

Prediction and Treatment of Risk Factors Affecting *In-Vitro* Fertilization Therapy

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Abstract

Background: Failure to conceive following regular or frequent unprotected intercourse for a year or more has been defined as infertility. *In-Vitro* Fertilization (IVF) is the most recommended treatment for unresolved infertility issues worldwide. There are various factors associated with the risk of infertility and if left untreated these may lead to an exaggerated damage that further results into recurrent IVF failure in these patients. **Materials & Methods:** This study was conducted at Krishna Medical Centre, Lucknow, Uttar Pradesh, from September 2012 to December 2019 in 800 patients experiencing infertility problem. The study includes females with valid indication for IVF treatment age between 20 years to 50 years. Various pathological, environmental and anatomical factors associated with infertility have been investigated in the patients. The surgical interventions used to modify the anatomical barriers leading to infertility in the patients have also been mentioned in the manuscript. **Result:** In this study it was found that there are various physical, physiological, environmental and anatomical risk factors that pose threat to successful pregnancy in the infertile couples. These factors also create restrictions in successful conception through *in vitro* fertilization in these subjects. If left untreated these factors may lead to permanent sterility and infertility in these couples. Hence timely treatment and proper medical care along with surgical intervention can help the patients overcome their fertility issues *via* IVF. **Conclusion:** This study contains the data of 800 female patients suffering from various types of infertility issues. The investigators have studied the factors associated with infertility and have also tried to treat the anatomical barriers posing threat to fertility in these subjects. The article is being produced with the hope to generate awareness to the infertile couple with knowledge and information of the medical advancements that can benefit them in overcoming their infertility issue and lead a successful life.

Keywords: *In vitro* fertilization; Hysteroscopy; Risk factors; Infertility

Introduction

Number of couples seeking infertility treatment is increasing drastically worldwide. World Health Organization (WHO) proposed that the couples must be together for treatment as much as possible. [1] There is a complex relation between fertility and psychological stress. [2] The work stress and low conception possibilities in women were reported by studies [3] however the relation of work stress and fertility in men is still under study. According to UN, the definition of reproductive fitness is "A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity in all matters relating to the reproductive system and to its functions and processes". [4] Failure to conceive following regular or frequent unprotected intercourse for a year or more has been defined as infertility. [5] The infertility diagnosis based on the failure to conceive in a year has been disputed to embroider the infertility risk seeing as about 50% of women who failed to conceive in the first year had the possibility to accomplish in the second year. [6] The preliminary consultation of these couple should comprise an evaluation of history for fertility problems. Information concerning normal conception patterns will provide reassurance about good chance of conception. Conversely, there should also be a detailed enquiry on the medical, surgical, sexual, contraceptive and pregnancy history and a general physical examination to detect abnormalities, as well as measurement of height and weight to evaluate BMI that helps to identify couples who are probably

experiencing delay in conception. [7] Information about lifestyle such as smoking and alcohol consumption habit, work load, diet of couples should be accessed to improve the fertility rates.

In Vitro Fertilization (IVF) technique assists the fertilization of eggs and sperms outside the body and is usually preferred on failure of other treatments. The use of IVF holds the following; a phase of expectant management in patients amid unexplained infertility, therapy for ovulation induction, treatment for male factor infertility (often in combination with Intra Cytoplasmic Sperm Injection (ICSI), treatment for endometriosis, IUI using partner or donor sperm, tubal disease treatment including severe tubal disease and severe male factor infertility. [8]

The cycle of IVF treatments following the stages, nevertheless depends on the protocol used properly at every stage or the stages were relinquished while treatment follow-up. Pre-treatment stimulates the IVF procedure by improving the exogenous hormone response, reduces the risk of cyst formation in Ovary and facilitates the IVF stimulation schedule to corroborate the time of oocyte recovery obtainable to laboratory or clinical

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staff. [8] Down regulation temporarily stops the function of the pituitary gland to reduce the risk of cancellation of cycle from early exposure to luteinizing hormone that could disrupt the development of normal follicle and oocyte or stimulate the release of an egg at pre-mature stage before retrieval. Controlled ovarian stimulation aims at surgical retrieval of numerous mature eggs before fertilization in laboratory. [9]

After stimulation phase, an ovulation trigger/stimulating hormones is used to mimic the function of the natural endogenous LH surge to initiate ovulation process. Oocytes and sperms were fertilized *in-vivo* and then one or two resulted embryo is transplanted into the uterus of women after 2-3 days, basically at the cleavage stage of embryo development. [10] The good quality eggs were used for longer laboratory culture and intra-uterine replacement was done after 5 to 6 days basically at blastocyst stage. [11] The early phase of pregnancy was supported by drugs to mimic the natural conception process. The IVF cycle may stop or be cancelled due to risk of ovarian hyper stimulation syndrome in women and/or because of negative response to the part of IVF treatment. [12] This mostly occurs before retrieval of Oocyte or during ovarian stimulation. However, Oocyte may be collected and frozen for future transfer. Ovulation triggering combined with intrauterine insemination is the most common and/or first choice of couples facing infertility problems because of their ease and affordability. [13] Most of the studies on fertility show that the results of IVF success depend on each cycle of treatment; however the patient focuses on the outcome of complete treatment.

*In-Vitro*Fertilization (IVF) is the recommended treatment of choice for unresolved infertility (NCCWCH NICE, 2013). Various studies have explored the impact of factors affecting the successful outcome of IVF in terms of pregnancy and/or livebirth. [11-14] Most of these studies have shown an inverse proportionate relation between the cycles of treatment and the numbers of co-varieties to the size of the dataset. [14]

Materials and Methods

This prospective study was conducted at Krishna Medical Centre, Lucknow, Uttar Pradesh, from September 2012 to December 2019 in 800 patients experiencing infertility problem. Each patient incorporated in this study was tested for age, duration of infertility, pregnancy failure history and all the factors associated to pregnancy failures being tubal pathology, unexplained sub-fertility, male factors, hormonal, cervical or immunological infertility and endometriosis. [8]

Inclusion criteria

Infertility patients, Age group 20-50 years, STD free.

Exclusion criteria

Patients >50 and <20 years age group. Those with pre-existing medical condition interfering with IVF treatment, abnormal IVF screening tests which includes Complete Blood Count, Varicella titer, Rubella titer, PAP smear, Syphilis, HIV 1 and 2, Hepatitis B, Hepatitis C, Chlamydia, and Gonorrhoea, Abnormal pap smear.

Results and Discussion

Table 1 illustrates the characteristics that have established the chances of pregnancy and live birth. The results for individual factors are described in more detail in Table 1. The study includes total 800 cycles of IVF undertaken between September 2012 and July 2019.

Age: Female age is the most important factor affecting fertility. Women have eggs in their ovary by birth and this number keeps decreasing each day from birth onwards. This decline is fairly gradual in younger women but it shows a steep decline as women approach their mid to late 30s, the decrease gets much steeper. It has been observed that not only the number, the quality of eggs also decline with age in females [15] and this bears a logical reason why older females find it more difficult to conceive and undergo a healthy pregnancy than the younger ones.

Loendersloot et al. in their study have shown that duration of infertility in women inversely relates with rate of pregnancy such that the rate of pregnancy decreases with increasing duration of infertility. The authors also found a significant difference between the different diagnostic categories; severe oligospermia post treatment gave the highest pregnancy chances while the immunological and tubal pathology gave the lowest chances of pregnancy. [16]

Medical conditions

Various minor medical conditions such as thyroid disease and vitamin D deficiency could be easily treated in infertile females whilst others that are more specific, for example, polycystic ovary syndrome, uterine fibroids and endometriosis needs a long-term specific treatment for a successful pregnancy outcome. [17]

Table 1: Characterization and diagnostic pathology faced by subjects.

Characteristic	Category	Number of subjects (N=800)	Number of cycles	Cumulative outcome of pregnancy (%)
Maternal age of subjects	20-30 (most fertile)	536	1	67%
	31-40	208	2	26%
	41-50	56	3	7%
Duration of infertility	1-2years	368	2	46%
	3-4 years	320	2	40%
	5-6years	56	2	7%
	7-8 years	24	2	3%
	9-10 years	24	2	3%
	11-12 years	8	2	1%
Causes of Infertility (Data in this category had an overlapping in many patients)	Tubal	160	1	20%
	Male (mild/severe)	176	1	22%
	Endometriosis	200	2	25%
	Hormonal	288	2	36%
	Immunological/cervical	296	1	37%
	Infective	160	2	20%
	Multiple reasons	400	3	50%

Previous pregnancy

Previously pregnant couples; irrespective of successful live birth have more chances of further successful pregnancies as compared to couples who have never been pregnant. [18]

Duration of infertility

The duration of efforts to get pregnant has been found to be inversely proportionate to the chances of successful pregnancy *i.e.* longer the duration to achieve pregnancy, more likely are the chances of failure and this probably could be due to certain underlying medical conditions. [19]

Ovulation and chances of pregnancy: In females having 28 days menstrual cycle, ovulation occurs on the 14th day of the cycle. The chance of getting pregnant is low at the beginning of the cycle and starts to increase from about day 8 onwards. [20] Post ovulation, the chances of getting pregnant decreases dramatically due to the surge in progesterone hormone that causes cervical mucus to become thick and sticky preventing the mobility of sperm. Frequency of copulation during ovulation and in the fertile window *i.e.* from 8th-16th day of the menstrual cycle increases the chances of pregnancy due to availability of good volume of fresh sperm in the female reproductive tract. [20]

Observations as per Table 2 show that certain life factors associated with environmental and chemical factors play a dubious role in exaggerating the risk of IVF treatment.

Lifestyle factors

Weight: Overweight/obese and underweight women usually face the challenges of irregular periods resulting into lesser chances of ovulation each month than women with regular periods thereby drastically affecting their chances of getting pregnant. Losing or gaining weight as per their weight issues, even as little as 5%-10% of the total body weight, may help these females in improving their fertility. Overweight conditions

are also associated with an increased risk of miscarriage or complexities during pregnancy and delivery. [21]

Smoking: Smoking reduces a woman’s ovarian reserve (so her ovaries will have fewer eggs in them than a woman of the same age who does not smoke) and damages the cilia inside the fallopian tube (which are important for transporting the egg and/or embryo along the fallopian tube into the uterus). Female smokers are thrice at risk of losing their pregnancy as compared to non-smokers. Male smokers have higher chances of having poor sperm quantity and quality. [21]

Caffeine: Excessive caffeine intake through tea/coffee has been found to be associated with poor fertility in couples. [20]

Alcohol: Some studies report that drinking more than 5 units of alcohol a week may reduce female fertility but others state that low to moderate alcohol consumption may be associated with higher pregnancy rates than non-drinkers. [19-21] Once pregnant, excessive alcohol consumption may lead to birth defects and developmental delay. The Royal College of Obstetricians and Gynaecologists and the Department of Health recommend that women trying to get pregnant should avoid alcohol because there is no ‘safe’ limit. In men, excessive alcohol may lead to difficulties maintaining an erection, impaired ejaculation and reduced sperm quality. [21,22]

Over-the-counter and recreational drugs: Non-steroidal anti-inflammatory drugs such as ibuprofen can interfere with ovulation. Aspirin may interfere with implantation. Recreational drugs such as marijuana and cocaine may interfere with ovulation and/or the function of the fallopian tube. [23] Anabolic steroids, which are abused by some body-builders, inhibit the production of sperm and this may be permanent even if the drug is stopped.

Environmental chemicals: Certain chemicals in our environment most likely have detrimental effects on fertility. The worst fertility disrupters are organochlorine compounds (chlorinated pesticides, polychlorinated biphenyls, and dioxins), Bisphenol A (BPA), and organophosphate pesticides and herbicides. Hormone disrupters have the ability to enter the body and mimic hormones (masquerading as estrogen), block hormone functions, and even to muddle the hormonal patterns taking place within the body. As a result, these chemicals affect the ability of the body’s hormones to control and regulate the function of the reproductive system, hindering or completely halting fertility. [19]

Artificial ovulation/ovarian stimulation: Artificially stimulating a woman’s ovaries for ovulation can place her at risk of Ovarian Hyper Stimulation Syndrome (OHSS), making them quite painful and swollen. Symptoms of this include mild to moderate abdominal pain, diarrhea and nausea or vomiting. Discomfort can last for a week prior to pregnancy. If OHSS occurs during pregnancy, symptoms can last for several weeks at a time. Bed rest is usually recommended for mild cases. Severe cases of OHSS can occur, but are fairly rare. If severely experienced, symptoms include shortness of breath and rapid weight gain which can be life-threatening if not managed appropriately. It is not uncommon for women on hormonal medications to experience bloating, mood-swings, headaches and abdominal

Table 2: Environmental risk factors affecting *in-vitro* fertilization treatment.

Risk factors	No. of patients	Percentage of subjects
Physical	800	
Fallopian tube damage or blockage	300	37.5
Ovulation disorders	106	13.25
Endometriosis	84	10.5
Uterine fibroids	82	10.25
Previous tubal sterilization or removal	90	11.25
Impaired sperm production or function	78	9.75
Unexplained infertility	60	7.5
Psychosocial	800	
Stress due to economic insecurity	446	55.75
Stress due to marital adjustment	354	44.25
Chemical environment	800	
Occupational, e.g. solvents, welding, agriculture	276	34.5
Lifestyle, e.g. alcohol, caffeine, smoking	524	65.5

discomfort. [24] If medications are administered by injection, bruising can also occur at the site of injection. Implantation of more than one embryo can result in the development of more than one baby. Multiples can carry increased risk of low birth weight in babies as well as premature labour. Even in instances where success is achieved with a single baby, the risk of premature labour/delivery and a low birth weight is increased if pregnancy occurs as a result of IVF treatment. The rate of miscarriage is higher with maternal age, as well as when frozen embryos are used. Naturally conceived embryos and IVF fresh embryos have a 15%-25% rate of possible miscarriage. An estimated 2%-5% of women undergoing IVF may experience an ectopic pregnancy (this is when the egg implants in the fallopian tube or somewhere other than the uterus). [24] It is not possible for a fertilised egg to survive outside of the uterus and a pregnancy will thus not be able to be continued.

Complications during egg harvesting (retrieval): The aspirating needle used to suction eggs from the ovaries can sometimes result in damage to the bladder, bowel or a blood vessel. A woman can thus experience possible infection, tissue damage or bleeding. Some woman may also have adverse reactions to sedative medications (anaesthetic) used in the retrieval and/or embryo transfer process. Most experiencing IVF treatments are likely to go through a little stress. The process is demanding on a person's pocket (financially) and quite taxing both physically and emotionally. [13] From a financial standpoint, most health insurance providers do not provide cover for fertility

treatment. This cost factor can be incredibly stressful, especially when multiple attempts are required. Having to take so many medications can also be a stress-factor for some women. If anxious or apprehensive, it is very important to discuss all concerns with a specialist. Often, many women cope better on the medications than they initially expected to. Although counselling is recommended by fertility specialists (and provided), it is also a good idea to build a caring support group throughout the process. [25] No matter how prepared a woman or couple are beforehand, treatment can have several ups and downs throughout the process. Battling infertility issues can result in depression for many, especially if treatment attempts have been tried and failed multiple times. Having effective support throughout treatment can often alleviate stress which can also impact chances of success.

Anatomical Factors: Any of the anatomical factors such as uterine fibroid, endometrioma, submucosal myoma, adenomyosis, ovarian cyst, tube blockage can prevent a female from getting pregnant. Table 3 shows the various complications in human females that if left untreated will lead to failures of *in vitro* fertilization treatments. The Figures 1-6 shows the various surgical procedures opted by the gynecological surgeons involved in this study for treatment of the factors and the subsequent results after the treatment.

Conclusion

Female age is a key predictor of failure to have a livebirth

Table 3: Factors that need to be carefully considered in the decision-making stages prior to undergoing IVF treatment.

Sr. No.	Complications
1	Ovarian hyperstimulation syndrome
2	Side-effects of medication
3	Possibility of multiple pregnancies
4	Increase risk of premature delivery and low birth weight
5	Miscarriage
6	Ectopic pregnancy
7	Stress



Figure 1: Uterine fibroid treatment before IVF in a 26 years old female (from semiurban background) suffering from severe family and societal stress diagnosed with uterine fibroid measuring 5 cm in diameter and several failed attempts of conception. Resulting into 5 years of infertility. BMI of the subject >25 kg/m², nonsmoker.

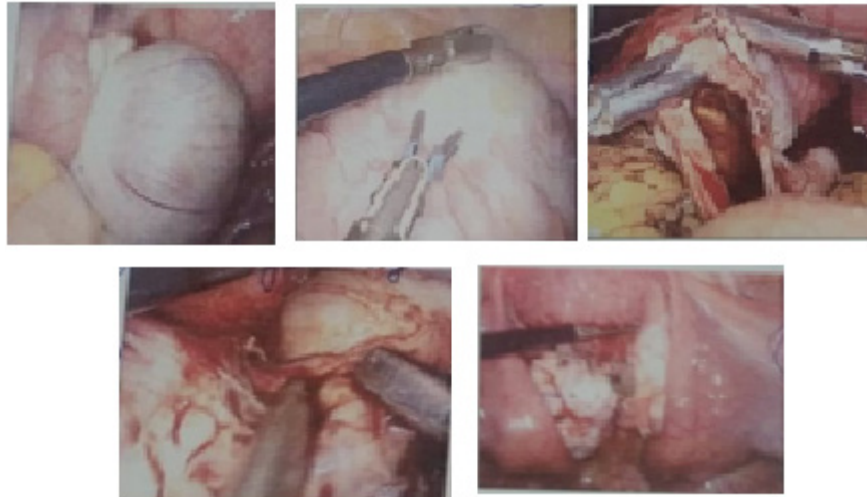


Figure 2: Endometrioma, preparation for removal of the endometrial cyst, steps showing the surgical removal of the endometrioma.



Figure 4: Adenomyosis and its surgical treatment.

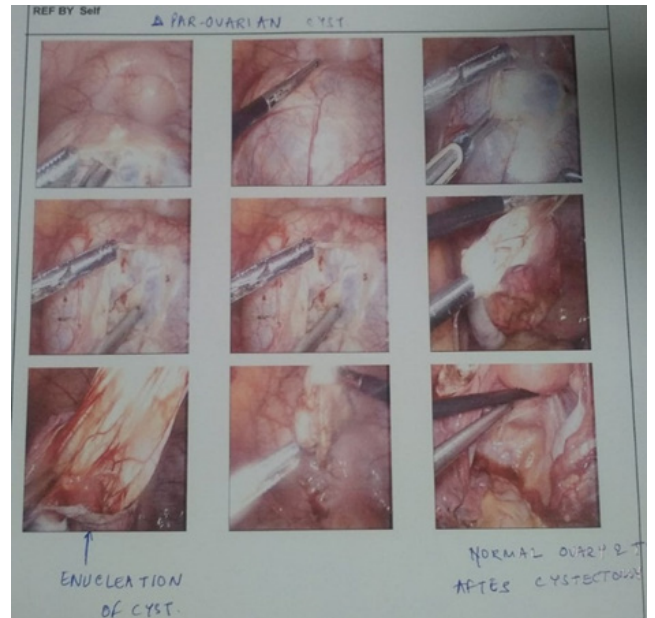


Figure 5: Ovarian cystectomy.

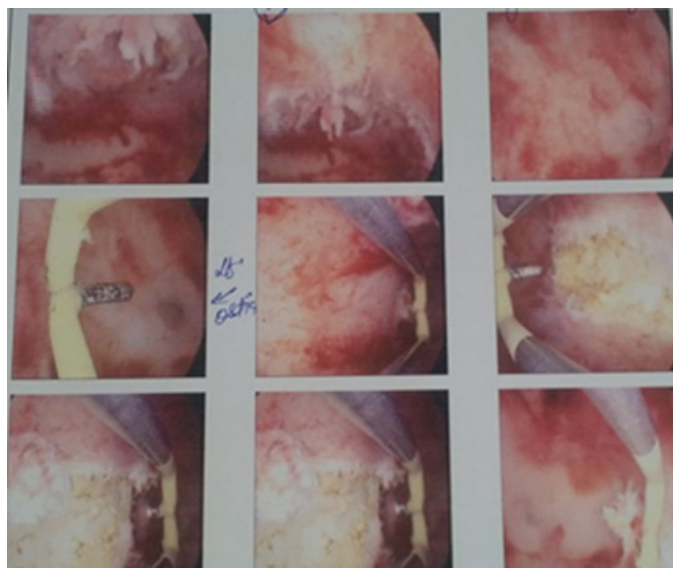


Figure 6: Uterine cavity, fundal septum resection and cavity after hysteroscopic myomectomy.

following IVF as well as the risk of poor performance at each stage of treatment. Increased duration of infertility is also associated with worse outcomes at every stage. Various environmental exposures and lifestyle factors associated with the risks of IVF treatment could be managed by the subjects willing to take the treatment while anatomical barriers could be treated by hysteroscopic surgical procedures that need to be done before the patient goes for IVF treatment for a successful pregnancy.

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Conflict of Interest

The authors declare that there is no conflict of interest to compete.

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