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A Comprehensive Reviews on Infertility Facing by Men and Women

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ABSTRACT:

Infertility is usually defined as a pair not being able to have a baby after a year of having sexual relations often and without protection. It impacts around one-fifth of American couples and at least one-hundred million people globally. As Infertility is mostly caused by female variables, which include various issues with ovulation, oocyte maturation, fertilisation competence, and the ability of a fertilised egg to undergo preimplantation development, implantation, and foetal growth. These factors account for at least 35% of all infertility cases. Additionally, male factors are thought to be responsible with 20–70% of occurrences, varying by latitude. A decrease in semen quality, showing as decreased sperm counts (or even the total deficiency of sperm in ejaculate), and abnormal sperm quality and function due to impaired spermatogenesis in the gonads and/or dysfunction of the adjunct glands, are symptoms of infertility of male, which can have a number of well-defined inherited or acquired causes. Consequently, this article provides comprehensive reviews of this important men's and women's health problem, how to evaluate infertility, the significance of using these methods, and basic and clinical studies investigating novel approaches to diagnostic tools, treatment options directed towards personalised medicine, and preventive strategies in male and female infertility.

Keywords: Infertility, Image Analysis, Gene analysis, Electronic Health Record.

1. Introduction

The WHO (World Health Organisation) explains infertility as the inability to comprehend after engaging in regular, undefended sexual activity for at least twelve months. One in six couples will experience infertility, and in around half of those belongings, a factor in male is either partially or entirely to blame. Regardless, male infertility is either ignored or misrepresented in the medical community. The main reasons for this include the fact that men's fertility is not often tested and the fact that infertility is commonly defined differently. A male factor of infertility is present when a man's sperm restrictions fall under the standard values set by the WHO. While semen examination is still the gold regular for studying infertility in male, there are some limits to this technology and new indicators have emerged. With the mounting evidence linking male infertility to an improved risk of oncologic, metabolic, cardiovascular and autoimmune diseases, as well as multiple studies showing a significant overall decline in men's sperm values over the past few decades, it is evident that male infertility is a concerning but understudied global health concern.

The main goal of a male and female infertility evaluation is to find out what's causing infertility, treat the reversible reasons, find out whether they can benefit from ART (Assisted Reproductive Techniques), and deliver counselling for the untreatable and irreversible factors. Infertility in male may be an indicator of a more grave illness in extremely rare instances. In order to identify and treat any serious underlying medical issues, it is necessary to conduct a thorough evaluation of both partners in infertile couples [2].

Consequently, this article provides comprehensive reviews of this important men's and women's health problem, how to evaluate infertility, the significance of using these methods, and basic and clinical studies investigating novel approaches to diagnostic tools, treatment options directed towards personalised medicine, and preventive strategies in male and female infertility.

1.1. Etiology

Infertility has several different root causes, each of which can be grouped according to their general aetiology [3]. General underreporting, cultural considerations, and regional variances make reliable data unattainable, therefore these are simply broad approximations. The likelihood of a tertiary referral centre reporting a patient's condition is higher than that of a private practice, which may never gather data from a patient [4]. The following is a partial list of potential causes:

- **Endocrine factors** such as Prader Willi syndrome, familial cerebellar ataxia, iron overload syndrome, congenital Gonadotropin Hormone (GnRH) releasing hormone deficiency (Kallmann syndrome), hyperthyroidism, intracranial radiation, head trauma or testosterone supplementation.
- **Idiopathic** - a male experiences infertility for no apparent reason (10% to 20% of the time), even though his sperm tests come back normal.
- **Genetic factors** - CFTR gene mutations, primary ciliary dyskinesia, Klinefelter's syndrome, Kallmann syndrome, Sertoli cell-only syndrome, Young syndrome, , Kal-1, Kal-2, GnRH1/GNRHR FSH, FGFS, LH, PROK2/PROK2R gene deficiencies, Y chromosome microdeletion, chromosomal abnormalities, gr/gr deletion, AR mutations, and chromosomal irregularities abound.
- **Birth defects** affecting the genitourinary system, such as a cystic ovary, an undescended testis, a vas deferens that is either non-existent, malfunctioning, or obstructed, or an ejaculatory duct problem.
- **Urogenital abnormalities** that can be acquired include: epididymitis, varicoceles, retrograde ejaculation, bilateral orchiectomy, orifice blockage or ligation, varicoceles, and

bilateral obstruction of the vas deferens. Examples of immunological reasons include lymphocytic hypophysitis, hemochromatosis, hemosiderosis, sarcoidosis, tuberculosis, fungal infections, histiocytosis and many more.

- Infections of **genital tract** (concurrent prostatitis and recurrent prostatovesiculitis, chlamydia, syphilis, tuberculosis, and gonococci).
- **Premature ejaculation**, anejaculation, few sexual encounters, and impotence are all examples of sexual dysfunction.
- An **overabundance of androgens** can be caused by the following malignancies: sellar masses, pituitary macroadenomas, craniopharyngiomas, as well as their surgical or radiation therapy; testicular tumours; or adrenal tumours.
- **GnRH inhibitors include:** certain medications (e.g., cannabis, opioids, psychotropic drugs), supplements containing testosterone or androgens, GnRH analogues and antagonists used to treat prostate cancer, long-term glucocorticoid treatment, alkylating agents, antiandrogens, ketoconazole, and cimetidine.
- **Toxins in the environment**, such as fungicides, pesticides, smoking, and excessive alcohol consumption.

2. Comprehensive Reviews on The Vital Issue Facing in Both Men and Women

Men fare worse than women in some areas of health, while women fare worse than men in others. It is complicated and very difficult to extrapolate future trends in sex differences due to the fact that sex variations in health have not been consistently measured across historical periods and nations.

A common misconception is that women have lower health and a shorter life expectancy than men [5]. There is no simple way to define the disparities between the sexes when it comes to health, and making such broad statements is an oversimplification [6]. By comparing death rates and various aspects of illness among men and women as they age, we show how nuanced the male-female health gap really is. Furthermore, we show that sex disparities differ among health variables, historical periods, and nations, illustrating the difficulty of sex alterations in health at older eternities.

At the people level, health changes with age are analysed using the magnitudes of the disease process, which classify various health signs [7]. This allows for an examination of sex variations in health. At the people level, changes in health with age begin with physiological dysregulation, like elevated total cholesterol and blood pressure levels; this is surveyed by an increase in the diagnosis of physical and mental illnesses; disability, loss of physical operative, and demise are the final stages of this procedure. Every person is unique, thus the sequence of events may be different for them, they could not feel all the dimensions, and the process could even go backwards. When trying to figure out why there are sex differences in death rates and which parts of health men and women do better or worse on, it's helpful to dimension the non-mortality components of health change. Despite the fact that changes in process dimensions are connected, prior research has demonstrated that changes in these morbidity aspects over time and population differences are not always identical [8]. In this study, we set out to compare and contrast these gender-based health indicators across nations and time periods to see whether there were any discernible variations. We were surprised to see that there were consistent gender disparities across a variety of health-related measures, as well as over time and between nations. We set out to demonstrate that, while broad statements regarding gender disparities in health and death rates are possible, it is impossible to characterise the vast majority of these inequalities with a single statement that applies across all nations and all eras.

Incorporating current indication on biomarkers and other physiological position, as well as (a) conducting a thorough analysis of ancient trends in life suspense and sex variances in disease occurrence and physical working, greatly enhances our understanding of the causes and pathways of sex variances in health.

In general, people can agree on what causes sex disparities in health and death rates. Some are inherent, based on biology, or connected to hormonal and genetic variations between the sexes. Due to the absence of a second X chromosome in males, the detail that women possess two X chromosomes might offer beneficial idleness. There may be a considerable sexual dimorphism in aged and a difficulty in existence for males due to asymmetric maternal inheritance of mitochondria, which may benefit women by giving harmful mutations to men. In addition to the potential protective effects of female hormones, women may exhibit more sensitive invulnerable functioning and their capacities to regulate homeostasis and decrease oxidative stress may vary from those of men [9–14]. Some aspects are based on conduct, such as the fact that women are extra likely to seek medicinal consideration when they are sick than males are [15]. The extent to which fundamental behavioural and biological variables impact health outcomes is influenced by macro factors as well. Infectious diseases used to play a significant role in predicting how long people lived, and that role extended well beyond childhood. The significance of biological disparities between sexes may have shifted in recent decades due to the increased prevalence of cardiovascular disease [16]. disparities in economic status, family obligations, and participation, as well as disparities in vocation, all contribute to the fact that the economic structure affects men's and women's health. Thus, it's reasonable to assume that gender disparities in health will change over time, across nations, and across different types of health outcomes. For the sake of consistency, we will refer to sex and sex differences throughout this review rather than gender and gender differences. However, it is important to note that the differences covered here encompass both biological and social aspects of women and men.

Life expectancy is the starting point for our discussion of the morbidity process, which will continue with physiological variations as the last component. In order to draw conclusions about the population as a whole, we combed through data from a wide variety of sources, all of which were nationally representative. There has been a dearth of nationally representative statistics on health-related variables, despite the fact that dependable mortality data have been accessible for quite around time from national and international organisations for the majority of nations. National surveys of older and middle-aged populations have been conducted by several nations in the last 20 years. These surveys have collected data on various aspects of illness from large trials of mutually sexes [17]. Analysed individual-level study data on the elder population from numerous studies to discuss sex differences in health. These studies include: China Health and Retirement Longitudinal Study (CHARLS), Korea Longitudinal Study of Ageing (KLoSA), Russia and India (WHO SAGE), a number of European countries (SHARE), the US (HRS), England (ELSA), Indonesia (IFLS), Taiwan (SEBAS), and Mexico (MHAS). One place you may find a lot of these datasets is the Gateway to Global Ageing Data [18]. The data used for the study at the individual level. A large, representative sample of individuals aged 50 and up is used in each of these research. Because many of the data sets have been harmonised, they are comparable across nations. On the morbidity aspects, we compared men and women in these nations. Data on risk factors for cardiovascular disease at the national level were recovered from the WHO’s database. To round things up, they used US HRS data on risk factors that mirrored fundamental ageing processes. Additionally, used data from the World Bank database to look at male and female life expectation rates in 198 different nations.

3. Assessment of Infertility in Men and Women

A comprehensive medical history, physical exam, hormone analysis, and imaging examination should all be part of the first diagnostic workup for infertility in both men and women. This will help to identify any underlying causes of the infertility.

3.1. Assessment of Health Status and Physical Status Markers

Finding potential risk factors and/or behaviours that may impact fertility should be the primary emphasis of the medical history. Considerations such as these encompass the following: the length of time the patient has remained unable to consider, the ages of both the patient and his spouse, any gynaecologic factors affecting the female partner, drugs that may impact the hypothalamic-pituitary-gonadal axis, cryptorchidism, illnesses pertaining to the sex organs or ejaculatory processes, the frequency with which sexual relations occur, the patient's smoking and alcohol consumption histories, genital surgery, and disorders related to pubertal development.

3.2. Imaging

When it comes to figuring out what's causing infertility, imaging is usually the way to go. It can help find things like congenital defects and illnesses that block sperm transport, which could be fixable. Myomas, pelvic masses or adnexal, adenomyosis, intrauterine polyps, congenital anomalies, polycystic ovarian disease, and other conditions can be better diagnosed with the use of imaging, which can also direct strategies for impregnating the female. Invasive procedures, Magnetic Resonance Imaging (MRI), and Ultrasonography (US) are the imaging modalities usually employed to assess the male and female reproductive systems.

3.3. Gene Analysis

One way to find out if you carry any recessive genes that could impact your offspring is to get a genetic screening. The fertility of both sexes can be affected by specific hereditary diseases. A hereditary illness develops when a change in DNA influences a gene or genes. One or both of your biological parents may be responsible for passing these alterations on to you. Your doctor will discuss your treatment choices after they determine the exact cause of your infertility. These can differ depending on the person and the specific health issue. Some couples may find success getting pregnant after having their hormone levels balanced or supplemented if they are experiencing low levels of hormones. Kallmann syndrome, which affects both sexes equally, is an example of this.

4. Evaluation for Infertility Prior to Treatment

In demand to maximise the efficiency of ART treatment and to assist with individual management decisions, it is crucial to accurately discover underlying reproductive problems. Semen analysis, the Post-Coital Test (PCT), uterine, ovulation assessment and tubal assessment, and laparoscopy are the five main types of clinical evaluations that can be performed on infertile couples [19]. The early plain patient work-up consists of three parts: a serum progesterone level measured mid-luteal phase, tubal patency evaluation, and semen analysis [20]. Yet, there is ongoing debate over the appropriateness of using certain core components of infertility testing, and there is some indication that European countries do not adhere to the present WHO guidelines for the normal/examination of infertile couples.

4.1. Analysing Sperm

The percentage of sperm that are considered "normal" is lower in humans than in many other species. There is a lot of overlay in the properties of infertile and fertile men's semen, even if there haven't been many investigations of semen analysis in men with established fertility [21]. Although high-quality semen analysis can be used to diagnose severe male infertility disorders, such as azoospermia or globozoospermia, it is not as reliable for predicting outcomes when there are moderate amounts of motile sperm present in an individual sample [22].

The analysis of sperm involves looking at their shape, motility, and concentration. In large-scale research, no one metric of semen analysis has been demonstrated to be diagnostic of infertility. The results of semen studies have been integrated into intricate prediction models in an attempt to enhance their value [23]. Be wary about drawing firm conclusions from these models' output due to the huge confidence intervals.

The WHO and the ESHRE (European Society for Human Reproduction and Embryology) both offer methods for analysing semen, but their recommendations offer the most thorough and reliable approaches [25,25]. 'Normal' according to the World Health Organisation (WHO) is a sperm concentration of $>20 \times 10^{1}$/ml, with >50% of the sperm becoming increasingly motile and the existence of sperm having standard morphology (no specifications given), even though a new manual is set to be released in 2009.

The WHO's guidelines for conducting semen analyses and reporting the results are not well followed in most laboratories [26,27]. Most laboratories still lack accurate procedures and proper training systems, even though there are recognized systems to increase staff exercise in semen examinations, like ESHRE courses [28]. The results of semen analysis can thus be somewhat unpredictable. Semen analysis has shown no signs of standardisation or rigorous quality control, which casts doubt on its diagnostic and prognostic utility.

In infertile couples, analysis of semen is commonly recycled to assess the fertility of the male partner, despite the restrictions mentioned. Results from sperm analyses also inform treatment options and can sway the decision to use expectant management, IVF, Intracytoplasmic Sperm Injection or Intrauterine Insemination (ICSI).

Improving the prognostic usefulness of semen analysis requires more laboratory evaluation accuracy and greater standardisation of semen analysis [29]. In addition, in order to aid in the decision-making procedure for ART treatment, high-quality readings are needed to determine threshold points are prognostic for treatment outcome. Although sperm function tests have the potential to be more predictive than conventional semen analysis, they must undergo rigorous validation before being used in everyday clinical practice [30].

4.2. Evaluation after Sexual Activity

Cervical cytology tests can detect anti-sperm antibodies, sperm-mucus interactions, and cervical mucus amount and quality [31]. This test is performed in the phase of pre-ovulatory and 8-12 hours following intercourse and comprises microscopic evaluation of retrieved endocervical mucus [31]. If more than half of 5 high-power (×400 magnification) microscope fields show at most one forward-progressing spermatozoon, it can be said that the PCT result is positive.

For partners who are vexing to conceive for less than three years and have not found any female factors that could be causing their infertility, the PCT could be a useful predictor of success. But research has demonstrated that basic infertility antiquity and analysis of semen results can predict the PCT outcome for 50% of infertile couples (when the female partner have steady menstrual cycle) [32]. Additionally, there is a lot of inter and intra observer erraticism in PCT

results. It is not advised to routinely employ this examination in clinical training due to extensive usage of ART in couples who have a PCT test negative.

4.3. Assessment of the Uterus and Tubules

Before beginning ART, it is crucial to assess the uterine and fallopian tube morphology [33]. A number of methods exist for visualising the uterine and tubal structures; these include laparoscopy, SIS, Hysterosalpingo Graphy (HSG), Transvaginal Ultrasonography (TVS) and Magnetic Resonance Imaging (MRI).

It is believed that 14% of couples in need of specialist therapy for infertility have tubal occlusion as the cause. There is currently no agreement of thought on the ideal screening method to assess tubal injury [34]. The subject is complex. Recent observational data comparing laparoscopy with other screening methods for tubal factor infertility is very useful [35]. It was proposed that Chlamydia trachomatis immunoglobulin G serology might serve as a helpful first screening test because it reliably differentiates between patients at low and high risk of tubal disease. HSG was useful for low-risk individuals to make sure there was no tubal disease and to give patients the chance to benefit from oil-soluble contrast medium tubal flushing. Individuals whose Chlamydia serology results were positive or who showed signs of bilateral tubal blockage on HSG may benefit from laparoscopy using dye testing.

Clinical pregnancy and live birth rates following IVF are negatively impacted by presence of hydrosalpinx [36]. Although the exact process by which a hydrosalpinx reduces the success rate of In-vitro Fertilisation (IVF) remains unclear, it is well-known that the procedure is vastly improved when the cyst is removed before IVF has compared to not having surgery, the pregnancy rate and live birth rate were significantly higher after salpingectomy. The odds ratio was 1.75 (95% CI 1.07-2.86) and the odds ratio was 2.13 (95% CI 1.24-3.65). One of these research found that patients whose fluid-filled hydrosalpinges were detectable on ultrasonography would benefit the most following salpingectomy. Patients who have an ultrasound-visible hydrosalpinx should be advised to have a preventative salpingectomy before undergoing in vitro fertilisation.

Less clear is the best way to treat endometriotic ovarian cysts in women who are unable to conceive. The conventional surgical method of treatment has been called into question by new data showing decreased reactivity to gonadotrophins after laparoscopic ovarian cystectomy [37]. It has been proposed that surgery should only be performed in cases where medical treatment has failed, when the patient has a big endometrioma, or when cancer has been ruled out [38].

No strong evidence suggests that routine hysteroscopy earlier IVF or repair of detected pathology improves treatment results, but unexpected hysteroscopic irregularities has been recorded in up to 40% of patients through ART work up [39]. There are a lot of drawbacks to HSG compared to hysteroscopy, such as a high false-negative percentage of 10–90% and high false-positive percentage of 22–24%. The specificity rate is low at 23–35%.

The most accurate way to detect intrauterine pathology is via a hysteroscopy [40], however ultra-sonographic methods are gradually replacing invasive screening procedures [41] due to technological advancements. Intrauterine anomalies including fibroids, polyps, synechiae, and Müllerian anomalies can be detected with the help of late follicular phase TVS [42]. SIS has the potential to be just as operational as hysteroscopy in detecting intracavitary irregularities [43,44], in addition to providing greater endometrial visualisation and intrauterine pathology detection than regular TVS. When a complex Müllerian anomaly is detected, MRI may be performed to evaluate the patient [45].

One in five women over the age of 30 may develop uterine fibroids, making them the most prevalent benign tumour in the female reproductive system [46]. Because these tumours vary in type, size, location, and quantity, it is problematic to determine which women will benefit from myomectomy before receiving ART treatment [47].
According to data collected in the past, ART treatment cycles are unaffected by fibroids smaller than 4 cm in diameter [48]. Further examination of the literature specifies that the only fibroids known to adversely impact ART implantation rates and pregnancy outcomes are those that invade the uterine cavity. Clinical pregnancy, implantation, and live birth rates are all ominously lower in women with submucosal fibroids linked to infertile women lacking the tumours. The relative risks for these outcomes are 0.36 (95% CI 0.18-0.74), 0.28 (95% CI 0.12-0.65), and 0.32 (95% CI 0.12-0.85), correspondingly. While there is some evidence that removing submucosal fibroids increases the likelihood of a successful pregnancy (RR 2.03, 95% CI 1.08-3.83), there is no indication for removing intramural fibroids improves treatment consequences.

In 16-27% of women who have infertility for reasons other than those listed above, endometrial polyps have been found by hysteroscopy [4,50]. The study found that hysteroscopic polypectomy had a positive effect on pregnancy rates compared to hysteroscopy plus polyp biopsy, with a cumulative pregnancy rate of 63.4% versus 28.2%, $P < 0.001$, for women with endometrial polyps diagnosed ultrasonically who were undergoing in vitro fertilisation (IVF) [51].

Five studies that did not use randomization found that polypectomy increased the likelihood of a woman becoming pregnant on her own. Hysteroscopic polypectomy increases the likelihood of conception for infertile women, irrespective of the size/number of polyps [52], and removing polyps from the utero-tubal junction may increase the likelihood of pregnancy for infertile patients [53]. Data imply that women with unexplained infertility may still advantage from polypectomy, even though the result of endometrial polyps on IVF is unknown.

4.4. Assessment of Potential Fertility

The art of reproductive technology makes usage of ovarian stimulus to facilitate retrieval of numerous oocytes by promoting multifollicular development [54]. A woman's ovarian reserve is the primary factor that determines the ovarian reply to gonadotrophin stimulation [55] and is a crucial determinant of the achievement of IVF [56,57].
The quality and quantity of follicles existing in the ovary, also known as ovarian reserve, is the surviving people of primordial and inactive follicles [55]. At any one moment, the number of antral follicles in the ovaries that can be stimulated into dominant follicle growth by exogenous Follicle-Stimulating Hormone (FSH) is the ovarian reserve, which provides an operational definition. As a result of traditional ovarian stimulation, women with what is considered a "normal" ovarian reserve will typically produce an equal number of oocytes and eight to ten dominant follicles. Fig. 1 shows that the pace of ovarian ageing varies considerably among individuals, even if chronological age is the main factor determining ovarian reserve [58]. Consequently, precise ovarian reserve testing might pave the way for personalised forecasts of oocyte production and the achievement of ART treatments in maintaining a pregnancy.

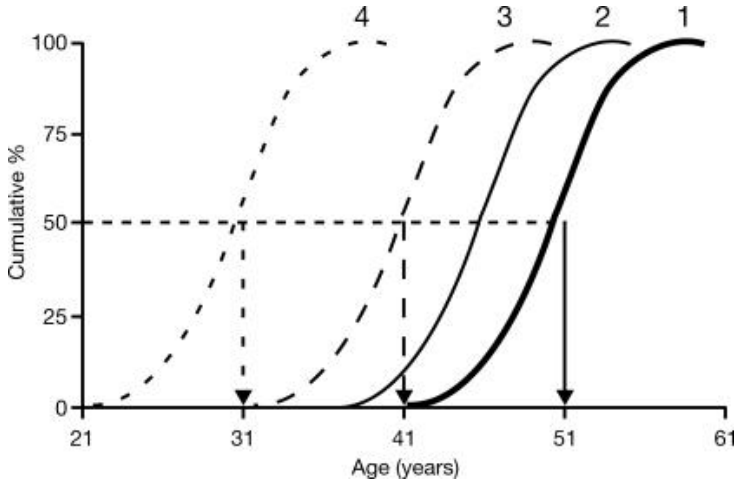

Figure 1: Reproductive ageing varies [58]

Ovarian reserve testing typically involves measuring serum FSH levels and evaluating Antral Follicle Counts (AFCs) using Transvaginal Sonography (TVS). Among the best available single predictors of ovarian response to stimulus, the AFC associates with the quantity of oocytes regained and ART results [59, 60]. Although serum Anti-Müllerian Hormone (AMH) stages are not routinely evaluated in practice, they have potential to reliably identify patients at danger of a severe ovarian retort.

Finding patients with regular menstrual cycles whose response to gonadotrophin stimulation is better or worse than expected for their chronological age may be possible with the use of an assessment of ovarian reserve. Theoretically, this would aid physicians in customising patient care by guiding them towards the most effective treatment plan, whether that means emphasising the need of starting treatment early or providing counselling against doing so. Results from studies examining the use of ovarian reserve examinations to regulate the optimal initial dosage of FSH has been inconsistent.

Despite the need for additional research into AMH, current ovarian reserve tests do not reliably predict clinical pregnancy or live babies following in vitro fertilisation [61]. Ovarian stimulation cycles are necessary for accurate assessment of a patient's ovarian reserve.

5. Health Care for Reproductive Purposes

The usage of precision medicine begins with medication, which is a crucial initial step. A systematic solicitation of molecular medicine, precision medicine involves developing a unique fingerprint of a patient's genetic, epigenetic, transcriptomic, and metabolomic features and using this data to inform treatment decisions [62]. This is necessary since there is emerging evidence that men and women react differently to certain reproductive treatments, both in terms of the medications themselves and the dosages prescribed to them [63,64]. This concept proposes tailoring treatment plans for infertility to the specific needs of each patient, rather than a cookie-cutter approach. On the other hand, knowing every patient's exact molecular profile is still a long way off from a rigorous implementation of personalised medicine. In this study, we review the present opportunities for this kind of action orientation and the primary obstacles that will prevent future clinical and molecular research from moving further in this direction [65].

5.1. Custom-made Medicine to each Individual

At the metabolic, molecular, and environmental contact levels, every person has distinct and unique traits; this is the premise upon which personalised medicine, also known as precision

medicine, is built. The provision of diagnoses and therapeutic therapies that are customised to these subtleties and distinct personal traits necessitates consideration of these particulars [66]. While some were sceptical about feasibility of using precision medicine for reproductive health care for humans, recent findings point to a path towards this objective in the medium to long term. Whatever the case may be, this kind of work can be done with the current crop of medical and biological information, even in the deficiency of a comprehensive guide.

5.2. Objectives are Attainable

Infertility care options can already contain some components of personalised therapy, even without a complete molecular record. A comprehensive medical history should provide the basis for these considerations, which should include a physical check-up of the male and ultrasound scanning of female pelvis, with hormone evaluation serving as the principal tool for study. Not only that, but it's important to think about the partners' ages, their medical histories (both personal and familial), and whether or not they have any comorbidities [67].

5.3. Custom-made Strategy for Managing Infertility

Personalised infertility care should include a series of steps that build upon one another, such as a personalised strategy, preventative measures, diagnostics, therapies, and post-treatment follow-up.

5.3.1. Custom-made Approach

The best course of action for an infertile couple will, of course, be condition-specific, as illustrated in figure 2. In order to minimise the needless expense associated with diagnostic procedures, a "wait-and-see" strategy may be the initial choice for younger individuals with infertility that has been present for a very short period of time. However, action is required if infertility continues, particularly in older women and men whose sperm abnormalities may be attributable to their own or their families' medical histories or to their own lifestyle choices.
A thorough medical history, physical exam, and study of the male partner's sperm should comprise the initial evaluation. It is recommended that in every instance, a testicular ultrasound, an endocrine evaluation, and a semen microbiological examination be conducted. When first-step analyses revealed abnormalities or when particular risk factors for infertility exist, they should be highly suggested. The clinical orientation and prior investigational results form the basis for genetic testing, histology/ testicular cytology, and further sperm tests for examination of sperm DNA integrity [68].

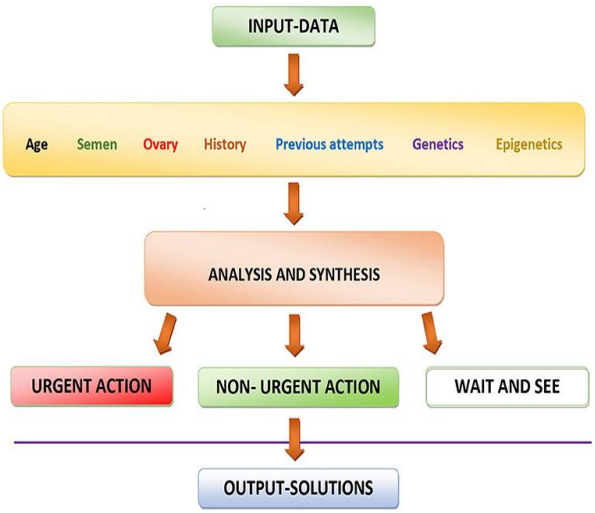

Figure 2: Action for an Infertile Couple Analysis

Vaginal ultrasound and standard hormone testing should be the first steps in a female patient's diagnosis. Patients with a past of endometrial polyps or intracavitary procedures, such as endometrial scraping, curettage, or persuaded abortion, may benefit from additional testing with hysteroscopy.

5.3.2. Custom-made Safety Protocols

Personalised preventative treatments can be considered if either partner's baseline exams reveal abnormalities. After considering all of the possible risks that could affect ovarian and testicular function, they will make a decision. The first step is to look for any and all recognised causes of reproductive dysfunction. A wide variety of factors can contribute to this, including heredity, epigenetic abnormalities, lifestyle choices (like smoking or excessive alcohol or drug use), occupational exposure to gametotoxic substances, the use of anabolic steroids and other hormones to enhance presentation in elite athletes, and multiple co-occurring disorders, like insulin resistance or abnormal thyroid function. Medication and behavioural modifications are usually sufficient to cure these types of problems.

Conversely, things get trickier when the root cause cannot be identified. Factors of epigenetic origin can impair testicular [69] and ovarian functioning, but they are harder to detect than genetic abnormalities. The oxidative stress in spermatozoa, oocytes, and related testicular and ovarian cells, whose malfunction might indirectly impact gamete quality, is a common undiscovered etiological component [70]. For this reason, antioxidant oral therapy is gaining popularity for the treatment and prevention of certain diseases [71]. On the other hand, keep in mind that the pathology you're trying to cure can respond negatively to a change in the redox balance away from oxidative stress and towards reductive stress. The overconsumption of antioxidants can lead to reductive stress, which in turn can harm the body's other processes.

5.3.3. Custom-made Medical Assessments

Personalised diagnostics are essentially an expansion of the procedures used to choose preventive actions. The role of genetic and epigenetic variables in the early embryonic death has lately been the subject of a comprehensive analysis [72]. But it seems that a collection of things, rather than just one, is to blame, as none of them stands out as a particular culprit. Due to issues that are yet not completely unspoken and seem to be extremely personalised, it is nonetheless possible for embryos to retain developmental competence, hence it is generally agreed that no embryo should be rejected only because a few defects have been detected [73].

5.3.4. Custom-made Medical Care

There are two crucial choices in developing a personalised treatment plan. First, the treatment's urgency; second, the treatment's specifics. These decisions must be based on a comprehensive assessment of each couple's specific condition, as shown in figure 2. They can range from a simple wait-and-see method, through comparatively "light" medicines, to assisted reproductive techniques, which are much more difficult and inflated, as shown in figure 3.

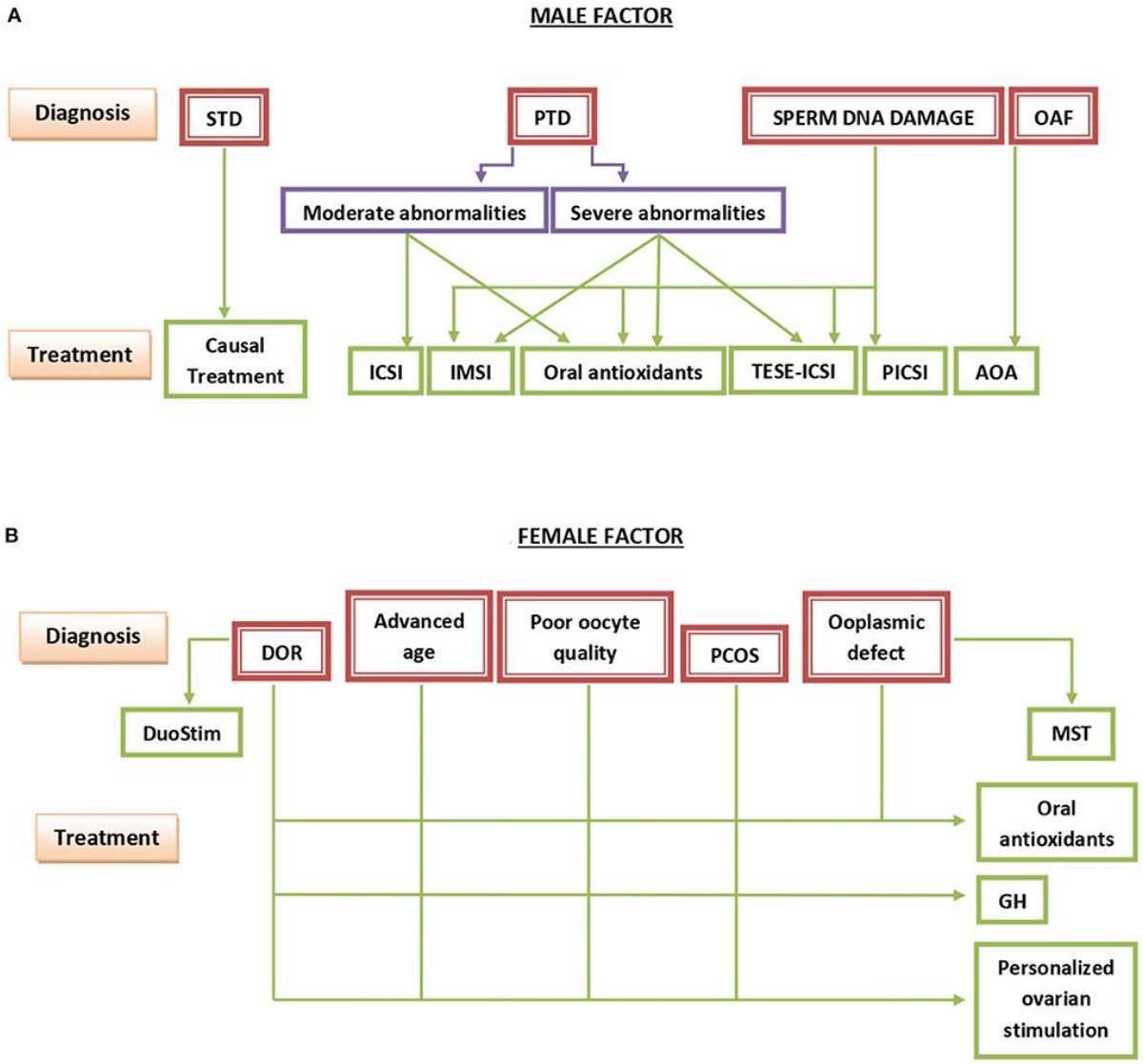

Figure 3: Factors of Male and Female Assisted Reproductive Techniques

5.4. Treatment Method Selection

In circumstances where the length of infertility is relatively brief, the wait-and-see method may be the most appropriate choice for young couples. If the condition does not improve on its own, doctors may prescribe medication with the help of clinical and laboratory controls to help patients synchronise their sexual activity with the embryo implantation window, when the mother's body is best able to encourage the implantation of her embryos in the uterus. If this method fails to produce the desired results, more advanced techniques may be used, like Intracytoplasmic Sperm Injection (ICSI), IVF, or Artificial Insemination (AI). It should be noted that couples or social security will bear a larger financial burden for more advanced methods. So, the ultimate adjustments to the selected therapy approach, bearing in mind the couple's overall state (figure 2), should receive the utmost focus.

5.5. Changes for Selected Treatment Approach

Conventional ICSI is the go-to for men with mild to moderate sperm irregularities, whereas Intracytoplasmic Morphologically Sperm Injection (IMSI) is the way to go for men with severe teratozoospermia or a high degree of sperm DNA fragmentation [74]. Based on the severity of the condition, a procedure of in vivo and in vitro treatments has been proposed for men with varying degrees of sperm DNA damage. This procedure starts with a humble oral treatment

with antioxidants and progresses to ICSI, Physiologic ICSI (PICSI), IMSI (ICSI with spermatozoa recovered by testicular biopsy), and finally TSE-ICSI (Testicular Sperm extraction followed by ICSI). Extreme oligoasthenoteratozoospermia or cryptozoospermia in males is another indication for TESE-ICSI. Before resorting to more complex and expensive operations like those shown in figure 3, men whose aberrant semen are caused by a known condition, like a hormonal imbalance or varicocele should get this rectified.
If a woman is nearing or beyond the age of 40 and wants to increase the quantity and excellence of oocytes she recovers via ovarian inspiration, she should take growth hormone during the process [75]. If a woman's endometrium is not developing properly or if her polycystic ovary condition is the cause of her inferior oocyte and endometrial quality, she should have the same treatment [76, 77]. Various adjustments can be made after carefully examining all elements that could contribute to the current infertility case, including those related to the male and female conditions, as shown in figure 3.

Oocytes and somatic cells in the ovary should have their energy metabolism protected by taking antioxidants. Since taking too many antioxidants at once might have negative effects on a patient's health, it is important to tailor the selection of antioxidant medication, treatment duration, and dosage to each individual's needs. For the best outcome, it's important to consider all relevant factors in each case, like the ovarian reserve and patient's age, as well as their personal and medical history, the outcomes of any prior treatment attempts, and if available, their genetic and epigenetic data.

There are other, more nuanced signs that may help solve this issue, as advanced maternal age is becoming a more significant cause of human infertility. The DNA of an oocyte is somewhat protected due to its intranuclear position and association with proteins, but many developmentally significant molecules in the cytoplasm are considerably more vulnerable to oxidative stress, as case with both physiological and premature ovarian ageing [78].

It was demonstrated over twenty years ago that enucleated donor oocytes might preserve fertility through nuclear transfer from ageing women, as opposed to full oocyte donation, which would involve the loss of the women's genetic material [79]. Another option was to try rejuvenating the oocytes during In-Vitro Fertilisation (IVF) by injecting a tiny volume of donor oocyte cytoplasm into the patients' oocytes during the ICSI procedure [80]. Both approaches enhanced embryo growth and embryo outcomes in older patients and those with a history of complications [81, 82]. Each of them contributed to the delivery of tens of thousands of healthy infants. The United States and most European countries outlawed this method of manipulating the oocytes' cytoplasm for reasons that are yet not fully understood. It was only a few years ago that nations without a ban started using the old nuclear transfer method again. To sidestep the first question of whether this approach can aid older women, its usage was initially restricted to younger women with known mutations in their oocyte mitochondrial DNA. Nuclear transfer may revitalise old animal oocytes, according to experimental investigations [83–85], thus this subject has to be revisited.

6. Image Analysis for the Detection of Female and Male Infertility

Finding the root of infertility and classifying it as either organic or non-organic is imaging's primary function [86]. Assisted reproductive procedures, such as sperm aspiration from epididymis or seminiferous tubules for IVF or intracytoplasmic sperm injection, can be guided by imaging in addition to its diagnostic uses [87]. Ultra-Sound (US), Magnetic Resonance

Imaging (MRI), and invasive procedures like venography and vasography are among the imaging modalities commonly employed to assess the male and female reproductive systems.

6.1. Evaluations of Female

6.1.1. Sonography

Diagnostic issues including ovarian cysts and uterine fibroids can be better understood with the use of ultrasound, a non-invasive technique that examines the female reproductive system. Most of the time, this surgery is done transvaginally at Women & Infants Fertility Centre.
Following the first appointment, the fertility expert may take an ultrasound picture of the woman's pelvic region (a sonogram) to identify any problems with her fertility. Issues including ovarian cysts and an irregularly shaped uterus can be identified with the use of a pelvic ultrasound.

6.1.2. Laboratory Testing for Hormones

A woman's hormone levels can be measured by taking blood samples at various points throughout her menstrual cycle. A woman's hormone levels need to be in a steady state for an egg to develop to a mature stage and for the ovaries to release an egg. If the woman is ovulating healthy eggs and the brain is delivering hormone signals to the ovaries correctly, the doctor conducting the blood hormone test will be able to tell. Most women get their Follicle-Stimulating Hormone (FSH) levels checked on the third day of their menstrual cycle, which is three days after the first day of their menstruation. Hormone panels may also look for estradiol and Anti-Müllerian Hormone (AMH).

6.1.3. Ovarian Reserve Test

The number of eggs a woman may have stored in her ovaries can be determined by an ovarian reserve test. Ultrasound or blood tests can be used to determine ovarian reserve.
If a woman has a great probability of experiencing a diminished ovarian reserve, these tests are advised. Some of these factors can increase the likelihood of infertility: being above the age of 35, having a history of premature menopause in one's family, having undergone reproductive surgery before, devising only one ovary, having undergone gonadotropin ovarian stimulation before, and having previously received toxic chemicals like chemotherapy.

6.1.4. Robotic Surgery

The surgeon performs laparoscopy, a type of minimally invasive surgery, by making a tiny incision at the belly button and then inserting a camera and other tiny surgical tools into the abdominal cavity. In addition to assessing and treating endometriosis, laparoscopic surgery can remove cysts, scar tissue, uterine fibroids and ovarian cysts.

6.1.5. Sonohysterogram

The uterine cavity is filled with saline solution and a transvaginal ultrasound is used to obtain a clear image of the uterus in a sonohysterogram. This method is useful for the diagnosis of fibroids, polyps, and other abnormal growths in the uterus.

6.1.7. Evaluating the Hysteroscope

An X-ray picture of the uterus and fallopian tubes is in use during a hysterosalpingogram. The fertility specialist will place a dye-filled catheter into the cervix to enhance the visibility of the uterine and fallopian tube structures on the X-ray. This treatment can discover an abnormally shaped uterus, polyps, fibroids, or other blockages in the fallopian tubes or uterine cavity.

6.1.8. Gynaecological Examination

The use of a tiny camera implanted into the cervix allows for the minimally invasive surgical examination and diagnosis of uterine polyps and fibroids. Fibroids, Polyps, uterine septa (a divided uterus), and scar tissue intimate the uterine cavity are some of the defects that can be repaired via hysteroscopy.

6.2. Evaluations for Male

6.2.1. Ultrasound

The primary method for evaluating male infertility is scrotal Ultrasound (US) because it is non-invasive, safe, and affordable [88]. While the patient is supine, a scrotal ultrasonography is conducted utilising a high-frequency linear array transducer.

Testicular volume measurement, colour flow Doppler ultrasonography of testes and spermatic cord, longitudinal and transverse sonograms of the testes are all part of a standard evaluation. Ultrasound of the scrotum can reveal anomalies in the testes and surrounding tissues, as well as any alterations caused by a blocked distal genital duct.

The typical adult testes are oval shaped, uniform, low-level echogenic constructions that size around 3 cm in area (AP) × 2-4 cm in transverse diameter (TR) × 3-5 cm in length, and have a size of 12.5-19 cc [8] (Figure 4). A small, echogenic fibrous ring encircles a testicle; this band stands in for the visceral tunica vaginalis and tunica albuginea. The tunica is often only visible as an echogenic structure at its hilum when there is no intra-scrotal fluid. At this point, it invaginates into the testis to produce the mediastinum testis, which has a network of tubules termed rete testis that are used for sperm transport.

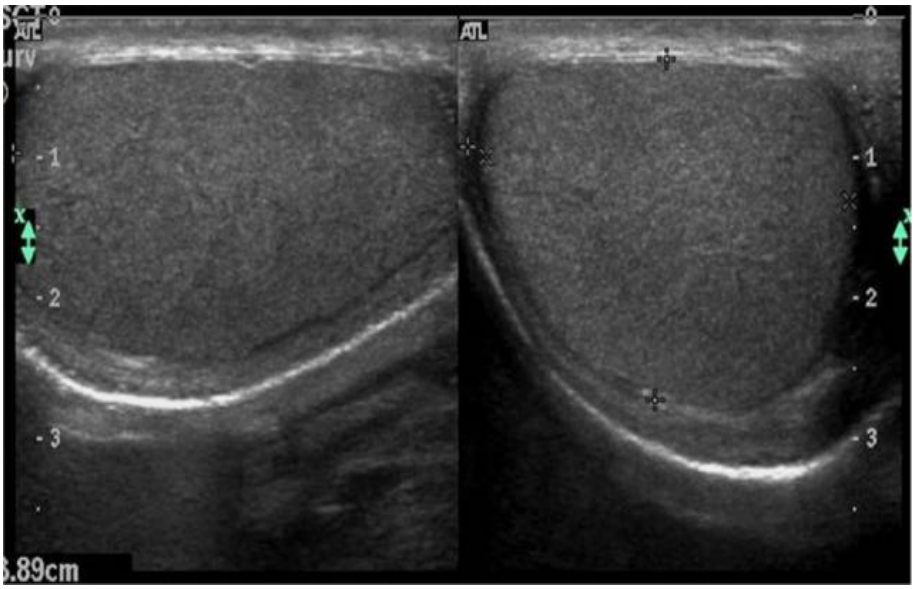

Figure 4: Example of Ultra-sound image for Male (Google Courtesy)

6.2.2. Mammography using Magnetic Resonance Imaging

An alternate to conventional invasive vasography, Magnetic Resonance Imaging (MRI) is preferable to trans-rectal Ultra-Sound (US) for assessing the distal genital tract [92,93]. The pathophysiologic features of the reproductive tract, such as the seminal vesicles, ejaculatory ducts, and prostate, can be better demonstrated by MR imaging thanks to its multi-planar abilities and outstanding soft-tissue contrast. Due to its ability to generate high-quality, multi-planar images, MRI has largely supplanted vasography as imaging modality of optimal for assessing the distal genital canal and male infertility.

6.2.3. Computerised Tomography

Infertility evaluations with Computed Tomography (CT) are unusual due to the imaging modality's poor soft tissue resolution. On the other hand, CT is helpful for assessing stones and calcifications that are blocking the reproductive tract [94].

6.2.4. Vascular Scan

Duct filling, free spill and Retrograde contrast injection into the bladder to establish patency are all part of this operation, which can be performed blindly or with ultrasound guidance [95]. Ultrasound, Transvaginal Ultrasound (TRAS), MRI and other less offensive methods have largely supplanted it as the gold customary for assessing the male reproductive system [96].

6.2.5. Barriers to Conception

Any part of the ductal system the vas deferens, epididymis, ejaculatory ducts, seminal vesicles, or urethra is susceptible to obstruction. Using sonography, the source and degree of blockage can be more precisely determined. Epididymal blockage can be repaired with microsurgery, such as vaso-epididymostomy, and vaso-vasostomy, which has a reported success rate of 20-40% in preventing post-procedure pregnancy, so this knowledge is useful for surgical treatment planning [97]. Procedures such as TRUS-directed transurethral ejaculatory duct (TRU-ED) and prostatic cyst aspiration are examples of sonographically guided treatments for distal tract blockages [98].

7. Infertility Caused by Genetic Abnormalities in both Sexes

7.1. Infertility in females

Infertility in females can be caused by a number different genetic abnormalities, such as:

- **Turner syndrome:** a woman is born with either an abnormal X chromosome or an incomplete X chromosome in the case of Turner syndrome. Impaired ovarian development is one symptom of this disease.
- **Fragile X permutation:** This condition is characterised by a variant in the X chromosome gene FMR1. The ovaries become less prolific due to this genetic alteration, which in turn reduces fertility.
- **Kallmann syndrome:** Mutations in multiple genes can lead to Kallmann syndrome. The result is a delay or absence of puberty due to low amounts of gonadotropin-releasing hormone (GnRH) produced by the brain.
- **Primary Ovarian Insufficiency (POI)** can be caused by either Turner syndrome or the fragile X permutation. In Polycystic Ovary Syndrome (POS), ovulation occurs before the age of 40. When this occurs, ovulation stops and the eggs are unable to mature normally.
  In a slightly different way, Kallmann syndrome manifests its symptoms. Oestrogen and progesterone are essential for many parts of a woman's reproductive process, and GnRH instructs the ovaries to produce them. Therefore, decreased fertility is the result of low GnRH levels.

7.2. Infertility in Males

Infertility in males can be affected by a number different genetic abnormalities like:

- **Klinefelter syndrome** is a hereditary condition characterised by an extra X chromosome in males. So, they're X-chromosome carriers with a single Y chromosome. Male infertility is most commonly caused by Klinefelter syndrome, according to a Trusted Source chromosomal analysis. The generation of sperm is hindered by its effects. Klinefelter syndrome is associated with a complete lack of sperm production in males.

- Another hereditary reason of male infertility is **Y-chromosome microdeletions**. Many of the genes for what are popularly thought of as male sexual traits are located on the Y chromosome, which is normally existent in individuals who are assigned male at birth. A missing section of a gene is called a deletion. The ability to spermiate can be impacted by Y chromosomal microdeletions. For instance, men who have these deletions may experience issues with their fertility due to:
  - sperm that aren't shaped correctly
  - sperm that don't migrate effectively
  - low counts of sperm
  - no sperm at all
- **Changes in the CFTR gene:** Alterations in the CFTR gene can also impact a man's fertility. Some variations in this gene cause cystic fibrosis, but others can affect male fertility in various ways, such as: reducing sperm count, preventing sperm transport through reproductive system of male, or causing the male reproductive system to develop improperly. One such condition is Kallmann syndrome, where low GnRH production results in reduced testosterone production, which is crucial for sperm development.

8. Conclusion

Many people in our society struggle with infertility, particularly those who wait until they are older to have a family, perhaps they can focus on building a successful profession. Fertility in men and women can be instigated by a variety of factors, some of which are reversible and some of which are permanent. Age, drugs, surgical history, environmental toxin exposure, hereditary issues and systemic disorders are some other factors that could impact both couples. The main goal of an infertility evaluation is to ascertain what causes are leading to his/her infertility, with what treatment that can be reversed, assess his suitability for Assisted Reproductive Techniques (ART) and deliver counselling for those that cannot be treated. The infertility may be an indicator of a more serious illness in extremely rare instances. This also supports the need for infertile couples to undergo thorough evaluations of their partners. In order to detect and evaluate any serious underlying health issues using three advances: The Electronic Health Record, image analysis, and gene analysis.

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