Saudi Journal of Medicine (SJM)
Scholars Middle East Publishers
Dubai, United Arab Emirates
Website: www.saudijournals.com

ISSN 2518-3389 (Print)
ISSN 2518-3397 (Online)

Factors Affecting Outcomes of IVF in Unexplained Infertility

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Article History
Received: 06.12.2018
Accepted: 15.12.2018
Published: 30.12.2018

DOI:
10.36348/sjm.2018.v03i12.005

Abstract: Unexplained infertility refers to the absence of a definable cause for infertility despite a thorough evaluation. Subtle abnormalities like mild endometriosis, minor tubal dysfunction as evidenced by presence of peritubal adhesions or partial fimbrial phimosis, endometrial defects, may be unearthed by thorough investigations in these couples labelled with unexplained infertility. Primary objective of the study was to determine if IVF outcomes in unexplained infertility are different from other cause of infertility like male or tubal factor infertility. Secondary objectives were to find out what intrinsic or extrinsic factors in unexplained infertility influence IVF results. Based upon these factors, to help in prognosticating couples with unexplained infertility before they enter IVF. The study was explained to all eligible couples undergoing IVF at centre. They were offered participation in study and given a patient information sheet to understand the study. Those who accepted to take part in the study were enrolled in study. After applying inclusion and exclusion criteria, three cohorts of unexplained, male and tubal are formed according to their indication of IVF cycle. Age of female partner was the only variable which showed statistically difference. Mean age of female partner of unexplained group was 34.12 ± 3.69 years, and of tubal & male group it was 33.00 ± 4.2years 3, 32.13 ± 3.69 years respectively (p value 0.047 < 0.05). Laparoscopy and hysteroscopy offered not only to establish the diagnosis but also helping couple knowing their chances of successful pregnancy in IVF.

Keywords: Unexplained Infertility, IVF, Laparoscopy.

INTRODUCTION

Unexplained infertility refers to the absence of a definable cause for infertility despite a thorough evaluation. According to Practice Committee of the American Society for Reproductive Medicine (ASRM), necessary test before labelling a couple with unexplained infertility are semen analysis, assessment of ovulation and assessment of tubal patency by HSG or by laparoscopy [1]. Unexplained infertility remains a diagnosis of exclusion. Our inability to find a cause does not mean that there is no cause existing for infertility. About 15-30 % of all infertile couples have unexplained infertility [2].

Subtle abnormalities like mild endometriosis, minor tubal dysfunction as evidenced by presence of peritubal adhesions or partial fimbrial phimosis, endometrial defects, may be unearthed by thorough investigations in these couples labelled with unexplained infertility. After excluding these subtle causes, unearthed by a second line of investigation, the incidence of unexplained infertility is approximately 10-15 % [3]. Causes attributable to true unexplained infertility may have to do with ovum/sperm quality, including ability of spermatozoa to negotiate utero-tubal junction, processes like capacitation, sperm oocyte interaction, fertilization, cleavage and the ability of oocyte to support early embryonic development [4]. These causes cannot be determined by routine methods of investigation.

While some of the steps involved in embryogenesis, (till the level of sperm- oocyte interaction) may be bypassed by in vitro fertilization or intracytoplasmic sperm injection (IVF-ICSI), the downstream events post sperm entry vis-à-vis, fertilization, cleavage, blastulation or implantation cannot be bypassed by these procedures. These steps are loosely considered a function of sperm/oocyte quality [5]. Studies have shown that unexplained infertility has poor results of IVF compared to other obvious reasons like male factor or tubal factor. Audibert *et al*., in 1989 found lower fertilization and pregnancy rate in unexplained infertility compared to tubal group .In their study fertilization rate was 45.7% vs. 59.8 % and pregnancy rate was 13.8 % vs. 19.5% in unexplained infertility.

Then Hull *et al*., in 1998 also observed lower fertilization rate in patients with unexplained infertility

in IVF compared fertilization rate in patients with endometriosis. Fertilization rate was 56% (n=194) in endometriosis and it was 52% (n=327) in unexplained group.

These poor IVF results in unexplained infertility may be due to inherent poor oocyte quality in these patients which cannot be overcome by IVF/ICSI [6].

What are the intrinsic factors in patients with unexplained infertility, are associated with this lower success rate of IVF has not been studied, in detail, till now.

In 1989, Collin JA *et al.*, (n=470) studied the impact of base line characteristics on likelihood of live birth among infertile couples and found that addition of each one month in duration of infertility, reduced the success of IVF by 2% and addition of 1 year in age of female partner, where duration of infertility was ≥ 3 years, reduces the prognosis by 9% [7].

These were the studies from old past, from then now through various studies, it has been possible to prognosticate the success of IVF in unexplained infertility based on the age of female partner.

According to Human Fertilisation Embryology Authority HFEA, the average success rate of IVF in unexplained infertility is [8].
28.2% for women <35years
23.6% for women aged 35–37years
18.3% for women aged 38–39 years
10.6% for women aged 40–42years

Present live-birth rate among women with unexplained infertility, according to Practice Committee Bulletin of ASRM, 2006, is approximately 30.4% [9].

Given this background this prospective, cohort study was sought to add on in our knowledge about impact of intrinsic factors such as type of infertility, BMI, serum AMH levels and previous treatment history, on success of IVF in unexplained infertility.

Primary objective of the study was to determine if IVF outcomes in unexplained infertility are different from other cause of infertility like male or tubal factor infertility.

Secondary objectives were to find out what intrinsic or extrinsic factors in unexplained infertility influence IVF results. Based upon these factors, to help in prognosticating couples with unexplained infertility before they enter IVF.

MATERIALS & METHODS

A Prospective observational cohort study was completed tertiary care teaching hospital in New Delhi with in time period July 2017 to January 2018.

Sample Size

For this observational study, sample size calculation was done by defining a relevant difference of 15% in IVF outcome between the cohorts of unexplained infertility and the cohorts of tubal & male factor infertility. Using a one tailed alpha value of (0.05) and a beta value of (0.2), 128 patients per group would be needed per cohort to detect a significant difference.

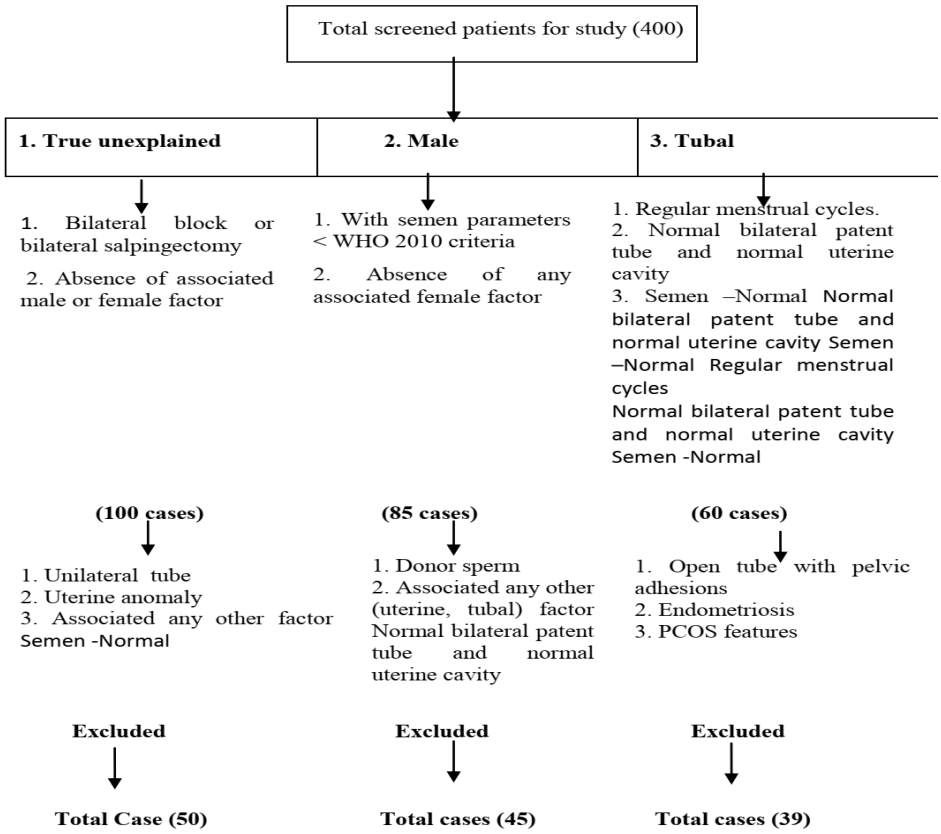
METHODOLOGY

The study was explained to all eligible couples undergoing IVF at our centre. They were offered participation in study and given a patient information sheet to understand the study. Those who accepted to take part in the study were enrolled in study. After applying inclusion and exclusion criteria, three cohorts of unexplained, male and tubal are formed according to their indication of IVF cycle.

Inclusion and exclusion criteria:

	Inclusion criteria	**Exclusion criteria**
Unexplained Infertility	Normal semen parameters (WHO 2010 criteria)	Open tube with pelvic adhesion
	Regular menstrual cycles implying presence of ovulation	Endometriosis
	Bilateral patent tubes on HSG/ laparoscopy	PCOS feature
		Coexisting mild or severe male factor.
Male Factor	Semen parameters < WHO 2010 criteria	IVF cycle with donor sperm
	Absence of any associated female factor	Associated female factor
Tubal Factor	Bilateral block or bilateral salpingectomy	Unilateral tube
	Absence of associated male or female factor	Uterine anomaly

Flow chart



Demographic variables noted in each group were:

- Age
- BMI
- Menstrual cycle characteristics
- Type of infertility primary or secondary.
- Duration of infertility
- Obstetric history, previous obstetric outcome.
- History of previous IUI or IVF
- History of previous laparoscopy with hysteroscopy done or not, if done findings of pelvic adhesions or endometriosis was present or not / surgical procedure done or not, status of tubes /tubo-ovarian relationship was also saught if available.
- AMH value in pmol/l.

Characteristics of IVF cycle noted in each group were:

- Total dose of gonadotropins
- Peak serum estradiol and endometrial thickness on day of trigger
- No. of oocytes retrieved
- M2 retrieved
- Fertilization rate.
- Total day 2/3 embryos utilized
- Total day 5/6 blastocysts utilized.

Outcomes measured in each groups were:

- Primary outcome- On going pregnancy rate i.e. pregnancy continued after 12 weeks
- Secondary outcomes–

1. Positive beta hCG rate both in fresh transfer and frozen embryo transfer cycles i.e. beta hCG>25 miu/ml 16 days after oocyte pic up in fresh transfer cycles, beta hCG>25 miu/ml on day 14 of D2 embryo transfer, on day 13 of D3 embryo transfer, on day 11 of D5 embryo transfer in case of frozen embryo transfer cycles.
2. Pregnancy loss rate-pregnancy loss due to biochemical pregnancy, ectopic pregnancy, blighted ovum, missed abortion.

Characteristics and outcomes of unexplained infertility was compared with male and tubal group.

Statistical analysis

The comparison between three groups was performed by using Student's t-test. Categorical variables were compared by using the chi square test.

Multiple Logistic Regression analysis was performed on all studied variables to determine those factors, most influencing IVF outcomes.

P<0.05 was considered stastically significant. Data analysed using the SPSS software version 13.0.

RESULTS

Table-1: Demographic variables comparison in three groups

S. No	Variable	Unexplained (50)	Tubal (39)	Male (45)	p- value
1.	Mean age (years)	34.12 ± 3.69	33.00 ± 4.23	32.13 ± 3.69	0.047
2.	Mean BMI (Kg/m2)	25.90 ± 0.51	25.84 ± 0.76	25.52 ± 0.57	0.891
3.	Mean duration of infertility(years)	4.38 ± 2.97	4.76 ± 3.1723	3.95 ± 2.97	0.329
4.	Type of infertility (Prim/sec)	72%:28%	56.4%:43.6%	75.6%:24.4%	0.137
5.	Previous live issue (yes/no)	12%:88%	20.5%:79.5%	11.1%:88.9%	0.401
6.	Mean S.AMH (pMol/l)	19.56 ± 15.88	22.56 ± 14.22	20.59 ± 14.64	0.378

Table-1 shows comparison of basic demographic variables among three groups, variables like mean BMI, mean duration of infertility, type of infertility, previous live issue, mean serum AMH levels, were comparable (p value > 0.05). Mean age in unexplained group was 34.12 ± 3.69 years which was higher compared to male and tubal groups and this was statistically significant also. (p value 0.047, < 0.05).

Table-2: IVF cycle characteristics comparison in three groups

S. No	Variable	Unexplained(50)	Tubal(39)	Male (45)	p- value
1.	Total dose (IU)	2235.40 ± 874.41	2144.87 ± 914.67	2211.67 ± 864.87	0.306
2.	Peak Estradiol (pg/ml)	9.28 ± 1.77	2131.51 ± 1233.94	11.11 ± 7.07	0.448
3.	Endometrial thickness (mm)	10.90 ± 7.48	8.83 ± 1.88	5.77 ± 4.03	0.456
4.	Mean no. of oocyte	5.98 ± 4.639	12.15 ± 6.49	58.6% ± 29580	0.389
5.	Mean no.of 2 PN	49% ± 28.09%	6.85 ± 3.910		0.310
6.	Embryo utilization rate		55% ±30.13%		0.349

Table shows that IVF Cycle characteristics like total dose of gonadotropin required for stimulation, peak estradiol levels, endometrial thickness, mean no of oocytes retrieved, mean no of 2 PN formed and embryo utilization rate, in each group of unexplained, male and tubal factor infertility were not significantly different (p value > 0.05).

Table-3: Fresh transfer cycle outcomes comparison in three groups

S. No	Variable	Unexplained (50)	Male (45)	Tubal (39)	p value
1.	Positive beta hCG rate	8/32 (25%)	9/28 (32.14%)	8/26 (30.7%)	p-0.91 (T vs M) p-0.11 (U vs M) p-0.11 (U vs T)
2.	Pregnancy loss rate	¼ (25%)	3/9 (33.3%)	1/8 (12.5%)	p-0.57 (T vs M) p-1.00 (U vs M) p-1.00 (U VS T)
3.	Ongoing pregnancy rate	7/32 (21.8%)	6/28 (21.42%)	7/26 (26.9%)	p-0.90 (T vs M) p-0.28 (U vs M) p-0.16 (U vs T)

Table-3 shows fresh transfer cycle outcomes in terms of positive beta hCG rate and ongoing pregnancy rate. Positive beta hCG rates were 25 %, 32.14%, and 30.7% while ongoing pregnancy rates were 21.8%, 21.42% and 26.9% in unexplained, male and tubal groups respectively. Although the numerical values of outcomes were almost comparable in three groups, were not significantly different (p >>0.05). But a trend of lower outcome measures values was seen in unexplained group (25% vs 32.14%, 30.7%).

Table-4: Frozen embryo transfer cycle outcome comparison in three groups

S. No	Variable	Unexplained (50)	Male (45)	Tubal (39)	p- value
1.	Positive beta hCG rate	7/11 (63.63%)	11/14 (78.57%)	9/15 (60%)	p-0.42 (T vs M) p-0.65 (U vs M) p-0.70 (U vs T)
2.	Pregnancy loss rate	1/7 (14.28%)	1/14 (7.1%)	0/9 (0%)	p-1.00 (T vs M) p-1.00 (U vs M) p-0.43 (U vs T)
3.	Ongoing pregnancy rate	6/11 (54.5%)	10/14 (71.4%)	9/15 (60%)	p-0.69 (T vs M) p-0.43 (U vs M) p-1.00 (U vs T)

In frozen embryo transfer cycles also unexplained group had lower on going pregnancy rate compared to tubal and male factor infertility, 54.5% vs 60% & 71.4%, although the difference is not reaching up to the level of statiscally significance. (p>0.05)

Table-5: Comparison of pregnancy rate per patient in three groups

S. No	Variable	Unexplained (50)	Male (45)	Tubal (39)
1.	Pregnancy rate	13/43 (30.23%)	15/41 (36.58%)	13/37 (35.13%)
2.	p- value	p-0.172 (Unexplained vs Male)	p-0.231 (Unexplained vs Tubal)	p-1.00 (Tubal vs Male)

Table shows pregnancy rate calculated per patient, in three groups. It was 30.23 %, 36.58% and 35.13 % in unexplained, male and tubal groups respectively.(p>0.05)

Table-6: Factors prognosticating success of IVF in unexplained group

S. No	Variable	Spearman's Correlation Coefficient	p- value
1.	Age	-0.216	0.132
2.	BMI	-0.128	0.376
3.	Duration of infertility	-0.200	0.164
4.	AMH	-0.070	0.631
5.	Previous IUI	0.021	0.885
6.	Previous IVF	-0.247	0.083
7.	Laparoscopy + hysteroscopy	-0.387	0.006

Table shows multiple logistic analysis of characteristics of unexplained infertility group to find out factor influencing success of IVF. Age of female partner, duration of infertility, history of previous failed IUIs, had negative impact on IVF outcome measures in patients with unexplained infertility.

DISCUSSION

IVF is the treatment of choice for unexplained infertility when not only less costly, but also less successful, treatment modalities like ovarian stimulation with intrauterine insemination OS-IUI have failed. Approximately only one-third of couples with unexplained infertility achieve a live birth after OS-IUI. Therefore remaining two third patients will seek IVF to have a successful pregnancy [10, 11].

In this study, for first time, we compared base line characteristics of couples with unexplained infertility, with other two groups of infertility male and tubal factor, who undergone IVF at our centre.

Then sub analysis of unexplained infertility was done to find out which intrinsic factors maximally affected the outcomes of IVF in this group.

We found that basic variables like mean BMI, mean duration of infertility, type of infertility, previous live issue, and mean serum AMH levels were not statistically differed in all three groups (p value > 0.05).

Age of female partner was the only variable which showed statistically difference. Mean age of female partner of unexplained group was 34.12 ± 3.69 years, and of tubal & male group it was 33.00 ± 4.2years 3, 32.13 ± 3.69 years respectively (p value 0.047 < 0.05). This observation may be denoting the fact that, couples with unexplained infertility had either opted IVF after many years of their infertility because no obvious cause was there to sort out or they had approached to IVF as the treatment modality after investing their time either in other treatment modalities like IUIs or being gone through diagnostic modalities

like laparoscopy ± hysteroscopy for actually finding out their cause of infertility.

IVF cycles of this study of three groups were fixed antagonist protocol. IVF cycle characteristics, total dose of gonadotropin required for optimal stimulation, peak estradiol level, endometrial thickness achieved at the time of trigger was given, were statistically comparable in all three groups (p value > 0.05).

Mean no of oocytes retrieved, mean no of 2 PN formed and embryo utilization rate, in each group of unexplained , male and tubal factor infertility were also not significantly different.(p value > 0.05).This implied that none of IVF cycle parameter were going to affect the primary or secondary outcome of each group of cohorts.

Pregnancy outcomes were calculated in terms of positive beta hCG rate and ongoing pregnancy rate. In fresh transfer cycles positive beta hCG rates were 25 %, 32.14%, and 30.7% in unexplained, male and tubal groups respectively. Out of these patients, pregnancies that resulted in blighted ovum, or missed abortion or ectopic pregnancies during follow up period of 12 weeks or were biochemical nature, were excluded from further analysis. Only pregnancies continuing beyond 12 weeks were included to calculate ongoing pregnancy rates of each group. Ongoing pregnancy rate dropped down to 21.8%, 21.42% and 26.9% in unexplained, male and tubal groups respectively due aforementioned causes.

Although both positive beta hCG rate and ongoing pregnancy rate in three groups for fresh transfer cycles, were not significantly different (p >0.05), but a trend of lower positive beta hCG rate and ongoing pregnancy rate was seen in unexplained group (25% vs 32.14%, 30.7%).

Frozen transfer cycles have better pregnancy results due to less supra physiological levels of hormones, better synchronization of endometrium and embryo and state of uterine quienence. Positive beta hCG rate in frozen embryo transfer cycles, compared to fresh cycles increased, from 25 % to 63.63%, from 32.14 % to 78.5 % and from 30.7% to 60 % in all three, unexplained, male and tubal cohorts respectively. Pregnancy losses due to blighted ovum, missed abortion, and ectopic pregnancies also happened in frozen transfer cycles, but to a lesser extent, pregnancy loss rates were 25 % vs 14.28%, 33.3% vs 7.1% 12.5% vs 0% for unexplained, male and tubal factor cohort respectively.

After these losses on going pregnancy rate dropped down from 63.63% to 54.5 % in unexplained group and , from to 78.5 to 71.4 % in male group .Tubal group did not suffered any loss .But still going pregnancy rates of frozen transfer cycle were higher than fresh cycles, 21.8% vs 54.5 %, 21.42% vs71.4 %, and 26.9% vs 60% .

Although this difference in pregnancy outcome measures of three cohort is not statistically significant, that we also found in fresh transfer cycles (p value >0.05),but trend of lower on going pregnancy rates in unexplained group was as, as it was seen in fresh transfer cycles, 54.5% vs 60% & 71.4%.

Separate analysis of base line characteristics, like age of female partner ,BMI, duration of infertility, serum AMH value ,history of previous failed IUIs and previous IVF of unexplained infertility cohort , was done by multiple logistic analysis, to find out correlation of these characteristics and success of IVF cycle , if there was or not.

Analysis of correlation with success of IVF was done by calculating Spearman's correlation coefficient value for each of characteristics. Negative value of Spearman correlation coefficient of certain characteristic denotes that it has negative correlation to particular outcome, that is ongoing pregnancy rate in this study and numerical value of coefficient tells about how strong is the correlation. Value approaching nearer to one have stronger impact than those having values in decimals.

Age of female partner, BMI and duration of infertility had spearman correlation coefficient values, -0.216, -0.128 and -0.200 respectively .So it can be concluded that older females, with obesity and longer duration of unexplained infertility have lesser chances of successful pregnancy after IVF, although this statement cannot generalised for each and every patient of unexplained infertility because p values of these characteristics were 0.132, 0.337 and 0.164 that is >> 0.05. This may be because of small size of population studied.

Out of these three characteristics, p value of Spearman's correlation coefficient of duration of infertility, seems to approaching nearer to the level significance (p value -0.164). From this we can say that even older females, but with short duration of infertility, will have better prognosis of IVF than younger females with long duration of infertility.

Out of all these base line factors, history of previously failed IVF and findings of no obvious pathology in pelvis and or uterus in laparoscopy and hysteroscopy, showed most strong correlation with success of IVF.

Spearman's correlation coefficient value for history of previous failed IVF was -0.247 with p value

of 0.083 and for documentation of diagnosis of true unexplained infertility by previous laparoscopy and hysteroscopy, it was -0.387 with p value of 0.006 ($p << 0.05$).

Duration of infertility and diagnosis of true unexplained infertility made after negative laparoscopy and hysteroscopy, are two most strong base line factors that can prognosticate successful pregnancy in patients with unexplained infertility before they enter IVF.

SUMMARY & CONCLUSION

Unexplained infertility a diagnosis of exclusion in the sense that cause remains unknown even after an detailed work up .There is a constant debate on the need of evaluation of pelvis and uterine cavity by laparoscopy and hysteroscopy before the diagnosis of unexplained infertility is made. According to ASRM, laparoscopy should be performed in women with signs or symptoms of endometriosis, or in whom reversible adhesive tubal disease is suspected [12].

If laparoscopy and hysteroscopy can be used prognosticate, other than just being used for establishing a diagnosis of unexplained infertility is not even questioned yet. From this study we have concluded that the IVF gives good results in unexplained infertility, when it is offered in couples with lesser duration of infertility, younger age of female partner.

Duration of infertility and diagnosis of true unexplained infertility made after negative laparoscopy and hysteroscopy, are two most strong base line factors that can prognosticate successful pregnancy in patients with unexplained infertility before they enter IVF.

So laparoscopy and hysteroscopy should be offered not only to establish the diagnosis but also helping couple knowing their chances of successful pregnancy in IVF.

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