 39, 4:459-461.
14. OO Adetoro, and EW Ebomoyi. African Journal of Medicine and Medical Sciences, 1991, 20,1:23-7.
15. Barton D. The Natural Guide to Infertility and Depression. 2014. Natural Fertility Info.com, 2014
16. Bartholow L. Stress, Trauma & Depression Talk. Portland Plant Medicine Gathering. 2012.
17. Akker O. Coping, Quality of Life and Psychological Symptoms in Three Groups of Sub- Fertile Women. Patient Educ Couns. 2005;57:183–189. doi: 10.1016/j.pec.2004.05.012. http://www.ncbi.nlm.nih.gov/pubmed/15911191.
18. Chachamovich J, Chachamovich E, Zachia S, Knauth D,Passos E. What Variables Predict Generic and HealthRelated Quality of Life In A Sample of Brazilian Women Experiencing Infertility? Hum Reprod. 2007;22:1946–1952. doi: 10.1093/humrep/dem080. http://www.ncbi.nlm.nih.gov/

pubmed/17428881.

19. Wischmann T, Stammer H, Scherg H, Gerhard I, Verres R. Psychosocial Characteristics of Infertile Couples: A Study by the Heidelberg Fertility Consultation Service. Hum Reprod. 2001;16:1753–1761. doi: 10.1093/humrep/16.8.1753.
20. Nelson C, Naughton C, Ohebshalom M, Mulhall J.Sexual Function and Quality Oo Life in The Male Partner of Infertile Couples: Prevalence and Correlates of Dysfunction. J Urol. 2008; 179:1056–1059. doi: 10.1016/j.juro.2007.10.069.
21. Fassino S, Piero A, Boggio S, Piccioni V, Garzaro L.Anxiety, Depression and Anger Suppression in Infertile Couples: A Controlled Study. Hum Reprod. 2002;17:2986–2994. doi: 10.1093/humrep/17.11.2986.
22. Inhorn M. Global Infertility and The Globalization of New Reproductive Technologies: Illustrations from Egypt. Soc Sci Med. 2003;56:1837–1851. doi: 10.1016/S0277- 9536(02)00208-3.
23. Orji E, Kuti O, and Fasubaa O. Impact of Infertility on Marital Life in Nigeria. Int J Gynaecol Obstet. 2002;79:61–62. doi: 10.1016/S0020-7292(02)00180-7.
24. Paolo T. Clinical Management of Male Infertility: Prevalence, Defifi- nition, and Classifification of Infertility. Springer; 2015; 5-11.
25. McKinney E, James S, Murray S, et al. Maternal Child Nursing. Saunders: Elsevier, Canada. 2009; 202.
26. Wheaton B. The twain meet: distress, disorder and the continuing conundrum of categories (comment on Horwitz). Health. 2007;11: 303-319. http://dx.doi.org/10.1177/1363459307077545
27. Mirowsky J, CE. Ross. Selecting outcomes for the sociology of mental health: Issues of measurements and dimensionality. J Heal Soci Behavi. 2002; 43: 152-170. PMid:12096697 http://dx.doi.org/10.2307/3090194
28. Hamilton-Fairley D, Taylor A. ABC of subfertility: Anovulation. BMJ. 2006;327:546– 549
29. Sam S, Dunaif A. Polycystic ovary syndrome: syndrome XX? Trends Endocrinol Metab. 2003;14:365–370
30. Panidis D, Farmakiotis D, Kourtis A, Rousso D. Resistin as a local factor in polycystic ovary syndrome: a novel view of "adipo(cyto)kines"? Hum Reprod. 2004;19:1681–1682.
31. Panidis D, Balaris C, Farmakiotis D, et al. Serum parathyroid hormone concentrations are increased in women with polycystic ovary syndrome. Clin Chem. 2005;51:1691– 1697
32. Panidis D, Farmakiotis D, Koliakos G, et al. Comparative study of plasma ghrelin levels in women with polycystic ovary syndrome, in hyperandrogenic women and in normal controls. Hum Reprod. 2005;20:2127–2132
33. Panidis D, Farmakiotis D, Rousso D, Katsikis I, Kourtis A, Diamanti-Kandarakis E. Serum luteinizing hormone levels are markedly increased and significantly correlated with Delta 4-androstendione levels in lean women with polycystic ovary syndrome. Fertil Steril. 2005;84:538–540
34. Hughesdon PE. Morphology and morphogenesis of the Stein-Leventhal ovary and of so- called 'hyperthecosis'. Obstet Gynecol Surg. 1982;37:59–77
35. Webber LJ, Stubbs S, Stark J, et al. Formation and early development of follicles in the polycystic ovary. Lancet. 2003;362:1017–1021

36. Jonard S, Dewailly D. The follicular excess in polycystic ovaries, due to intra-ovarian hyperandrogenism, may be the main culprit for the follicular arrest. Hum Reprod Update. 2004;10:107–117
37. Ehrmann D. Polycystic ovary syndrome. N Eng J Med. 2005;352:1223–1236
38. Azziz R, Ehrmann D, Legro RS, Whitcomb RW, Hanley R, Fereshetian AG. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. J Clin Endocrinol Metab. 2001;86:1626–1632
39. Panidis D, Farmakiotis D, Rousso D, et al. Obesity, weight loss and the polycystic ovarysyndrome: effect of treatment with diet and orlistat for 24 weeks on insulin resistance and androgen levels. Am J Clin Nutr. 2006:in–press.
40. Greenblatt RB, Bafriield WE, Jungck EC, Ray AW. Induction of ovulation with MRL/41. Preliminary report. J Am Med Assoc. 1961;178:101–104
41. Homburg R, Insler V. Ovulation induction in perspective. Hum Reprod Update. 2002;8:449–462
42. Hoek A, Schoemaker J, Drexhage JA. Premature ovarian failure and ovarian autoimmunity. End Rew. 1997;1:163–169
43. Starup J, Sele V. Premature ovarian failure. Acta Obstet Gynecol Scand. 1973;52:259– 268
44. Alper MM, Garner PR. Premature ovarian failure: its relationship to autoimmune diseas. Obstet Gynecol. 1985;66:27–30
45. Philip J, Sele V, Trolle D. Secondary hypergonadotrophic amenorrhea. Acta Obstet Gynecol Scand. 1966;45:142–147.
46. Sele V, Starup J. Premature ovarian failure. Acta Obstet Gynecol Scand. 1971;50:24
47. Zarate A, Karchmer S, Gomez E, Castelazo-Ayala L. Premature menopause. A clinical, histologic, and cytogenetic study. Am J Obstet Gynecol. 1970;106:110–114
48. Turner HH. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology 1938; 28:566
49. Z Kinderheilk. Über typische Kombinationsbilder multipler Abartungen. Eur J Pediatr 1930; 49:271
50. Bondy CA, Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab 2007; 92:10.
51. Cockwell A, MacKenzie M, Youings S, Jacobs P. A cytogenetic and molecular study of a series of 45,X fetuses and their parents. J Med Genet 1991; 28:151.
52. Nielsen J, Wohlert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Hum Genet 1991; 87:81.
53. Gunther DF, Eugster E, Zagar AJ, et al. Ascertainment bias in Turner syndrome: new insights from girls who were diagnosed incidentally in prenatal life. Pediatrics 2004; 114:640.
54. Baena N, De Vigan C, Cariati E, et al. Turner syndrome: evaluation of prenatal diagnosis in 19 European registries. Am J Med Genet A 2004; 129A:16
55. Iyer NP, Tucker DF, Roberts SH, et al. Outcome of fetuses with Turner syndrome: a 10- year congenital anomaly register based study. J Matern Fetal Neonatal Med 2012; 25:68.
56. Hassold T, Pettay D, Robinson A, Uchida I. Molecular studies of parental origin and mosaicism in 45,X conceptuses. Hum Genet 1992; 89:647.

57. Romero ST, Geiersbach KB, Paxton CN, et al. Differentiation of genetic abnormalities in early pregnancy loss. Ultrasound Obstet Gynecol 2015; 45:89.
58. Levy B, Sigurjonsson S, Pettersen B, et al. Genomic imbalance in products of conception: single-nucleotide polymorphism chromosomal microarray analysis. Obstet Gynecol 2014;124:202.
59. Azmanov DN, Milachich TV, Zaharieva BM, et al. Profile of chromosomal aberrations in different gestational age spontaneous abortions detected by comparative genomic hybridization. Eur J Obstet Gynecol Reprod Biol 2007; 131:127.
60. Eiben B, Bartels I, Bähr-Porsch S, et al. Cytogenetic analysis of 750 spontaneous abortions with the direct-preparation method of chorionic villi and its implications for studying genetic causes of pregnancy wastage. Am J Hum Genet 1990; 47:656.
61. Chernausek SD, Attie KM, Cara JF, Rosenfeld RG, Frane J. Growth hormone therapy of Turner syndrome: the impact of age of estrogen replacement on final height. Genentech, Inc., Collaborative Study Group. The Journal of clinical endocrinology and metabolism. 2000;85(7):2439-45.
62. Attar AF, Mousavi P, Javadnoori M, Malehi AS. The Relationship between Gynecologic Age and Maternal/Fetal Weight Gain in Adolescent Pregnancies. J. Biochem. Tech. 2019;10(3):50-5.
63. Bondy CA, Bakalov VK. Investigation of cardiac status and bone mineral density in Turner syndrome. Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society. 2006;16 Suppl A:S103-8.
64. Hindmarsh PC, Dattani MT. Use of growth hormone in children. Nature clinical practice Endocrinology & metabolism. 2006;2(5):260-8
65. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. International Journal of Women's Health. 2011;3:25. DOI: 10.2147/IJWH.S11304
66. Legro RS, Dodson WC, Kunselman AR, et al. Benefit of delayed fertility therapy with preconception weight loss over immediate therapy in obese women with PCOS. The Journal of Clinical Endocrinology and Metabolism. 2016;101:2658-2666. DOI: 10.1210/jc.2016-1659
67. Biller BM, Luciano A, Crosignani PG, Molitch M, olove D, Rebear R, et al. Guidelines for the diagnosis and treatment of hyperprolactinemia. J Reprod Med.1999;44(Supp112):1075-84
68. Vilar L , Naves LA , Gadelha MR . Pitfalls in the diagnosis of hyperprolactinemia . Arq Bras Endocrinol Metab . 2003 ; 47 (4): 347 - 57
69. Vilar L , Naves LA . Avaliação diagnóstica da hiperprolactinemia . In: Vilar L , et al , editors. Endocrinologia Clínica . 5a ed . Rio de Janeiro : Guanabara Koogan ; 2013 . p.39 - 49
70. Huang W , Molitch M . Evaluation and management of galactorrhea . Am Fam Physician . 2012 ; 85 (11): 1073 - 80 .
71. Vilar L , Czepielewsk MA , Naves LA , Rollin GA , Casulari LA , Coelho CE . Substantial shrinkage of adenomas cosecreting growth hormone and prolactin with use ofcabergoline therapy . Endocr Pract . 2007 ; 13 (4): 396 - 402.
72. Talwar PP. Prevalence of infertility in different population groups in India and its determinants 1986 in establishing an ART in low resource setting‐page 55. In: Handbook
73. of Managing Infertility. 1st edn. New Delhi; India: Jaypee Brothers Medical Publishers;2012
74. Unisa S. Childlessness in Andhra Pradesh, India. Reprod Health Matters. 1999;7:54‐64
75. Raber W, Nowotny P, Vytiska‐Binstorfer E, Vierhapper H. Thyroxine treatment modified in

infertile women according to thyroxine‐releasing hormone testing: 5 year follow‐up of 283 women referred after exclusion of absolute causes of infertility. Hum Reprod. 2003;18:707‐14
76. Trokoudes KM, Skordis N, Picolos MK. Infertility and thyroid disorders. Curr Opin Obstet Gynecol. 2006;18(4):446-51.
77. Davis LB, Lathi RB, Dahan MH. The effect of infertility medication on thyroid function in hypothyroid women who conceive. Thyroid. 2007;17:773–7
78. Dajan CM, Saravanan P, Bayly G. Whose normal thyroid function is better –yours or mine? Lancet. 2002;360:353–4
79. Harvard Medical School. Female infertility. 2009
80. Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am. 2012;39(4):535-549. doi:10.1016/j.ogc.2012.10.002
81. Magdy N, El-Bahrawy M. Fallopian tube: Its role in infertility and gynecological oncology. World J Obstet Gynecol. 2014;3(2):35-41. doi:10.5317/wjog.v3.i2.35
82. Rebar RW. Problems With the Fallopian Tubes and Abnormalities in the Pelvis. Merck Manual Consumer Version. Updated February 2019
83. American Society for Reproductive Medicine. Intrauterine Adhesions: What Are They? 2015.
84. Brigham and Women's Hospital. Endometriosis and Fertility.
85. Shah SM, Towobola OA, Masihleho M. Diagnosis offallopian tube patency. East Afr Med J. 2005Sep;82(9):457-62
86. Watson A, Vandekerckhove P, Lilford R, et al. A meta-analysis of the therapeutic role of oil soluble contrastmedia at hysterosalpingography: a surprising result? FertilSteril 1994;61:470–77
87. Jenkins C, Williams S, Schmidt G. Salpingitis isthimicnodosa: a review of the literature, discussion of clinicalsignificance, and consideration of patient management.Fertil Steril 1993; 60:599–607
88. De Witt W, Gowrising CJ, Kuik DJ, et al. Onlyhydrosalpinges visible on ultrasound are associated withreduced implantation and pregnancy rates after IVF. HumReprod 1997; 12:170.
89. Donnez J, Casanas-Roux F. Prognostic factors of fimbrialmicrosurgery. Fertil Steril 1986; 46:1089–92.
90. Young PE, Egan JE, Barlow J, Mulligan WE.Reconstructive surgery for infertility at the BostonHospital for Women. Am J Obstet Gynecol 1970;108:1092–97
91. Novy M, Thurmond AS, Patton P, Uchida BT, Rosch J.Diagnosis of cornual obstruction by transcervical fallopiantube cannulation. Fertil Steril 1988; 50:434–40
92. Honore GM, Holden AE, Schenken RS. Pathophysiologyand management of proximal tubal blockage. Fertil Steril1999; 71:785–95
93. Thurmond AS, Novy M, Rosch J. Terbutaline in diagnosisof interstitial fallopian tube obstruction. Invest Radiol1988; 23:209–10
94. William D. A new hysterographic approach to theevaluation of tubal spasm and spasmolytic agents. FertilSteril 1983; 39:105–7
95. Winfield AC, Pittaway D, Maxson W, et al. Apparentcornual occlusion in hysterosalpingography: reversal byglucagon. Am J Roentgenol 1982; 139:525–27.
96. Cooper JM, Rigberg HS, Houck R, Aiken M. Incidence,significance, and remission of tubal spasm during attemptedhysteroscopic tubal sterilization. J Reprod Med 1985;30:39–42

97. Hurd WW, Wyckoff ET, Reynolds DB, et al. Patientrotation and resolution of unilateral cornual obstructionduring hysterosalpingography. Obstet Gynecol 2003;101:1275–78
98. -Bélisle S, Collins JA, Burrows EA, Willan AR. The value of laparoscopy amonginfertile women with tubal patency. J Soc Obstet Gynaecol Can. 1996;18:326–336
99. Ngowa JD, Kasia JM, Georges NT, Nkongo V, Sone C, Fongang E. Comparison of hysterosalpingograms with laparoscopy in the diagnostic of tubal factor of female infertility at the Yaoundé General Hospital, Cameroon. Pan Afr Med J. 2015;22:264–264. doi: 10.11604/pamj.2015.22.264.8028
100. Fayez JA, Mutie G, Schneider PJ. The diagnostic value of hysterosalpingography and laparoscopy in infertility investigation. Int J Fertil. 1988;33:98–101.
101. Simon A, Laufer N. Unexplained infertility: A reappraisal. Ass Reprod Rev. 1993;3:26–36
102. McDougall AN. Laparoscopy in the investigation of infertility. Scott Med J.
103. 1976;20:209–216. doi: 10.1177/003693307502000506.
104. Karande VC, Pratt DE, Rao R, Balin M, Gleicher N. Elevated tubal perfusion pressures during selective salpingography are highly suggestive of tubal endometriosis. Fertil Steril.1995;64:1070–1073. doi: 10.1016/S0015-0282(16)57962-X
105. Yu X, Cai H, Zheng X, Feng J, Guan J. Tubal restorative surgery for hydrosalpinges in women due to in vitro fertilization. Arch Gynecol Obstet. 2018;297:1169–1173. doi: 10.1007/s00404-018-4695-7
106. Chan YY, Jayaprakasan K, Tan A, Thornton JG, Coomarasamy A, Raine-Fenning NJ. Reproductive outcomes in women with congenital uterine anomalies: a systematic review. Ultrasound in Obstetrics & Gynecology. 2011; 38: 371-382
107. Tomaževič T, Ban-Frangež H, Ribič-Pucelj M, Premru-Sršen T, Verdenik I. Small uterine septum is an important risk variable for preterm birth. European Journal ofObstetrics & Gynecology and Reproductive Biology. 2007; 135: 154-157
108. Acién P. Reproductive performance of women with uterine malformations. Human Reproduction. 1993; 8: 122-126
109. Rock JA, Schlaff WD. The obstetric consequences of uterovaginal anomalies. Fertility and Sterility. 1985; 43: 681-692.
110. Rackow BW. Congenital uterine anomalies. Ultrasound Imaging in Reproductive Medicine. 2019; 12: 121-135
111. Lovelace D. Congenital uterine anomalies and uterine rupture. Journal of Midwifery & Women's Health. 2016; 61: 501-506
112. Society TAF. The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions. Fertility and Sterility. 1988; 49: 944-955
113. Troiano RN, McCarthy SM. Mullerian duct anomalies: imaging and clinical issues. Radiology. 2004; 233: 19-30
114. Iverson RE, DeCherney AH, Laufer MR. Clinical manifestations and diagnosis of congenital anomalies of the uterus. UpToDate. 2015. (Accessed in April).
115. Mazouni C, Girard G, Deter R, Haumonte J, Blanc B, Bretelle F. Diagnosis of Müllerian anomalies in adults: evaluation of practice. Fertility and Sterility. 2008; 89: 219-222
116. Chan YY, Jayaprakasan K, Zamora J, Thornton JG, Raine-Fenning N, Coomarasamy A. The

prevalence of congenital uterine anomalies in unselected and high-risk populations: a systematic review. Human Reproduction Update. 2011; 17: 761-771

117. Marcal, L.; Nothaft, M.A.; Coelho, F.; Volpato, R.; Iyer, R. Mullerian duct anomalies: MR imaging. Abdom. Imaging 2011, 36, 756–764
118. Jayaprakasan, K.; Chan, Y.Y.; Sur, S.; Deb, S.; Clewes, J.S.; Raine-Fenning, N.J. Prevalence of uterine anomalies and their impact on early pregnancy in women conceiving after assisted reproduction treatment. Ultrasound Obstet. Gynecol. 2011, 37, 727–732
119. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364(9447):1789–99
120. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril. 1997;68(4):585–96
121. Farland LV, Shah DK, Kvaskoff M, Zondervan K, Missmer SA. Epidemiological and Clinical Risk Factors for Endometriosis. In: D'Hooghe T, editor. Biomarkers for Endometriosis. Springer Science; New York: 2015
122. Anaf V, Simon P, El Nakadi I, Fayt I, Simonart T, Buxant F, et al. Hyperalgesia, nerve infiltration and nerve growth factor expression in deep adenomyotic nodules, peritoneal and ovarian endometriosis. Hum Reprod. 2002;17:1895–900
123. Wang G, Tokushige N, Markham R, Fraser IS. Rich innervation of deep infiltrating endometriosis. Hum Reprod. 2009;24:827–34
124. Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. Science. 2005;308:1587–9
125. Bulun SE. Endometriosis. N Engl J Med. 2009 Jan 15;360(3):268–79. doi: 10.1056/NEJMra0804690
126. Ferguson BR, Bennington JL, Haber SL. Histochemistry of mucosubstances and histology of mixed mullerian pelvic lymph node glandular inclusions: evidence for histogenesis by mullerian metaplasia of coelomic epithelium. Obstet Gynecol. 1969;33:617–25
127. Sampson JA. Metastatic or embolic endometriosis due to menstrual dissemination of endometrial tissue into the venous circulation. Am J Pathol
128. Carter JE. Combined hysteroscopic and laparoscopic findings in patients with chronic pelvic pain. J Am Assoc Gynecol Laparosc. 1994;2:43–47
129. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, Jenkinson C, Kennedy SH, Zondervan KT. World Endometriosis Research Foundation Global Study of Women's Health consortium. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril. 2011 Aug;96(2):366–373.e8. doi: 10.1016/j.fertnstert.2011.05.090. Epub 2011 Jun
130. 30. This multi-site study reported that endometriosis is highly debilitating disease which affects socioeconomic quality and work life of patients. This is one of the articles which identified the diagnostic delay in women with endometriosis
131. Greene R, Stratton P, Cleary SD, Ballweg ML, Sinaii N. Diagnostic experience among 4,334 women reporting surgically diagnosed endometriosis. Fertil Steril. 2009;91:32–9.
132. Dun EC, Kho KA, Morozov VV, Kearney S, Zurawin JL, Nezhat CH. Endometriosis in adolescents. JSLS. 2015;19(2) doi: 10.4293/JSLS.2015.00019. pii: e2015.00019.
133. Laufer MR. Current approaches to optimizing the treatment of endometriosis in adolescents. Gynecol Obstet Invest. 2008;66(Suppl 1):19–27

134. Dierschke DJ, et al. Circhoral oscillations of plasma LH levels in the ovariectomized rhesus monkey. Endocrinology. 1970;87:850–853
135. Clarke IJ, Cummins JT. The temporal relationship between gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH) secretion in ovariectomized ewes. Endocrinology. 1982;111:1737–1739
136. Knobil E. The neuroendocrine control of the menstrual cycle. Recent Prog Horm Res.
137. 1980;36:53–88

138. Belchetz PE, et al. Hypophysial responses to continuous and intermittent delivery of hypopthalamic gonadotropin-releasing hormone. Science. 1978;202:631–633
139. Wetsel WC, et al. Intrinsic pulsatile secretory activity of immortalized luteinizing hormone-releasing hormone-secreting neurons. Proc Natl Acad Sci U S A. 1992;89:4149–4153
140. Advis JP, et al. Regulation of gonadotropin releasing hormone release by neuropeptide Y at the median eminence during the preovulatory period in ewes. Neuroendocrinology. 2003;77:246–257
141. Clomiphene citrate and ovulation induction Vol 4. No 3. 303–310 Reproductive BioMedicine Online; www.rbmonline.com/Article/47
142. Fauser BC, Macklon NS. Medical approaches to ovarian stimulatin for infertility. In: Strauss JF, Barbieri RL, editors. Yen and Jaffes Reproductive Endocrinology. 5th edn. Elsevier Saunders Inc; pp. 965–1012
143. Fauser BC, van Heusden AM. Manipulation of human ovarian function: physiological concepts and clinical consequences. Endocr Rev. 1997;18:71–106
144. 139.-van Santbrink EJ, Donderwinkel PF, van Dessel TJ, Fauser BC. Gonadotropin induction of ovulation using a step-down dose regimen: single-centre clinical experience in 82 patients. Hum Reprod. 1995;10:1048–53
145. Thurin A, Hausken J, Hillensjo T, et al. Elective single-embryo transfer versus double- embryo transfer in in vitro fertilization. N Engl J Med. 2004;351:2392–2402
146. Samir Babayev, M.D.GynecologistReproductive Endocrinologist Rochester, MN https://www.mayoclinic.org/diseases-conditions/female-infertility/diagnosis- treatment/drc-20354313
147. NICE - National Institute for Health and Care Excellence . London: NICE; 2013. Fertilityproblems:assessment and treatment.https://www.nice.org.uk/guidance/cg156?unlid=86583397720167208641
148. ESHRE Capri Workshop Group Intrauterine insemination. Hum Reprod Update.
149. 2009;15:265–277. doi: 10.1093/humupd/dmp003.
150. zhao Y, Brezina P, Hsu CC, Garcia J, Brinsden PR, Wallach E. In vitro fertilization: four decades of reflections and promises. Biochim Biophys Acta. 2011 Sep;1810(9):843-52.
151. Sunderam S, Kissin DM, Crawford SB, Folger SG, Boulet SL, Warner L, Barfield WD. Assisted Reproductive Technology Surveillance - United States, 2015. MMWR Surveill Summ. 2018 Feb 16;67(3):1-28.
152. Siristatidis CS, Gibreel A, Basios G, Maheshwari A, Bhattacharya S. Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction. Cochrane Database of Systematic Reviews 2015, Issue 11. [DOI: 10.1002/14651858.CD006919.pub4]

153. Al-Inany HG, Youssef MAFM, Aboulghar M, Broekmans FJ, Sterrenburg MD, Smit JG, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. Cochrane Database of Systematic Reviews 2016, Issue 4. [DOI: 10.1002/14651858.CD001750.pub4
154. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet 1999;340:17–8.
155. Benadiva CA, Nulsen J, Siano L, Jennings J, Givargis HB, Maier D. Intracytoplasmic sperm injection overcomes previous fertilization failure with conventional in vitro fertilization. Fertil Steril 1999;72:1041–4
156. 150.3. Kastrop PM, Weima SM, Van Kooij RJ, Te Velde ER. Comparison between intracytoplasmic sperm injection and in-vitro fertilization (IVF) with high insemination concentration after total fertilization failure in a previous IVF attempt. Hum Reprod 1999;14:65–9
157. 151.. Practice Committee of the American Society for Reproductive Medicine;Practice Committee of the Society for Assisted Reproductive Technology. Genetic considerations related to intracytoplasmic sperm injection (ICSI).Fertil Steril 2006;86:103–5.
158. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST,Coutifaris C, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001;345:1388–93.
159. Tournaye H, Verheyen G, Albano C, Camus M, Van Landuyt L, Devroey P,et al.Intracytoplasmic sperm injection versus in vitro fertilization: a randomized controlled trial and a meta-analysis of the literature. Fertil Steril 2002;78:1030–7.
160. Van Rumste MM, Evers JL, Farquhar CM. Intra-cytoplasmic sperm injectionversus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility. Cochrane Database Syst Rev 2003;2:CD001301
161. 155.8. Jain T, Gupta RS. Trends in the use of intracytoplasmic sperm injection in theUnited States. N Engl J Med 2007;357:251–7.
162. American Society for Reproductive Medicine. Intracytoplasmic sperm injection (ICSI). Fertil Steril 2008;90:S187
163. American Society for Reproductive Medicine. (2012). Third-party reproduction (sperm, egg, and embryo donation and surrogacy): A guide for patients. Retrieved May 31, 2016,
164. Sherman JK, Bunge RG. Effect of glycerol and freezing on some staining reactions of human spermatozoa. Proc Soc Exp Biol Med. 1953;84:179–80.
165. Critser JK. Current status for semen banking in the USA. Hum Reprod. 1998;13:55–67.

166. Botchan A, Hauser R, Gamzu R, Yogev L, Paz G, et al. Results of 6139 artificial insemination cycles with donor spermatozoa. Hum Reprod. 2001;16:2298–304
167. We care health services article egg donation in india The procedure of Egg Donation in India https://wecareindia.com/egg-donation-in-india/
168. Shenfield F, Pennings G, Cohen J, Devroey P, de Wert G, Tarlatzis B. ESHRE TaskForce on ethics and law 10: Surrogacy. Hum Reprod. 2005;20:2705–7
169. Maheshwari A, Griffiths S, Bhattacharya S. Global variations in the uptake of single embryo transfer. Hum Reprod Update. 2011;17:107–20
170. Jadva V, Murray C, Lycett E, MacCallum F, Golombok S. Surrogacy: The experiences of

surrogate mothers. Hum Reprod. 2003;18:2196–204
171. AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE • 1209 Montgomery
172. Highway • Birmingham, Alabama 35216-2809
173. Dural O, Yasa C, Keyif B, Celiksoy H, Demiral I, Ozgor BY. Effect of infertility on quality of life of women: a validation study of the Turkish FertiQoL. Jhuman Fertility. 2016;19(3):186–91.
174. Cousineau TM, Domar AD. Psychological impact of infertility. Best Pract Res Clin Obstet Gynecol. 2007;21(2):293308.
175. Kamel Remah M. Management of the infertile couple: an evidence-based protocol. J Reprod Biol Endocrinol. 2010;8(1):301–6.
176. van Balen F, Bos HM. The social and cultural consequences of being childless in poor- resource areas. Facts Views Vis Obgyn. 2009;1(2):106–21.
177. Obi SN, Onah HE, Okafor II. Depression among Nigerian women following pregnancy loss. Int J Gynecol Obstet. 2009;105(1):602
178. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Jhum Reprod Update. 2015;21(4):411–26.
179. Farrokh Eslamlou HR, Haji Shafiha M, et al. The effect of primary infertility on the quality of life of women of Oroumieh, Iran. Oroumieh Med J. 2014;25(598):604–7
180. Maroufizadeh S, Karimi E, Vesali S, Omani SR. Anxiety and depression after failure of assisted reproductive treatment among patients experiencing infertility. Int J Gynaecol Obstet. 2015;130(3):253–6.
181. Shoham Z, Zosmer A, Insler V. Early miscarriage and fetal malformations after induction of ovulation (by clomiphene citrate and/or human menotropins), in vitro fertilization, and gamete intrafallopian transfer. Fertil Steril 1991; 55: 1–11.
182. 175.2. Hull MGR, Glazener CMA, Kelly NJ et al. Population study of causes, treatment and outcome of infertility. Br Med J 1985; 291: 1693–7.
183. Greenblatt RB, Barfield WE, Jungck EC, Ray AW. Induction of ovulation with MRL-41.
184. JAMA 1961;178: 101.
185. Greenblatt RB, Roy S, Mahesh VB, Barfield W, Jungck EC. Induction of ovulation. AmJ Obstet Gynecol 1962; 84: 900–7.
186. Karow WG, Payne SA. Pregnancy after clomiphene citrate treatment. Fertil Steril 1968;19: 351–62
187. MacGregor AH, Johnson JE, Bunde CA. Further clinical experience with clomiphene citrate. Fertil Steril 1968; 19: 616–22.
188. Adashi EY, Rock JA, Sapp KC et al. Gestational outcome of clomiphene-related conceptions. Fertil Steril 1979; 31: 620–6
189. Garcia J, Jones GS, Wentz AC. The use of clomiphene citrate. Fertil Steril 1977; 28:707–17.
190. Kurachi K, Aono T, Minagawa J, Miyake A. Congenital malformations of newborn infants after clomiphene-induced ovulation. Fertil Steril 1983; 40: 187–9.
191. Kousta E, White DM, Franks S. Modern use of clomiphene citrate in induction ofovulation. Hum Reprod Update 1997; 3: 359–65
192. Boue JG, Boue A. Increased frequency of chromosomal anomalies in abortions afterinduced ovulation. Lancet 1973; i: 679.

193. Dyson JL, Kohler HG. Anencephaly and ovulation stimulation. Lancet 1973; i: 1256–7.186.Harlap S. Ovulation induction and congenital malformations. Lancet 1976; ii: 961.
194. Cornel MC, Kate LPT, Dukes MN et al. Ovulation induction and neural tube defects.
195. Lancet 1989; i: 1386.
196. Mills JL, Simpson JL, Rhoads GG et al. Risk of neural tube defects in relation to maternal fertility and fertility drug use. Lancet 1990; 336: 103–4
197. Lunenfeld B, Serr DM, Mashiach S et al. Therapy with gonadotropins: where are we today? Analysis of 2890 menotropin treatment cycles in 914 patients. In: Insler V, Bettendorf G, eds. Advances in diagnosis and treatment of infertility. Amsterdam: Elsevier, 1981: 27–31.
198. Ben-Rafael Z, Dor J, Mashiach S et al. Abortion rate in pregnancies following ovulation induced by human menopausal gonadotropin/human chorionic gonadotropin. Fertil Steril1983; 39: 157
199. Miyake A, Kurachi H, Wakimoto H et al. Second pregnancy with spontaneous ovulation following clomiphene- or gonadotropin-induced pregnancy. Eur J Obstet Gynecol Reprod Biol 1988;27: 1–5.
200. Corsan GH & Kemmann E. Risk of a second consecutive first-trimester spontaneous abortion in women who conceive with menotropins. Fertil Steril 1990; 53: 817–21.
201. Balen AH, Braat DDM, West C, Patel A, Jacobs HS. Cumulative conception and live birth rates after the treatment of anovulatory infertility. An analysis of the safety and efficacy of ovulation induction in 200 patients. Hum Reprod 1994; 9: 1563–70.
202. Homburg R, Eshel A, Armar NA et al. One hundred pregnancies after treatment with pulsatile luteinising hormone-releasing hormone to induce ovulation. BMJ 1989; 298: 809–12.
203. Nillius SJ, Wilde L. Effects of prolonged luteinising hormone-releasing hormone therapy on follicular maturation, ovulation and corpus luteum function in amenorrheic women with anorexia nervosa. Uppsala J Med Sci 1978; 84: 21–35.
204. Braat DDM, Schoemaker R, Schoemaker J. Life table analysis of fecundity in intravenously treated gonadotropin-releasing hormone treated patients with normogonadotropic and hypogonadotropic amenorrhea. Fertil Steril 1991; 55: 266–71.
205. Van der Spuy ZM, Steer PJ, McCusker M, Steele SJ, Jacobs HS. Pregnancy outcome in underweight women following spontaneous and induced ovulation. BMJ 1988; 296: 962–5.
206. Armar NA, McGarrigle HHG, Honour JW et al. Laparoscopic ovarian diathermy in the management of anovulatory infertility in women with polycystic ovaries: endocrine changes and clinical outcome. Fertil Steril 1990; 53: 45–9
207. Out HJ, Coelingh Bennink HJ. Clomiphene citrate or gonadotrophins for induction of ovulation?. Hum Reprod 1998; 13: 2358–61
208. de Ruiter A, Mercey D, Anderson J, et al. British HIV Association and Children's HIV Association guidelines for the management of HIV infection in pregnant women 2008. HIV Med 2008; 9: 452–502.
209. Frodsham LCG BF, Barton S, Gilling-Smith C. Human immunodefi ciency virus infection and fertility care in the United Kingdom – demand and supply. Fertil Steril 2006; 85: 285–9.
210. Coll O, Lopez M, Vidal R, et al. Fertility assessment in non-infertile HIV-infected women and their partners. Reprod Biomed Online 2007; 14: 488–94.
211. Coll O, Fiore S, Floridia M, et al. Pregnancy and HIV infection: A European consensus on management. AIDS 2002; 16(Suppl 2): S1–S18.

212. Coll O, Lopez M, Hernandez S. Fertility choices and management for HIV-positive women. Currt Opin HIV AIDS 2008; 3: 186–92.
213. Martinet V, Manigart Y, Rozenberg S, et al. Ovarian response to stimulation of HIV- positive patients during IVF treatment: a matched, controlled study. Hum Reprod 2006; 21: 1212–17
214. Coll O, Suy A, Figueras F, et al. Decreased pregnancy rate after in-vitro fertilization in HIV-infected women receiving HAART. AIDS 2006; 20: 121–3
215. Brunham RC, Cheang M, McMaster J, Garnett G, Anderson R. Chlamydia trachomatis, infertility, and population growth in sub-Saharan Africa. Sex Transm Dis 1993; 20: 168– 73.
216. Brunham RC, Garnett GP, Swinton J, Anderson RM. Gonococcal infection and human fertility in sub-Saharan Africa. Proc Biol Sci 1991; 246: 173–7.
217. Frodsham LCG, Cox AD, Almeida PA, Rozis G, Gilling-Smith C. In vitro fertilisation in HIV positive women: risk of mother to embryo viral transmission. Hum Reprod 2004; 9(Suppl 1): 138
218. Gilling-Smith C, Almeida P. HIV, hepatitis B and hepatitis C and infertility: reducing risk. Hum Fertil (Camb) 2003; 6: 106–12..
219. Lutgens SP, Nelissen EC, van Loo IH, et al. To do or not to do: IVF and ICSI in chronic hepatitis B virus carriers. Hum Reprod 2009; 24: 2676–8
220. MacDonald M, Crofts N, Kaldor J. Transmission of hepatitis C virus: rates, routes, and cofactors. Epidemiol Rev 1996; 18: 137–48.
221. Pasquier C, Daudin M, Righi L, et al. Sperm washing and virus nucleic acid detection to reduce HIV and hepatitis C virus transmission in serodiscordant couples wishing to have children. AIDS 2000;14: 2093–9
222. Halfon P, Giorgetti C, Bourliere M, et al. Medically assisted procreation and transmission of hepatitis C virus: absence of HCV RNA in purifi ed sperm fraction in HIV co-infected patients. AIDS 2006; 20: 241–6