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Original Research

Factors affecting success rates of IVF

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***ABSTRACT*:**
Background: Infertility is caused by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. If the success rate predicted was found to be low then the candidate's couple can take a conclusive decision such as not to go with the IVF cycle. The purpose of this study was to determine various factors affecting success rates and outcome. **Materials and method:** This clinical study entitled was carried out to assess the factors affecting success rates of IVF in the Department of Obstetrics and gynaecology, Muzaffarnagar Medical College, Muzaffarnagar. The total sample size was determined to be 100 subjects. Follicular growth was monitored by measurements of serum oestradiol and progesterone and by performing transvaginal sonography. Delivery rates were calculated according to cycle characteristics, including the number of oocytes retrieved, the number of transferred embryos and whether or not there had been the option of choosing embryos for transfer. **Results**: The mean age of the study population was 33.05±4.07 years with a age range of 26-40 years. The successful pregnancies (delivery rate %) was 30.0% among 26-30 years age group, 39.0% among 31-35 years age group and 31.0% among 36-40 years age group. The Fertilization rate (2 PN/oocytes exposed to sperm) was 66.0%. The Successful implantation rate was 27.0%. Majority (42.0%) reported that the main reason for infertility was male factor followed by mechanical (20.0%), Anovulation (23.0%) and Unknown among 15.0% subjects. **Conclusion**: Age at the time of IVF and FSH serum levels are the crucial factors to get success in assisted reproductive technology and frozen embryo transfer (FET) techniques, and should be considered.
Keywords: Assisted reproductive technology, Frozen embryo transfer, Infertility, IVF

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Introduction

Infertility is caused by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse as defined by the World Health Organization. In most cases, infertility is preventable and may be treated. In about eight per cent uses the advance treatment includes assisted reproductive techniques (ARTs). The pregnancy rate per initiated ART cycle and the delivery rate remains around 30 percent. Unsuccessful occurrence of ART is a stressful event not only to the couples but also to the family.[1]

The state of infertility can be classified into 2 different categories such as Primary infertility and Secondary infertility. Primary infertility refers to the condition of a total failure of the reproductive system to become pregnant and in this case couples never have a possibility of giving birth to child with natural or normal pregnancy. Secondary infertility explains the failure of a female to become pregnant after giving successful live birth to child in first pregnancy in a period of 12 months' time interval.[2,3]

The infertility may be due to ovulatory disorders, tubal disease, endometriosis, chromosomal abnormalities, sperm factors and unexplained infertility. In addition, physical, behavioural, genetic, socioeconomic as well as environmental or occupational factors may also contribute. Life style factors such as psychological stress, advanced age to start a family, nutrition, weight, physical exercise and occupational exposures can also have substantial effects on fertility and outcome. Further, other personal lifestyle factors such as tobacco smoking and chewing, illicit drug use and alcohol and excessive

caffeine consumption can also have a negative influence on fertility and outcome.[1]

The introduction of IVF and embryo transfer in the late 1970s revolutionized the treatment of infertility and spawned an entire new field of assisted reproduction technology. Traditional IVF was the optimal solution to infertility due to female mechanical factors. The next major breakthrough in treating infertility came with the introduction of intracytoplasmic sperm injection (ICSI),[4] a procedure that enables males with severe semen impairment to father their own children.

Fertility prediction models, before treatment, are treatment-independent and couples take part in these models before starting treatment.[5] They can be based on patient baseline characteristics. Alternative models have incorporated the characteristics of the intermediate results of the first treatment cycle, thereby improving the accuracy of probability estimates for future cycles.[6]

A number of factors have been reported as influencing the success of IVF, either positively or negatively. Women's age, antimullerian hormone (AMH) levels and antral follicle count (AFC) have been consistently shown to be associated with IVF success.[7] During the last few years, some important pretreatment predictors, which used live birth as the primary outcome, have been published.[8]

The assessment of success of IVF treatment has, however, long been controversial. It is usually evaluated by using crude pregnancy or delivery rates per treatment cycle,[9] or by calculating the cumulative pregnancy or delivery rates using timetable analyses.[10,11]

Nelson & Lawlor (2011) used this predictor model was made using a cohort of 144,018 IVF cycles (data from Human Fertilization and Embryology Authority - HFEA) undertaken in the United Kingdom (UK) between 2003 and 2007, to examine the predictors of live birth with IVF treatment. This predictor includes woman's age, infertility duration, source of eggs, cause of infertility, number of previous IVF cycles, previous pregnancies, medication use and type of treatment (IVF or ICSI). This model was built on considerably old datasets, pre-dating significant changes in clinical practice that occurred from 2008 onwards, therefore requiring a time adjustment.[12]

Approximately 12-28% of couples were found to be incident to the infertility condition with no significant medial changes and the predispositions.[13] Infertility in the male population was found be lesser compare to the other conditions and was reported in 20-30% of Infertility cases. Female infertility was little predominant in comparison with that of male infertility and contributes in 20-35 % of the total infertility. Most severe infertility was found to be combined infertility occurs due to the combined problems both the sexual parts and contributes 25-40 % causes of the world infertility.[14]

Deficiencies in semen structure, quality motility and total count were the most frequent causes of the male infertility, total absent or abnormal menstruation cycle manifest with the ovulation abnormalities are the major causatives in promoting female infertility. No significant reason was found in the 10-20 % cases of infertility.[15,16]

Assessing the genetic and other health fitness of the candidate couple to predict the accurate success rates and withdrawn the conclusive suggestions based on the predictions will help to take decision on the IVF procedure whether to undergo or not is the most critical, challenging and important step which principally decides the success of the IVF procedure.[3]

So it is advised to estimate the success rate of the candidate couple by assessing the various intrinsic and the extrinsic factors such as Intrinsic factors i.e, Genetic predisposition, Age, Body mass Index, Hormonal balance, Embryo viability, Sperm quality, Endometriosis and overall patient's response level of the candidate couple and the Extrinsic factors such as Medical equipment technology, Treatment methods, Personal experiences of clinicians and embryologists, Process time, Stress due to the lifestyle etc influencing the success of individual's IVF treatment cycles.[3]

Studies conducted over the past three decades have tried to determine the chances of successful reproduction before beginning treatment or after it. In the case of the latter, researchers have often considered the success rate of a particular treat-ment, have compared the existing conditions and have examined the effect of external factors on that particular treatment or on a combination of treatments.[17]

The majority of these studies have used a simple ratio-based approach while some have measured probabilities for determining the chances of a successful pregnancy. Using the simple ratio-based approach for determining the likelihood of treatment success is justified if the aim is to compare the success rate of different methods or to compare them with each other;[18] however, determining the likelihood of success based on the predictive factors helps use those factors for the analysis of the success rate.

If the success rate predicted was found to be low then the candidate's couple can take a conclusive decision such as not to go with the IVF cycle.[3] The purpose of this study was to determine various factors affecting success rates and outcome.

Materials and method

This clinical study entitled was carried out to assess the factors affecting success rates of IVF in the Department of Obstetrics and gynaecology, Muzaffarnagar Medical College, Muzaffarnagar. The total sample size was determined to be 100 subjects with 80% power.

Inclusion and Exclusion criteria

The study subjects were chosen as per the inclusion and exclusion criteria. The study include women reporting to the infertility clinic of Muzaffarnagar Medical College, Muzaffarnagar. The women with systemic illness and women in advanced age (> 40 years) of age were excluded from the study.

Study procedure

After approval from the Institutional Ethical committee all patients were selected as per inclusion and exclusion criteria. A detailed history, complete physical examination and routine & appropriate investigations were done for all patients.

These women were admitted to the IVF programme following thorough infertility investigation or failure of conventional infertility treatments or IVF in other centres. Two main protocols were used for the induction of follicular growth:

(i) approximately 85% underwent a long protocol of gonadotrophin-releasing hormone analogue (GnRHa) given either in the mid-luteal or early follicular phase of the menstrual cycle followed by human menopausal gonadotrophin or recombinant FSH (rFSH) later after verification of complete ovarian suppression; (ii) approximately 15% underwent ovarian stimulation using the flare-up protocol.

Follicular growth was monitored by measurements of serum oestradiol and progesterone and by performing transvaginal sonography. Human chorionic gonadotrophin (HCG) 10,000 IU, was administered when there were at least two follicles with a mean diameter of ≥18 mm and a serum oestradiol concentration of at least 1500 pmol/l was noted. Oocyte retrieval, culture, fertilization, embryo culture and transfer were carried out.

Delivery rates were calculated according to cycle characteristics, including the number of oocytes retrieved, the number of transferred embryos and whether or not there had been the option of choosing embryos for transfer. The latter opportunity was available when there were more than three fertilized oocytes or when the number of fertilized oocytes was less than or equal to three, but greater than the number of transferred embryos.

Biochemical pregnancy was defined as a ß-HCG level>10 UI/L, 14 days after oocyte retrieval, and live birth was defined as at least one infant born alive after 24 weeks gestation.

Statistical analysis

The data was entered into the Microsoft excel and the statistical analysis was performed by statistical software SPSS version 21.0. The Quantitative (Numerical variables) were present in the form of mean and SD and the Qualitative (Categorical variables) were present in the form of frequency and percentage.

The student t-test was used for comparing the mean values between the 2 groups whereas chi-square test was applied for comparing the frequency. The p-value was considered to be significant when less than 0.05.

RESULTS

Table 1: Basic profile of the study population

	Mean (Range)
Age	33.05±4.07 (26-40)
BMI	23.37±2.49 (19.8-30.0)
Duration of infertility (years)	6.59±3.26 (0.5-15.5)
Baseline FSH	6.15 (0.9-11.0)
Baseline estradiol (pg/mL)	47.11 (10-126)
Prolactin (ng/mL)	14.05 (1.5-44.5)
Endometrial thickness at baseline (mm)	4.18 (1.6-9.2)

The mean age of the study population was 33.05±4.07 years with a age range of 26-40 years. The mean Baseline FSH was 6.15 (0.9-11.0), Baseline estradiol (pg/mL) was 47.11 (10-126), Prolactin (ng/mL) was 14.05 (1.5-44.5) and Endometrial thickness at baseline (mm) was 4.18 (1.6-9.2).

Table 2:

Age at first treatment	No. women	No. successful pregnancies (delivery rate %)
26-30	30	30.0%
31-35	39	39.0%
36-40	31	31.0%

The successful pregnancies (delivery rate %) was 30.0% among 26-30 years age group, 39.0% among 31-35 years age group and 31.0% among 36-40 years age group.

Table 3:

		Number	Percent
Aetiology of infertility	Male factor infertility	42	42.0%
	Tubal factor infertility	23	23.0%
	Anovulation	23	23.0%
	Unknown	12	12.0%
	Previous pregnancies	34	34.0%
	Prior IVF cycle	21	21.0%
	Prior IUI cycle	51	51.0%

The reason for infertility were Male factor only among 42 (42.0%), Mechanical among 20 (20.0%), Anovulation among 23 (23.0%) and Unknown among 15 (15.0%) subjects.
Previous pregnancy were reported among 34 (34.0%), Prior IVF cycle among 10 (10.0%) and Prior IUI cycle among 51 (51.0%) subjects.

Table 4:

	Mean (Range)
Days of FSH treatment	9.4±1.5 (3-13)
Total FSH dose (IU)	2,678±871 (900-5,550)
Daily FSH dose (IU)	282±59 (142-427)
Total number follicles	21.2±10.4 (4-67)
Total oocytes retrieved	16.7 (0-54)
Total embryos (including fertilization noted on day 2)	10.5 (1-26)
Embryos transferred	2.3±0.6 (0-5)
Embryos frozen	3.8±3.9 (0-21)
Day of embryo transfer	3.5±0.9 (2-6)

The mean Days of FSH treatment was 9.4±1.5 (3-13), Total FSH dose (IU) was 2,678±871 (900-5,550), Daily FSH dose (IU) was 282±59 (142-427) and Total number follicles was 21.2±10.4 (4-67).
The mean Total oocytes retrieved were 16.7 (0-54) and Total embryos (including fertilization noted on day 2) were 10.5 (1-26).
The mean Embryos transferred were 2.3±0.6 (0-5), Embryos frozen were 3.8±3.9 (0-21) and day of embryo transfer were 3.5±0.9 (2-6).

Table 5:

	Number	Percentage
Fertilization rate (2 PN/oocytes exposed to sperm)	66	66.0%
Gestational sac	47	47.0%
Fetal heartbeat	44	44.0%
Live birth	39	39.0%
Multiple birth	38	38.0%
Implantation rate	36	36.0%
Successful implantation rate	27	27.0%

The Fertilization rate (2 PN/oocytes exposed to sperm) was 66.0%.
Gestational sac was found among 47 (47.0%), Fetal heartbeat among 44 (44.0%), Live birth among 39 (39.0%), Multiple birth among 38 (38.0%), Implantation rate among 36 (36.0%) and Successful implantation rate among 27 (27.0%) subjects.

Discussion

Despite extensive progress made in the area of ART, the pregnancy rate per initiated ART cycle and the delivery rate are still around 30-33%.[19-21] The data indicated that the couples residing in an industrial/agricultural area and male partners indulged in habits of tobacco chewing, smoking or alcohol consumption had less success rate of IVF outcome. This suggests that toxicants from such exposures may have some role, at least in part in the adverse IVF outcome. These observations are in agreement with the study of Zitzmann et al[22] which also reported that

male smokers had decreased success rates of ARTs, not only in IVF, but also in intracytoplasmic sperm injection (ICSI). Marginal DNA damage was also observed in sperm and blood cells of male partners with any habits, i.e. tobacco chewing/smoking or alcohol consumption in the present study.[1]

Recently, Heger et al[23] showed that smoking had a negative effect on endometrial thickness on the day of ET. This explains the detrimental influence of tobacco smoke on implantation. Klemetti et al[24] retrieved information on IVF women's background characteristics and suggested that no remarkable regional differences were observed according to the urbanity (rural, semi-urban and urban) of the living area with regards to IVF success rates. However, in the present study, couples residing in residential areas had more positive outcomes. This might be due to the possible low level of environmental toxicants in this area.

Veleva,[25] reported that the IVF success rates were influenced by the two different set of factors classified based on their origin such as Intrinsic and Extrinsic factors. Intrinsic factors are highly important and found to possess much higher level influence on the IVF success rates and were known as Genetic predisposition, Morphological Developmental Genetics, Female age, Body mass Index, Hormonal balance, Low ovarian response, Oocyte quality, Sperm quality, Endometrial receptivity, Metabolism, Overweight, obese, insulin resistantancy, Underweight women and overall patient's response level of the candidate couple and the Extrinsic factors such as Medical equipment technology, Treatment methods, Personal experiences of clinicians and embryologists, Process time, Stress due to the lifestyle Embryo quality, Quality of frozen-thawed embryos, Prognostic factors of LR Management of LRBMI as an outcome predictor of IVF/ICSI etc are equally important in the prediction of the success rates of the IVF procedure of the candidate couple, but most of the clinicians are not considering the combitorial influence of both the intrinsic and the extrinsic factors.[3]

Factors studies alone may not able to support for the accurate prediction of IVF success rates because most of the factors denoted in intrinsic and the extrinsic were interdependent on each other so it is must that both intrinsic and the extrinsic factors in combination will certainly supports in estimating more accurate success rates of the IVF procedure which intern helpful to be the clinician and the candidate couple to take right decision.[3]

FSH

Although a recent meta-analysis study[17] still listed basal FSH as an important predictor of pregnancy. Many studies have revealed that AFC is a better predictor of ovarian response and IVF outcome than basal FSH.[26-28]

The development of several stimulated follicles often is not perfectly synchronous. In general, 15-20% of oocytes are arrested in the germinal vesicle stage or at metaphase II after hCG injection during controlled ovarian hyperstimulation in IVF, rather than advancing to metaphase II to complete meiotic maturation. Clinically, the diameter of follicles is an important indicator to judge the maturation of oocytes and to decide the timing of hCG injection. Two embryonic variables, the total number of good-quality embryos and total number of embryos, ranked as the most important and second most important predictors of clinical pregnancy chance after a completed IVF/ICSI cycle. Most previous studies focused on the quality and number of transferred embryos because they aimed at the outcome of fresh cycles.[29-32]

Cai et al[33] used the total number of good-quality embryos and total number of embryos to assess the quality and quantity of all the embryos from one ovarian stimulated cycle in our study. Among 5000 stepwise variable selections, the total number of embryos and total number of good-quality embryos were retained in the same model 99% of times and the partial PEV for the total number of embryos is the second highest among all predictors. These results suggest that the total number of embryos contributes additional information to the predictive model that the total number of good-quality embryos lacks. It may be a surrogate marker for hormone factors and may act through the uterine receptivity.[34]

Age

Age is well known as one of the most important factors predicting IVF/ICSI outcome.[35-38] Cai et al[33] showed that the chance of conceiving after a completed treatment cycle decreases as age increases and there is a sharp decline in women > 35 years. This sharp decline coincides with the corresponding deeper drop in both the total number of embryos and total number of good-quality embryos after age 35 years. These findings suggest that the age-related decline on the success in IVF most likely lies in the progressively diminished ovarian reserve, with decreases in both quantity and quality of oocytes.[35,39,40]

Several studies attempted to compare the predictive value between embryo quality and age in fresh cycles. Terriou et al.[29] pointed out that the mean score of transferred embryos was a better predictor of pregnancy than age. Lee et al.[31] found out that embryo quality was more important for younger women (≤ 35), whereas age was more important for older women (> 35 years).

Cai et al observed that the total number of good-quality embryos' predictive value measured by marginal and partial PEV was much higher than age, with statistical significance in the overall population. The total number of good-quality embryos and total number of embryos were still more predictive than age for women < 40 years. Both the total number of

embryos and number of good quality embryos decrease after age 35 years but such a decline is not significant enough to affect their predictive power for women aged 35-40 years.[33]

Number of oocytes

Univariate analysis for evaluating the influence of the number of oocytes retrieved at each cycle on delivery rates revealed that the lowest delivery rates (6.3%) were recorded in the cycles in which 1–5 oocytes were retrieved. This is in contrast to previous reports[41,42] that found similar implantation and pregnancy rates following cycles with up to 3-5 follicles compared with cycles with more follicles, although these studies included only women with normal day 3 FSH or women aged <40 years. After adjustment for the woman's age, aetiology of infertility, number of transferred embryos and whether or not there was a choice of embryo, however, the number of retrieved oocytes was no longer significantly associated with successful delivery.[33]

Number of embryos transferred

This study has shown that transferring two or three embryos is superior to single-embryo transfer (adjusted success ratio 1.97 and 2.69 respectively). However, transferring three embryos was not significantly superior to two embryos. In addition, the multiple delivery rates following a two-embryo transfer (21.5% twins) were significantly lower compared with those associated with transferring three embryos (27.7% twins, 5.3% triplets) and four embryos (33.1% twins, 6.2% triplets).[33]

These findings are consistent with previous studies[43-45] demonstrating that transfer of two embryos does not decrease pregnancy rate (although it did reduce the risk of multiple pregnancies). Most of these findings, however, come from studies conducted on women ≤ 35 years of age who had good quality embryos.

The current study suggests that regardless of the women's age, transferring two embryos is the preferred option in IVF treatments as a way to reduce multiple pregnancies without decreasing delivery rates. Hunault et al.[30] suggested a predictive model, taking into account women's age and embryo quality for selecting patients for elective single embryo transfer in order to reduce the chance of twin pregnancy.

De Neubourg and Gerris,[46] and Gurgan and Demirol,[47] have shown that when a good prognosis group is chosen for a single-embryo transfer, pregnancy rate can be as high as 40%. However, in the double-embryo transfer group, pregnancy rates were higher compared with the single-embryo transfer group but there was a greater number of multiple pregnancies. Zegers-Hochschild et al.[48] suggested that multiple pregnancies are not solely dependent on the number of embryos transferred, but rather may reflect a subgroup of highly fertile women.

BMI

Obesity is a consequence of some genetic diseases also associated with infertility and has an adverse effect on male fertility.[49] Male obesity is emphasized by physicians in the process of infertility treatment so as to facilitate the success of the treatment (OR=1.104 in Table 3). The couple's BMI, which is often negatively correlated with fertility outcomes (20, 28), was not a con- founding variable in the present study, as the mean BMI was normal in half of the women while others were only mildly overweight. Obesi- ty appears to have a greater adverse effect on fertility in men.[50]

Zarinara et al[5] in their study reported that only 5% of the men had a BMI above 33 and the increase in BMI increases the chances of success by 6%. Perhaps this interpretation is surprising at first glance, but 41% of men had BMI lower than normal level and 3% were obese. Thus the increase in BMI has brought men's weight closer to normal for achieving success. This justification has also been raised in MacDonald et al[83] investigations. The interpretation needs to be more carefully considered as complementary research. In our research, family marriages (marriage with aunt or uncle's daughter) have not significant ef- fect on treatment success rate. Although research has been emphasized on the fate of pregnancy in family marriages by factors may activate immunologic or ambiguous factors.[51]

Summary and conclusion

The successful pregnancies (delivery rate %) was 30.0% among 26-30 years age group, 39.0% among 31-35 years age group and 31.0% among 36-40 years age group.

Majority (42.0%) reported that the main reason for infertility was male factor followed by mechanical (20.0%), Anovulation (23.0%) and Unknown among 15.0% subjects. Age at the time of IVF and FSH serum levels are the crucial factors to get success in assisted reproductive technology and frozen embryo transfer (FET) techniques, and should be considered. The other clinical factors (i.e. reason for embryo cryopreservation, ovulation-stimulating protocol, type of infertility, endometrial thickness at embryo transfer day, and the duration of treatment) seem to have no effects on the pregnancy outcome following FET.

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