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Original Research Article

Evaluation and Treatment of Unexplained Infertility in a Tertiary Care Centre

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Abstract

Background: Unexplained infertility is defined as the failure to conceive without any definitive cause for infertility. The incidence was 15-30% of all infertile couples. The diagnosis of unexplained infertility is made when regular investigations for infertility do not show any obvious barriers to conception. It was also termed as Idiopathic Infertility by some authors and included multiple and different conditions causing infertility.

Aims: To evaluate and treat couples who were diagnosed to have unexplained infertility; to evaluate the outcome following treatment.

Secondary Objectives: To compare and evaluate with couples who have other causes of infertility other than unexplained infertility.

Methods: A total of 80 couples were divided into a study and a control groups. 40 were belonging to study group, Control group contained 10 cases of oligospermia, 10 of PCOS, 10 of tubal block, 10 cases of hypothyroidism. All the investigations were carried out, treated according to the cause and compared the outcome in different groups. The study was primarily aimed at investigating the couples to evaluate the cause of unexplained infertility and treating them accordingly.

Results: According to the age of the couples, BMI did not show any significance as all were almost in normal limits. In case of PCOS, 60% had conceived with proper approach. HSA association in infertility has been proved where the p value was <0.05 which was statistically significant. In the control group out of oligospermia couples, 3 conceived with ICSI which showed a pregnancy rate of 30%. In Hypothyroid couples the conception rate was 40-50% which was statistically significant. IUI+COH was done in the study group on two days showed a conception rate of 45% when compared to OI alone.

Conclusions: Proper categorization of the infertile couples was essential and most important in planning the management and avoiding unnecessary investigations. Proper counselling plays an important role in all the unexplained infertility couple in regards with investigations and treatment. The fertility rate in the infertile couples could be improved even though the exact cause infertility could not be explained. Finally, we conclude that proper identification and management will show a good outcome, irrespective of the cause of infertility.

Keywords: Infertility, Unexplained infertility, idiopathic infertility, clomiphene and HCG

Introduction

Infertility is customarily defined as the inability to conceive after 1 year of regular unprotected intercourse. The infertility evaluation is typically initiated after 1 year of trying to conceive, but in couples with advanced female age (35 years), most practitioners initiate diagnostic evaluation after an inability to conceive for 6 months [1]. Typically, 80% of couples (aged 18-28 years) will conceive over a one-year period and another 10% conceive during the following year. The Practice Committee of the American Society for Reproductive Medicine (ASRM) has published guidelines for a standard infertility evaluation [1]. It includes a semen analysis, assessment of ovulation, a hysterosalpingogram and if indicated, tests for ovarian reserve and laparoscopy. When the results of a standard infertility evaluation are normal, practitioners assign a diagnosis of unexplained infertility. Although estimates vary, the likelihood that all such test results for an infertile couple are normal (i.e, that the couple has unexplained infertility) is approximately 15% to 30% [2] Reasons for the increasing incidence of infertility include postponement of childbearing, increased pelvic infections and in some countries, deteriorating sperm quality [3]. The reasons for infertility are related to female factors, male factors, to a combination of the two or to unknown causes, each comprising 25%. The most frequent causes for infertility are ovulatory disorder or anovulation, tubal factor, abnormal semen parameters, endometriosis and uterine or cervical factor [4]. Less common causes for infertility are immunological factors and genetic defects. Smoking also decreases the ability to conceive [5]. Infertility in many couples has multiple aetiologies; however, in approximately 15-30% of couples, no reason for infertility is found and the infertility is defined as unexplained [6]. Despite advances in diagnostic assessment of infertility, many couples still have no explanation for their infertility. Even the most sophisticated evaluation cannot reveal all of the possible defects in conception as it arise from these shortcomings in our inability to utilize all of current knowledge; unexplained infertility is a challenge for both biological and clinical research [7]. This research attempts to summarize some clinical issues in management of unexplained infertility, prevalence of disorder, problems in definition and possible explanations for existence of this diagnostic category. It reviews outcome based clinical publications as a guide to decision making on what diagnostic tests to use provides a summary of untreated prognosis and evaluates study results that may serve as a basis for treatment decisions in this puzzling diagnostic category of infertility. Infertility is a burning problem in the country; unexplained infertility is as such frustrating problem to the couple. In this study we want to show that proper evaluation and management in a tertiary care centre can solve the problem. A diagnosis of unexplained fertility can be highly frustrating for patients, who may interpret this as meaning that there is apparently “no cause” for their sub-fertility and hence no effective treatment. Unexplained sub-fertility is a diagnosis of exclusion. Up to 25% of patients who present for investigation in a reproductive medicine clinic are diagnosed with unexplained fertility. The diagnosis is usually made after investigations show normal semen parameters, ovulatory concentrations of serum progesterone in the mid-luteal phase, tubal patency, and a normal uterine cavity [8]. The objective of our study was to summarize some clinical issues in

management of unexplained infertility, prevalence of disorder, problems in definition and possible explanations for existence of this diagnostic category, to properly investigate the couple, treat them according to the cause and to try for a better outcome. Clinicians know how strong the pressure is to treat those whose infertility is unexplained. We contend that in many cases a much more rigorous investigation of such couples will uncover reasons to explain the unexplained and may, thereby, provide at least some hope for rational and effective treatment in the future.

Materials and Methods A prospective analytical study was conducted including 80 couples attending the Obstetrics OPD of Viswabharathi Medical College and Hospital, Penchikalapadu, Kurnool, A.P, a tertiary care hospital. An institutional ethics committee clearance was obtained before commencing the study. An ethics committee approved consent form and proforma were used for the study.

Inclusion Criteria: Couples attending the infertility clinic with history of infertility were included in the study. Couples of child bearing age were included. Couples willing to participate in the study and get evaluated were included.

Exclusion Criteria: Couples who had already investigated and a known cause of infertility was established were excluded from the study. Couples with associated presence of hypothyroidism, congenital abnormalities of the reproductive tract were excluded. Couples with diagnosed malignant diseases were excluded.

Study design: The present study was a prospective, descriptive and analytical study. Among the 80 couples, 40 couples were considered as actual sample and the remaining 40 couples were considered as control group. Study duration was between Jan 2019 and Dec 2021.

Sample Size Determination:

Estimated sample size of 40 and with control group 40.

$$n = \frac{X^2 * N * P * (1 - P)}{(ME^2 * (N - 1)) + (X^2 * P * (1 - P))}$$

Where

N = sample size

X^2 = Chi Square for the specified confidence level at 1 degree of freedom

N = Population size

P = Population proportion (.50 in this table)

ME = Desired margin of Error (Expressed as a proportion)

Statistical tests and analysis: The Data was analyzed using descriptive and inferential studies. The Statistical Package for Social Science (SPSS) 18.0 software package was utilized to analyze the data. All values were expressed as mean and standard deviation. Mean and median were calculated based on the distribution of parameters. We calculated descriptive statistics for continuous variables. Chi-square test was used to calculate the significance of the association for continuous variables between groups. A p value of <0.05 was taken as statistically significant. A p value of <0.01 was taken as highly significant. Statistical operations were done through statistical presentation system.

Results

Association between different age groups:

A comparison was made between the unexplained infertility group and control group in relation to age and infertility. Most of the study population was less than 25 years of age in both the groups. As the maternal age increased the infertility outcome was less. In the unexplained infertility group even though the age was less, the infertility outcome was poor when compared to other groups as the cause could not be defined. The association

between age and infertility were measured using chi square test and its value was 5.000 which was not statistically significant (p-0.777), **(Table 1 and Fig 1).**

This could be due to study population was aged less than 35 years. Age more than 35 years is usually associated with poor fertility outcomes.

Table 1: Age distribution of two groups (n-40 in each group)

Crosstab				
Age Results Observations		**Groups**		**Total**
		Control	**Unexplained**	
Age	<25 years count	18	20	38
	% within age	47.4%	52.6%	100%
	% within groups	45%	50%	47.5%
	25-30 years count	15	12	27
	% within age	55.6%	44.4%	100%
	% within groups	37.5%	30%	33.8%
	>30 years count	7	8	15
	% within age	46.7%	53.3%	100%
	% within groups	17.5%	20%	18.8%
Total count		40	40	40
% within age		50%	50%	50%
% within groups		100%	100%	100%

Inference: Samples were age matched with chi square 0.505, p=0.777.

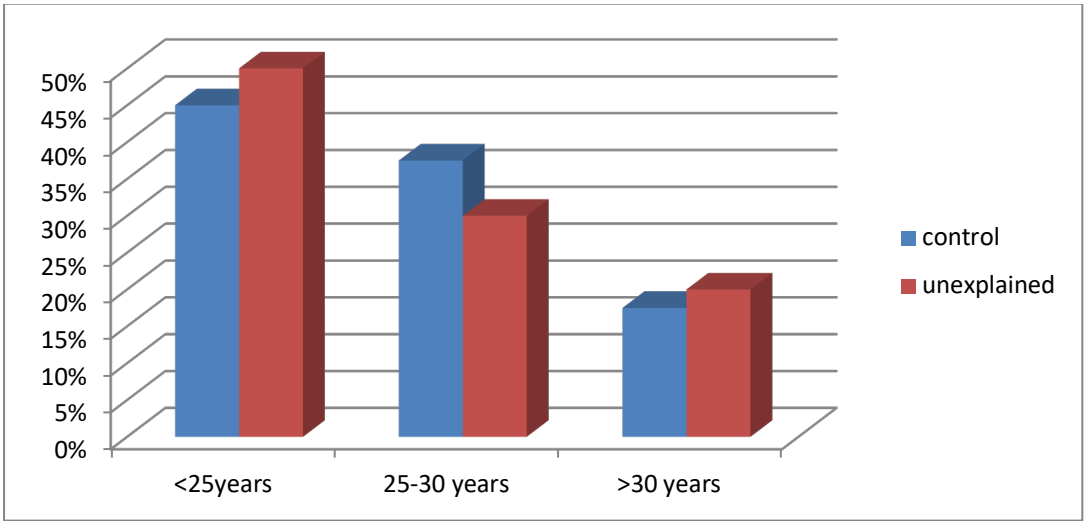

Figure 1: Age distribution between both groups

Association between caffeine intake in control and unexplained groups:

Association between caffeine intake in control and unexplained groups were observed. Couples of study group and control group who consumed caffeine were comparatively less than those who did not consume caffeine. Those who consumed caffeine also took only two to three cups of

caffeine per day. There was no association between the caffeine consumers and incidence of infertility in the study (chi square value of 0.058 with a p value of 0.809), **(Table 2).**

Table 2: Caffeine intake in both groups

Crosstab					
Results Observation			**Control**	**Unexplained**	**Total**
Caffeine Intake	No	Count	28	27	55
		% within caffeine intake	50.9%	49.1%	100.0%
		% within Groups	70.0%	67.5%	68.8%
	Yes	Count	12	13	25
		% within caffeine intake	48.0%	52.0%	100.0%
		% within Groups	30.0%	32.5%	31.3%
Total		Count	40	40	40
		% within caffeine intake	50.0%	50.0%	100.0%
		% within Groups	100.0%	100.0%	100.0%

Inference: samples were compared, chi square of 0.058, p value=0.809.

Association between body mass index [BMI] and infertility outcome

In this study the associations between weights of both study groups were observed. In unexplained infertility group, most of them were in normal BMI. In control group also, most of them were in normal BMI, except for the PCOS group, where there BMI is more. In the above table, chi square value of 2.296 with p value of 0.130 which statistically showed that there was no significant association between BMI and infertility. **(Table 3)**

Table 3: Association of weight between two groups

Crosstab			
BMI Observations Results	**Groups**		**Total**
	Control	**Unexplained**	
Normal count	31	36	67
%within BMI	46.3%.	53.7%	100%
% within groups	77.5%	90%	83.8%
Overweight count	9	4	13
%within BMI	69.2%	30.8%	100%
% within groups	22.5%	10%	16.3%
Total count	40	40	80
%within BMI	50%	50%	100%
% within groups	100%	100%	100%

Inference: Both groups compared, chi square 0f 2.296, p value=0.130

Association between tobaccos in take in different study groups

In this study an observation was made between the tobacco intake and the infertility in both the groups. Neither the study group nor the control group, were associated with tobacco intake. We have considered only tobacco intake of female partner in this study. (Table 4)

Table 4: Comparison of tobacco intake in two groups

Crosstab			
Results Observation	**Groups**		**Total**
	Control	**Unexplained**	
Tobacco No count	40	40	80
%within tobacco intake	50%	50%	100%
%within groups	100%	100%	100%
Total count	40	40	80
%within tobacco intake	50%	50%	100%
%within groups	100%	100%	100%

Association between alcohol intakes in different groups:

In this study observation was made to study the association between alcohol intake in both the groups and infertility and found that neither the study group nor the control group were associated with alcohol consumption. **(Table 5)**

Table 5: Alcohol intake in both groups

Crosstab			
Results Observations	**Groups**		**Total**
	Control	**Unexplained**	
Alcohol intake No count	40	40	80
% within alcohol Intake	50%	50%	100%
% within groups	100%	100%	100%
Total count	40	40	80
% within alcoholIntake	50%	50%	100%
% within groups	50%	50%	100%

In this study the association between duration of marital period and infertility outcome was observed and found that most of the study group populations were in a martial period of less than two years, as evaluation for infertility has been started early these days. The chi square value was 4.925 which was not statistically significant (p-0.177). (Table 6)

Table 6: Association of marital period in both groups

Results Observation		**Control**	**Unexplained**	**Total**
Marital Period (years)	<2yrs Count	10	18	28
	% within marital period	35.7%	64.3%	100%
	% within groups	25%	45%	35%
	2-5 yrs Count	25	18	43
	% within marital period	58.1%	41.9%	100%
	% within groups	62.5%	45%	53.8%
	5-10 yrs Count	5	3	8
	% withinmarital period	62.5%	37.5%	100%
	% within groups	12.5%	7.5%	10%
	20yrs Count	0	1	1
	% within marital period	0%	100%	100%
	% within groups	0%	2.5%	1.3%
Total Count		40	40	80
% within marital period		50%	50%	100%
% within groups		100%	100%	100%

Interpretation: two studies compared, chi square of 4.925 with p value=0.17

Association between menstrual cycles and infertility outcome

In this study the association between menstruation and infertility were studied and found that in case of unexplained infertility group, menstrual periods were regular. Even in control group the periods were regular for most of all the population, except for PCOD group and few of Hypothyroid population. There was no association of menstruation with infertility in this study group. But in cases where cycles were irregular, menstruation showed high significance where the p value was < 0.001. **(Table 7)**

Table 7: Effect of menstrual cycles in both groups

Crosstab			
Menstruation Results Observations	**Groups**		**Total**
	control	**unexplained**	
Menstrual Regular Countcycle	29	40	69
% within menstrual cycle	42%	58%	100%
% within group	75%	100%	86.3%
Irregular Count	11	0	11
% within menstrual cycle	100%	0%	100%
% within group	27.5%	0%	13.8%
Total Count	40	40	80
% within menstrual Cycle	50%	50%	100%
% within groups	100%	100%	100%

Interpretation: Two studies showed chi square value of 12.754 with p value <0.001

Association of TSH in infertility

In the present study the TSH values for all the unexplained populations were in normal limits. But in the control group population, there were 10 patients whose TSH values were elevated. This study has given us chi square value of 10.141, whose p value is 0.001, which is statistically significant, showing that there was a significant association between raised TSH values and infertility**. (Table 8)**

Table 8: Thyroid association in infertility in both groups

Crosstab				
Investigation Results observation		**Groups**		**Total**
		Control	**Unexplained**	
TSH	High count	10	0	10
	% within TSH	100%	0%	100%
	% within groups	30%	0%	12%
	Normal count	30	40	70
	% within TSH	40%	60%	100%
	% within groups	70%	100%	88%
Total		40	40	80
		50%	50%	100%
		100%	100%	100%

Interpretation: Chi square value of 10.141, p value of 0.001

Association between hysterosalpingogram [HSG] and infertility:

In this study the association between HSG values and its incidence in both groups was studied. In the unexplained infertility group the HSG values were abnormal but in the control group they were normal. The abnormal HSG values were studied for their association with Infertility. The chi square value is 22.937 where the p value is < 0.001, which showed highly statistical significance between abnormal HSG values and infertility outcome. **(Table 9)**

Table 9: Association of HSG in infertility

Crosstab				
Investigation Results Observations		**Groups**		**Total**
		Control	**Unexplained**	
Hystero Salpingogram [HSG]	Not done Count	18	8	26
	%within hysterosalpingogram	69.2%	30.8%	100%
	%within group	45%	20%	32.5%
	Normal Count	12	32	44
	%within hysterosalpingogram	27.3%	72.7%	100%
	%within groups	30%	80%	55%
	Abnormal Count	10	0	10
	%within hysterosalpingogram	100%	0%	100%
	%within groups	25%	0%	12.5%
Total Count		40	40	80
%within hysterosalpingogram		50%	50%	100%
%within groups		100%	100%	100%

Interpretation: chi square 22.937, p value of <0.05

Association between trans vaginal ultra sound [TVS] and infertility

In the present study population, it was observed that there was association between ultrasound in unexplained infertility and control group. In unexplained infertility group, the entire study group had normal ultra sound findings. In control group, 25% of the pregnant women showed that the ultrasound findings were polycystic ovaries [PCOD] with normal uterus. The chi square value was 11.429 with p value of <0.05, which showed significant association between abnormal scan findings i.e, PCOD and infertility. **(Table 10)**

Table 10: Association of ultrasound in both groups

Crosstab				
Investigation result Observation		**Groups**		**Total**
		Control	**Unexplained**	
Trans vaginal USG	PCOD Count	10	0	10
	%within trans vaginal ultra sound	100%	0%	100%
	%within groups	25%	0%	12.5%
	NAD Count	30	40	70
	%within trans vaginal ultra sound	42.9%	57.1%	100%
	%within groups	75%	100%	87.5%
Total Count		40	40	80
%within trans vaginal ultra sound		50%	50%	100%
%within groups		100%	100%	100%

Interpretation: Chi square of 11.429 with p value 0.001

Association between laparoscopy and infertility

In this study the association between laparoscopy findings and infertility were studied. As laparoscopy was not routinely done in our set up, this diagnostic procedure was done whenever there was doubt about HSG levels or to confirm bilateral fallopian tubal block. It was used as an investigation to decide whether to proceed to next step in treatment or not; the treatment was either IVF or ICSI. The chi square value was 39.298 where the p value was less than 0.05, which showed significant association between laparoscopy findings and infertility management where ever it was indicated. **(Table 11)**

Table 11: Association of laparoscopy in infertility

Crosstab					
Laparoscopy		**Observation**	**Groups**		Total
			Control	**Unexplained**	
	Not done	Count	35	7	42
		% within laparoscopy	83.3%	16.7%	100%
		% within groups	87.5%	17.5%	52.5%
	Normal	count	5	33	38
		% within laparoscopy	13.2%	86.8%	100%
		% within groups	12.5%	82.5%	47.5%
Total		Count	40	40	80
		% within laparoscopy	50%	50%	100%
		% within groups	100%	100%	100%

Interpretation: Chi square value of 39.298, p value of <0.001

Association between semen analysis and infertility:

In this study the association between various morphological features of sperms like, concentration, motility and morphology were studied in both the groups. It was observed that there was strong association between abnormal values of motility, concentration and morphology was observed in the infertility group and less with the normal control group. The p values were <0.05 for morphology was <0.05, < 0.001 with concentration and motility values respectively showing statistical association between these values and infertility. **(Table 12)**

Table 12: Sperm analysis between two groups

Groups	N	Mean	St. deviation	Std error mean
Morphology Control	40	39.0000	21.24943	3.35983
Unexplained	40	57.6500	21.12545	3.34023

P value < 0.05, statistically significant.

Groups	N	Mean	St. deviation	Std error mean
Control Motility	40	42.0250	21.81330	3.44898
Unexplained	40	59.6250	19.59158	3.09770

P value < 0.001, highly significant.

Groups	N	Mean	St. deviation	Std error mean
Control Concentration	40	60.3950	46.57011	7.36338
unexplained	40	78.7425	45.51693	7.19686

P value <0.001; highly significant

Expectant management and infertility:

In this study the measures taken to treat the unexplained infertility were weight reduction and other life style modifications such as diet modifications and physiotherapy. As the study population were not well satisfied with expectant management alone, infertility treatment also was started after three months of expectant management. In the table 13 the groups in whom the expectant management was given and in the group in whom the expectant management was not given were tabulated. The chi square value calculated was 80 with a p value of less than 0.05, which showed that there was significant association between expectant management and infertility outcomes. **(Table 13)**

Table 13: Expectant management in two groups:

Crosstab					
Expectant Management	**Results**	**Observation**	**Groups**		**Total**
			Control	**Unexplained**	
	Nil	Count % within expectant Management % within groups	30 100% 75%	0 0% 0%	30 100% 37.5%
	Weight reduction	Count % within expectant Management % within groups	10 100% 25%	0 0% 0%	10 100% 12.5%
	Other life style changes	Count % within expectant Management % within groups	0 0% 0%	40 100% 100%	40 100% 50%
Total		count % within expectant Management % within groups	40 50% 100%	40 50% 100%	40 50% 100%

Interpretation: chi square value of 80.000, p value <0.001

Association between clomiphene citrate therapy and GnRH treatment in infertility:

In this study it was found that the association between clomiphene citrate usage combined with GnRH in unexplained infertility group and its positive outcome were observed. This combination was usually tried in infertility management, where there was no required follicular development with clomiphene alone. The chi square value was 5.333 where the p value was 0.069. (There was no statistically significant difference between the additions of gonadotrophins in treatment of unexplained infertility). But there was significant association between addition of gonadotropins and infertility in case of PCOS. **(Table 14)**

Table 14: Association of CC+ Gn RH in both groups

Crosstab					
CC+GnRH	**Results**	**Observation**	**Groups**		**Total**
			Control	**Unexplained**	
	Not given	count % within GnRH+CC % within groups	32 47.1% 80%	36 52.9% 90%	68 100% 85%
	Given	count % within GnRH+CC	8 66.7%	4 33.3%	12 100%

		% within groups	20%	10%	15%
Total		Count	40	40	80
		%within GnRH+CC	50%	50%	100%
		% within groups	100%	100%	100%

Interpretation: Chi square value of 5.333, p value of 0.069.

Controlled ovarian hyper stimulation and intra uterine insemination [COH+ IUI] in infertility:

In this study the association between COH and IUI in the study group and control group were observed and found that except in cases where sperm count was very low and when bilateral tubal block was found and in whom either IVF or ICSI procedures have to be undertaken, there was no significant association. The study group was very small for such comparison but the study revealed no significant association in unexplained infertility group. **(Table 15)**

Table 15: Association of COH +IUI in infertility

Crosstab			
COH with IUI Results Observation	**Groups**		**Total**
	Control	**Unexplained**	
Not done count	25	21	46
% within COH+ IUI	54.3%	45.7%	100%
% within groups	62.5%	52.5%	57.5%
Done count	15	19	34
% within COH+IUI	44.1%	55.9%	100%
% within groups	37.5%	47.5%	42.5%
Total count	40	40	40
% within COH+IUI	50%	50%	100%
% within groups	100%	100%	100%

Interpretation: Chi square of 0.818 with p value 0.366

Association between ART procedures and infertility outcome:

The present study actually showed that in unexplained infertility couple, the chances of ART or ICSI were increasing. But it was observed in this study that there was a chance of conception in 50 % of couple after ART especially ICSI procedures. **(Table 16)**

Table 16: Association of ART in infertility in two groups

	Groups		**Total**
	Control	**Unexplained**	
Not done count	28	36	64
% within ART	43.8%	56.3%	100%
% within groups	70%	90%	80%
Done count	12	4	16
% within ART	75%	25%	100%
% within groups	30%	10%	20%
Total count	40	40	80
% within ART	50%	50%	100%
% within groups	100%	100%	100%

Discussion

It would be difficult to name a field of medicine that has undergone more rapid and profound advancement over the past 50 years than the field of infertility treatment. Couples often describe the "hope and despair" cycle, as they hope each month that they will finally conceive and then despair when once again it does not happen. Men and women experience the stress and grief of infertility quite differently; this can create substantial personal and marital stress. Treatments are physically, emotionally and financially draining.

This was a prospective study, which included couples who came to our infertility clinic at GKNM for evaluation between Jan 2019 and Dec 2021. In this study 40 couples with unexplained infertility and 40 couples as control group were included. The study group population included unexplained infertility and control groups in which 10 couples had oligospermia, 10 had hypothyroidism, 10 were having tubal block, 10 with polycystic ovaries [PCOD]. About half of the pregnancies were conceived in the first 6 months after the first visit at the fertility clinic and most pregnancies were conceived within 1 year after first visit. IUI pregnancies occurred mainly between 6 and 18 months after first visit, while IVF pregnancies occurred between 12 and 30 months after first visit. Unexplained infertility is one of the most common diagnoses in our fertility clinic as shown in trials, Hull *et al*., 1985; Adamson and Baker, 2003; Brandes *et al*.,2010 [7]. Couples were diagnosed as unexplained infertility if the findings in the standard work-up were normal. Couples, who conceived before fertility work-up was completed, were also diagnosed with unexplained infertility, if at least no abnormalities were found until that moment. However, the Practice Committee bulletin on unexplained infertility (ASRM, 2006) mentioned that the basic evaluation should provide evidence of ovulation, adequate sperm production and patency of Fallopian tubes [8]. In this study in the specialty clinic of infertility initially Thyroid stimulating hormone [TSH] was evaluated, husband's semen analysis [HAS] and evidence of ovulation were investigated. Couples who experience problems in conceiving have been seen together because both partners are affected by decisions surrounding investigation and treatment. Counseling has been offered before, during and after investigation and treatment, irrespective of the outcome of these procedures in our clinic as per NICE guidelines 2004. Basal FSH was not tested routinely in all couples in our clinic. Only if the women were older than 36 years or had a positive family history of premature ovarian failure, basal FSH level was measured as was done by van der Steeg *et al*., 2007 [9]. Women who started IVF were all tested for basal FSH, in order to choose the correct dosage of recombinant FSH as was proven by Broekmans FJ *et al* in their study [10]. Age is an important independent predictor for determining the infertility outcome. Most of the couples are in age less than 30 years. This is also seen in the present study where it is shown that women at the age of 32 or less have the highest chance of a future live. Age of the women had the best predictive value of live birth, which is also known from previous studies by Chuang CC *et al* 2003, Wang JG *et al* 2010 [10,11]. From 2002 CDC data, live birth rates per cycle range from just over 40% in women aged 27 years, down to 6% at age 43 and only 2% in women who are over 43 years of age. Female age and duration of infertility indirectly influenced treatment policy as they are part of the prediction model of Hunault *et al*. (2004) [12]. We initiated treatment to the couple after 1 year of their married life as increasing female age lowers the chance of achieving both a spontaneous and an induced ongoing pregnancy according

to Steures *et al*., 2004; Lintsen *et al*., 2007 [13,14]. The increasing age has also been associated with a shortening length of the menstrual cycle and women with cycle length less than 26 days have been shown to have significantly lower pregnancy rates after infertility treatment compared with the women with cycle length more than 34 days according to Brodin T *et al*. [15]. However, this could not been shown in our study, where the menstrual cycle length was not related to the pregnancy outcome in our study group. But in control group as in PCOS, it showed significance. In this study most of the couples were in a normal BMI except for those with PCOS and few hypothyroid people. So BMI was not statistically significant with the infertility outcome in the present study. However, menstrual disorders in women with hypothyroidism are rarer than previously reported as in Krassas GE *et al* 2000 [16]. In this study TSH as a single variable was not predictive for future live birth, but the combination with age of 32 or less, ovulatory cycle and TSH ≤ 2.5 mIU/L resulted in a predictive value of 88%. According to Poppe K *et al* [17] 2007, Of 394 infertile women, 23.9% were hypothyroid (TSH > 4.2 μIU/ml). After treatment for hypothyroidism, 76.6% of infertile women conceived within 6 weeks to 1 year. Measurement of TSH should be done at early stage of infertility check-up rather than straight away going for more costly tests or invasive procedures. Simple, oral hypothyroidism treatment for 3 months to 1 year was of great benefit to conceive in otherwise asymptomatic infertile women. In this study we have taken only 10 cases as control and correction of Hypothyroid was done along with infertility treatment, 40% of couples conceived. No one required ART procedures. Routinely day 2 scan for our patients were done who were on treatment. Day two scan for this study group was normal and we have taken 10 patients of PCOD in our control group after following Rotterdams criteria 2004.

Couples of both the groups were advised weight reduction and were taught physiotherapy as weight loss prior to conception improved live birth rate in obese women with or without PCOS according to Moran *et al*., 2006 [18]. The main factors that predicted the outcome of treatment were obesity, hyperandrogenemia and age, as also shown by Imani *et al*., [19] 2002 and Eijkemans *et al*., [20] 2003. We have given CC up to 150 mgs as the recommended maximum dose is 150 mg/day, as there is no clear evidence of efficacy at higher doses and this is in accordance with FDA recommendations of 750 mg/treatment cycle and also by Dickey *et al*., 1996. [21] Approximately 75–80% of patients with PCOS ovulated after CC and GnRH as per Homburg, 2005 [22] Out of the 10 patients taken as control 60% of them conceived which correlates almost with the study of Eijkemans *et al* 2003 [20] which showed 72% conception rate following the combined analysis of ovulation induction using CC medication as first-line treatment and exogenous gonadotrophins as second-line treatment. As ovulation is an important problem, couples were given CC alone for 1 patient and CC + GnRH for the rest of 5 conceived patients. 3 patients were still on follow up at the end of this study. HAS [Husband semen analysis] was routinely done for the patients in their first visit. In the present study population, HSA were normal for all. 10 couples were included in this study control group had who were labeled as oligospermia following the strict criteria of recent WHO classification. In case of borderline count an IUI was used and swim up technique was used similar to Berg *et al* (1997), [23] showed that pregnancy rate increased after IUI in correlation to motile sperm after swim up, in 6 couple, then proceeded for ICSI in unsuccessful cases. In

cases where counts were extremely low, direct ICSI was done. Out of 10 patients, 3 conceived showing a pregnancy result of 30% which is almost near to the usual success rate of 40% with ICSI. Tubal flushing has proved to be of some use in increasing the chance of pregnancy in unexplained infertility and early stages of endometriosis. Hysterosalpingography, contrast sonography have been well documented in achieving spontaneous pregnancy as per Johnson *et al*., 2005 [24]. HSG values estimation was done in our patients after 4 cycles of OI. As tubal factor is also an important cause of female infertility, 10 cases of tubal factor were included in the control group, among which 7 couples had unilateral and 3 had bilateral blocks. In case of unilateral blocks IUI was tried and in bilateral blocks the only option was IVF/ ICSI.

One hundred and eighteen patients with unexplained infertility were treated with clomiphene in a randomized placebo-controlled cross-over study lasting up to 3 months with each preparation. There were several studies addressing the effect of IUI on 2 consecutive days over single IUI [25]. Although some studies like Alborzi *et al* 2003, [26] Ransom *et al* 1994 [27] and Silverberg KM *et al* [28] 1992, suggested marginal benefits of double IUI over single, the most recent randomized trial concluded that among patients undergoing COH/IUI, results of single and double IUI do not statistically differ [29]. Therefore, double IUI is not routinely offered. But as the available trials on this issue are difficult to interpret because they are not restricted to patients with unexplained infertility, but also included subjects with other types of infertility, such as male factor and cervical factor, we have done two day IUI in our clinic. In 1991, Kirby and colleagues reported a RCT of 73 couples with unexplained infertility that were either randomized to IUI or timed intercourse. [30]. Conceptions occurred in 6 of 145 (4.1%) of the IUI cycles and 3 of 123 (2.4%) of the timed intercourse cycles according to Kirby *et al*. In our study there is a definite improvement in pregnancy rate 09 out of 20 conceived with IUI + OI and 6 out of 20 only with OI. A recent Cochrane review by Verhulst *et al* [31] 2006, on this confirmed that IUI with ovulation induction increased the live birth rate compared with IUI alone. Zeynelgu *et al* [32] (1998) study confirmed that addition of IUI to superovulation alone increase the pregnancy chance anywhere from 30% to 160. Several studies have demonstrated an improvement in pregnancy rates with the addition of IUI to the ovulation induction protocol Chaffkin *et al*. 1991; Guzick *et al*. 1998 [33,34]; of the pregnancies, 98.6% were conceived within 3 years after first visit. IUI and IVF were responsible for 12.6% (45/356) and 13.5% (48/356) of all pregnancies, respectively. In general, 42.3% of the couples who received IUI and 62.8% of those who received IVF achieved a pregnancy. Many couples, however, fail to conceive after IUI treatment and more advanced fertility treatment such as IVF or intracytoplasmic sperm injection (ICSI) may subsequently be employed. In a group of patients who fail to conceive after three IUI treatment cycles, the frequency of patients experiencing reduced fertilization potential is likely to be increased.

In unexplained infertility, the cycle fecundity in the first three trials of COH and IUI was higher than in cycles 4–6, with a statistically significant difference. Patients should be offered IVF or ICSI if they fail to conceive after three trials of COH and IUI as per Aboulghar M, *et al* 2001 [6] which were followed in our study. In accordance with this, several previous studies have shown a lower fertilization rate after IVF as compared with ICSI in this particular group of patients as per Aboulghar *et al*., 1996, 1999 Fishel *et al*., 2000 [6,35]. Hence we usually prefer ICSI to our couples with unexplained

infertility. According to L Bungum 2010, Included was the first IVF/ICSI treatment of 248 unexplained infertile couples who had failed to conceive after three IUI cycles [36]. An overall pregnancy rate per embryo transfer of 57% was observed. A significantly better fertilization rate was obtained after ICSI as compared with IVF (68 versus 46%) ($P < 0.005$), and total fertilization failure following ICSI and IVF treatment was seen in 4.4 and 25% of the cycles respectively. A maximum of two embryos were transferred on days 2, 3 or 5 after oocyte retrieval according to embryo development. The best embryos were always picked for transfer, irrespective of the fertilization method used, i.e. mixed transfers (IVF/ICSI) were accepted. On days 2 and 3, embryos were scored using criteria set up by Ziebe *et al*. (1997) [37]. On day 5, embryos were assessed according to scoring criteria for blastocysts according to Gardner and Schoolcraft, 1999. All embryo transfers were performed with a Cook Soft catheter. We have done ICSI for 4 of our patients where two were conceived, 50% which was proved even in the study by Nygren and Nyboe Andersen 2001 [44].

Conclusion

Unexplained infertility as such is a frustrating problem to the couple, where no cause can be identified. Basic investigations were done as per ASRM and NICE guidelines and labeled them according to their cause of infertility. If no cause was identified, we have labeled them as unexplained infertility. Proper categorization of the infertile couples was essential and most important in planning the management and avoiding unnecessary investigations. Proper counseling plays an important role in all the unexplained infertility couple in regards with investigations and treatment. The fertility rate in the infertile couples could be improved even though the exact cause infertility could not be explained. Finally, we conclude that proper identification and management will show a good outcome, irrespective of the cause of infertility.

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