A 3 YEAR ANALYSIS OF THE OUTCOME OF VARIOUS TYPES OF MANAGEMENT FOR UNEXPLAINED INFERTILITY IN HOSPITAL USM (2010-2013)

By:

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Dr W Fadhlina Binti W Adnan

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LIST OF ABBREVIATIONS

ART	- Assisted Reproductive Technique
BMI	- Body Mass Index
CC	- Clomiphene Citrate
COH	- Controlled Ovarian Hyperstimulation
DF	- Dominant Follicle
DNA	- Deoxyribonucleic Acid
EM	- Expectant Management
ET	- Endometrial Thickness
FSH	- Follicle Stimulating Hormone
GDG	- Group Development Guidelines
GnRH	- Gonadotrophin Releasing Hormone
hCG	- Human Chorionic Gonadotrophin
hMG	- Human Menopausal Gonadotrophin
HUSM	- Hospital Universiti Sains Malaysia
ICSI	- Intra cytoplasmic injections
i.e.	- *id est*, that is
IM	- Intramuscular
IU	- International Unit

IUI	- Intrauterine Insemination
IVF	- In Vitro Fertilisation
LH	- Luteinizing Hormone
mm	- Milimeter
N	- Number
NICE	- National Institute of Clinical Excellence
OHSS	- Ovarian Hyperstimulation Syndrome
PCOS	- Polycystic Ovarian Syndrome
RCOG	- Royal College of Obstetrics and Gynaecology
rFSH	- Recombinant Follicle Stimulating Hormone
SC	- Subcutaneous
SD	- Standard Deviation
SFA	- Seminal Fluid Analysis
TAS	- Trans abdominal scan
TVS	- Trans vaginal scan
UK	- United Kingdom
USA	- United States of America
vs	- Versus
WBC	- White Blood Count
WHO	- World Health Organization

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ABSTRACT

INTRODUCTION: A 3 year analysis of the outcome of various types of management for Unexplained Infertility in Hospital USM (2010-2013)

OBJECTIVE: To evaluate the outcome of patients diagnosed with Unexplained Infertility undergoing Expectant Management (EM) compared to Controlled Ovulation Hyperstimulation (COH) and Controlled Ovulation Hyperstimulation and Intrauterine Insemination (COH+IUI). The primary outcome is the pregnancy rate. The secondary outcomes are the ovarian response and the endometrial response among patients receiving stimulated cycles. Apart from that we have also assessed the risk of developing Ovarian Hyper-stimulation Syndrome (OHSS) and multiple pregnancy among these patients.

STUDY DESIGN: This is a retrospective and prospective cohort study among women with unexplained infertility from 1st December 2010 until 30st November 2013, aged 18-44 years old undergoing their treatment at Hospital Universiti Sains Malaysia (HUSM). The subjects were recruited from the infertility clinic at HUSM. They were given EM, COH or COH+IUI.

RESULTS: Total of 109 patients was enrolled in this study; 36 patients under EM, 36 patients under COH and 37 patients under COH+IUI. There were no significant statistical differences between the 3 treatment groups, in terms of the socio demographic and characteristics of unexplained infertility i.e. age, BMI, ethnicity, husband's smoking status, type of infertility and duration of Infertility. (p-value > 0.05)

There is a significant difference in terms of pregnancy rate between the 3 treatment groups (p-value = 0.00). In EM group, 17 patients (47.22%) managed to conceive within the 12 months of follow-up. In the COH group, 13 of them (36.1%) managed to conceive using this regime .In COH+IUI group 2 of them (5.4%) managed to conceive using this regime, 1 patient from using CC + IUI and another one from using recombinant FSH +IUI.

For correlation between ovarian response and pregnancy rate, result showed that patients in COH group had higher pregnancy rate with even 1 dominant follicle (69.2%) While in the COH+IUI group, the pregnancy rate is similar in patients with 1 dominant follicle and 2 dominant follicles. As a whole, there is significant correlation between pregnancy rate and number of dominant follicles (p-value= 0.01)

For correlation between endometrial receptivity and pregnancy rate, result showed that patients in COH group had higher pregnancy rate when the endometrial thickness is between 6-10mm (69.2%). In the COH+IUI group, there is no significant difference seen in terms of pregnancy rate in couples with ET 1-5mm and ET 6-10mm. As a whole, ET is not a significant predictor for pregnancy rate for stimulated cycles (p-value=0.55)

There were no differences between COH and COH+IUI group in terms of risk of developing OHSS and rate of multiple pregnancies.

CONCLUSION: Expectant management is comparable to COH and IUI in the management of unexplained infertility in terms of pregnancy rate.

ABSTRAK

PENGENALAN: Analysis tentang keberkesanan pelbagai jenis perawatan untuk masalah ketidaksuburan tanpa sebab di Hospital USM untuk tempoh 3 tahun (201-2013)

OBJEKTIF: Untuk mengkaji keberkesanan perawatan tunggu dan lihat (Expectant Management (EM)) terhadap pesakit yang menghadapi masalah ketidaksuburan tanpa sebab, berbanding dengan pesakit yang menggunakan rawatan hiperstimulasi ovary terkawal (Controlled Ovulation Hyperstimulation (COH)) dan hiperstimulasi ovary terkawal dan permanian berhadas (Controlled Ovulation Hyperstimulation and Intrauterine Insemination (COH+IUI)). Kesan utama yang dikaji adalah kadar kehamilan. Kesan sampingan yang dikaji adalah kesan terhadap ovari dan kesan terhadap lapisan endometrium bagi pesakit yang mendapat perawatan hiperstimulasi ovary terkawal (COH) dan hiperstimulasi ovary terkawal dan permanian berhadas (COH+IUI). Selain daripada itu kami juga mengkaji kadar kesan sampingan seperti sindrom hiperstimulasi ovari (Ovarian Hyperstimulation Syndrome (OHSS)) dan kandungan kembar (Multiple Pregnancies).

KAEDAH KAJIAN: Ini adalah merupakan kajian retrospektif dan prospektif terhadap pesakit yang mengalami masalah ketidaksuburan tanpa sebab dari 1hb Disember 2010 sehingga 31hb November 2013, berusia 18-40 tahun, yang mendapat perawatan di Klinik Infertilti, HUSM. Mereka telah dibahagikan di dalam 3 kumpulan berdasarkan rawatan yang diterima, perawatan tunggu dan lihat (EM), hiperstimulasi ovary terkawal (COH) dan hiperstimulasi ovary terkawal dan permanian berhadas (COH+IUI).

KEPUTUSAN: Seramai 109 orang pesakit telah menyertai kajian ini, 36 pesakit dalam kumpulan perawatan tunggu dan lihat (EM), 36 pesakit dalam kumpulan hiperstimulasi ovary terkawal (COH) dan 37 pesakit dalam kumpulan hiperstimulasi ovari terkawal dan permanian berhadas (COH+ IUI). Kajian tidak mendapati sebarang perbezaan ketara dalam

kadar kehamilan berdasarkan faktor sosio demografik dan ciri-ciri ketidaksuburan tanpa sebab seperti umur pesakit wanita, “body mass index [BMI]”, kumpulan etnik, status merokok dikalangan suami, jenis infertiliti dan tempoh ketidaksuburan.

Kajian menunjukkan perbezaan ketara dalam kadar kehamilan jika dibandingkan di antara ketiga-tiga kumpulan rawatan (p-value: 0.00). 17 pesakit (47.2%) di dalam kumpulan perawatan tunggu dan lihat (EM), berjaya hamil dalam tempoh 12 bulan. Manakala, di dalam kumpulan hiperstimulasi ovary terkawal (COH), 13 pesakit (36.1%) berjaya hamil. Dan di dalam kumpulan hiperstimulasi ovari terkawal dan permanian berhadas (COH+IUI), hanya 2 pesakit (5.4%) berjaya hamil .

Dalam mengkaji hubungan di antara kesan terhadap ovari dan kadar kehamilan, keputusan mendapati bahawa di dalam kumpulan hiperstimulasi ovary terkawal (COH), kadar kehamilan adalah lebih tinggi di kalangan pesakit yang mempunyai 1 follicle yang dominan (69.2%). Sementara itu, tiada perbezaan kadar kehamilan di anatara pesakit yang mempunyai 1 dan 2 follicle yang dominan. Secara keseluruhannya, kadar kehamilan boleh ditentukan melalui jumlah follicle yang dominan (p-value=0.01)

Dalam mengkaji hubungan di antara kesan terhadap lapisan endometrium dan kadar kehamilan, keputusan mendapati bahawa, di dalam kumpulan hiperstimulasi ovary terkawal (COH), kadar kehamilan adalah lebih tinggi di kalangan pesakit yang mempunyai lapisan endometrium 6-10mm (69.2%). Di dalam kumpulan hiperstimulasi ovary terkawal dan permanian berhadas (COH+IUI) , tidak ada perbezaan kadar kehamilan di antara pesakit yang mempunyai lapisan endometrium 1-5mm dan lapisan endometrium 6-10mm. Secara keseluruhan, tahap ketebalan lapisan endometrium bukan merupakan faktor penting dalam menentukan kadar kehamilan (p-value=0.55)

Kajian juga mendapati tiada perbezaan risiko pesakit mengalami masalah sindrom hiperstimulasi ovary (OHSS) dan kandungan kembar (multiple pregnancies) di antara ketiga-tiga kumpulan rawatan

KESIMPULAN: Kajian ini mendapati bahawa kesan perawatan tunggu dan lihat (EM) adalah setanding dengan hiperstimulasi ovary terkawal (COH) dan hiperstimulasi ovary terkawal dan permanian berhadas (COH+IUI) untuk pesakit yang menghadapi masalah ketidakhamilan tanpa sebab.

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INTRODUCTION: Unexplained infertility has been shown to be one of the most common causes for infertility. Unexplained infertility is diagnosed when there is persistent failure to conceive despite basic investigations such as seminal fluid analysis (SFA), tubal patency tests and assessment of ovulation showed normal results. There are a number of therapeutic approaches used to actively managed unexplained infertility: controlled ovulation hyperstimulation (COH) and intrauterine insemination (IUI) and in vitro fertilization (IVF). However the best practice in managing couple with unexplained infertility is expectant management (EM) which can be considered for up to 3 years, while taking into account the women's age. This study aimed to study the outcome of patients with unexplained infertility receiving expectant management (EM) as compared to controlled ovulation hyperstimulation (COH) and controlled ovulation hyperstimulation and intrauterine insemination (COH+IUI).

OBJECTIVE: To evaluate the outcome of patients diagnosed with Unexplained Infertility undergoing Expectant Management (EM) compared to Controlled Ovulation Hyperstimulation (COH) and Controlled Ovulation Hyperstimulation and Intrauterine Insemination (COH+IUI). The primary outcome is the pregnancy rate. The secondary

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Assoc Prof Adibah Ibrahim: Supervisor

ABSTRAK

ANALYSIS TENTANG KEBERKESANAN PELBAGAI JENIS PERAWATAN UNTUK MASALAH KETIDAKSUBURAN TANPA SEBAB DI HOSPITAL USM UNTUK TEMPOH 3 TAHUN (2010-2013)

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PENGENALAN: Penyakit ketidaksuburan tanpa sebab merupakan salah satu penyebab kepada masalah inefrtiliti. Ketidaksuburan tanpa sebab ini bermaksud apabila masalah infertility ini berterusan walaupun kajian dasar seperti ujian air mani, ujian ketelusan salur fallopian dan ujian kesuburan adalah normal. Ada beberapa cara yang digunakan untuk merawati masalah ini secara aktif; hiperstimulasi ovary terkawal (COH) dan permanian berhadas (IUI) dan perawatan tabung uji (IVF). Namun, kaedah perawatan yang terbaik untuk pesakit yang menghadapi masalah ini adalah kaedah tunggu dan lihat yang boleh diguna untuk tempoh 3 tahun, dengan mengambil kira umur ibu. Kajian ini bertujuan melihat keberkesanan perawatan yang diberikan kepada pesakit menghidapi masalah ketidaksuburan tanpa sebab ini; kaedah tunggu dan lihat (EM), kaedah hiperstimulasi ovary terkawal (COH) dan kaedah hiperstimulasi ovary terkawal dan permanian berhadas (COH+IUI).

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Prof Madya Adibah Ibrahim: Penyelia

1.0 INTRODUCTION

Infertility is defined as failure to conceive after regular unprotected sexual intercourse for 2 years. Infertility affects 80 million couples worldwide **(Vayena et al 2002)**. In UK it is estimated that 1 in 7 couples suffers from infertility. In Malaysia alone, the Ministry of Health estimates that 10-15% of couples suffered from infertility, a figure similar to most developing countries. Recent estimates put the figure about 300,000 couples in Malaysia.

It appears that there has been no major change in the prevalence of infertility in recent years, however the numbers have shown that more couples are seeking medical attention than previously **(RCOG, 1999). Boivin et al 2007** estimated that 50% couples have sought medical assistance for infertility.

A district health authority may see around 230 new referrals each year for infertility concern **(RCOG, 1999)**. In Malaysia, the Ministry of Health estimate that infertility accounts for 15-20% of gynaecology patients in our hospital.

Hospital USM has established itself as one of the secondary/tertiary centre offering infertility service in the East Coast Malaysia for at least more than 10 years. It is therefore justified the need to evaluate the effectiveness of the treatment provided to our patients and provide database on our services for future research and treatment protocol.

There was a variety distribution of causative factors of infertility in different communities. In UK, causes of primary infertility are male factor (30%), unexplained infertility (25%), female factor which include ovulatory disorders, tubal disease and uterine or peritoneal cause (45%). In 20% of cases, the male and female factors co-exists.

A local study which was done at Hospital Sultanah Bahiyyah, Alor Setar, Kedah showed that causes of infertility are ovulatory dysfunction (46%), unexplained (22%), mixed (13%) , male (6%), tubal (5%), cervical (3%) and others (5%).

Unexplained infertility has been shown to be one of the most common causes for infertility, which we choose to evaluate in our study. Unexplained infertility is diagnosed when there is persistent failure to conceive despite basic investigations such as seminal fluid analysis (SFA), tubal patency tests and assessment of ovulation showed normal results.

Some studies have shown the prevalence can be as high as 60% in certain centres **(Templeton & Penney et al, 1982).** Meanwhile, the reported incidence of unexplained infertility has also been shown to be varied between different studies based on the age and selection criteria (**Aboulghar et al 2003, Isaksson & Tiitinen, 2004**). In the study, we assessed their socio demographic criteria to determine the characteristics of couples with unexplained infertility among our population.

The decision to treat patients with unexplained infertility would depend on the female's age, the duration of infertility and the type of infertility (i.e. primary and secondary infertility) **(Hull et a,l 1985, Lenton et al, 1977).**

Female's age is the most important factor that influences a couples' fertility.

Table 1: The Percentage Women become childless based on Maternal Age

Age of women at which started to try to conceive (years)	Remain childless (%)
20-40	6
25-29	10
30-34	15
35-39	30
40-44	>60

Adapted from Menken J et al 1986

Table 1 showed that female fertility reduces with age. Women aged >35 years old, has increased rate of remain childless ≥ 30 %. Even when regular sexual intercourse, 94% of fertile women aged 35 years and reduced to 77% of those aged 38 years will conceive after 3 years of trying **(NICE Cllinical Guidelines, 2004).**

Studies have shown that there is a correlation between the female's age and the number of antral follicles in women with infertility. **Castro et al 2012** showed a linear pattern of decline in antral follicle count (AFC) with age in all percentiles.

There is also a correlation between increased in chromosomal errors with advanced maternal age. This is supported by increase in spontaneous abortion and chromosomal abnormalities in babies born to mothers with old age (**Hook EB et al, 1983, Munne S et al, 1994**)

An advancing age of a women may give effect on the treatment result and a lowered natural fecundity and increase in spontaneous abortion rate (30% at age 40 years old) must be taken into account when counselling is given to women age over 35 years old.

Duration of infertility is another important factor in determining the treatment plan. Studies have shown many couples with unexplained infertility will have spontaneous conception and have a live birth without treatment 92-4% per menstrual cycle). Pregnancy rate in 1 year is 15%, 35% in 2 years and 80% in 3 years **(Isaksson & Tiitinen, 1998, Hull et al, 1985, Guzick et al, 1998).** This shows that women with longer duration of infertility, their chance to conceive reduced.

As shown in Table 2, the chance of a women to conceive increases with the increasing number of months trying. However, there is a drastic fall in the chance to conceive after two years of trying.

Table 2: The Chance for Spontaneous Conception based on duration

Duration of trying (months)	Chances for spontaneous conception (%)
1	20
6	70
12	85
18	90
24	95
36	40
48	4

Adapted from Quick Guideline to the Management of Infertility (USM), 2011

Infertility can be categorised based on Primary and Secondary Infertility. Primary infertility refers to couple who have not become pregnant after at least 1 year of unprotected sexual intercourse. Secondary infertility refers to couple who have been pregnant previously regardless of the outcome **(World Health Organisation).** Studies have shown that couples with secondary infertility are more commonly associated with successful spontaneous pregnancy compared to couples with primary infertility.

The best practice in managing couples with unexplained infertility is expectant management (EM) which include advice on lifestyle and successful conception. Expectant management (EM) for up to 3 years can be considered, taking into account the women's age. However expectant management is not attractive to couples with unexplained infertility and even clinicians, as most would prefer an active management.

A number of therapeutic approaches have been used to actively manage unexplained infertility: Controlled Ovulation Hyperstimulation (COH), Intrauterine Insemination (IUI) and In Vitro Fertilisation (IVF). Ovarian hyperstimulation with IUI is effective although IVF is more preferred.

Fertility treatments are costly. In this case IVF treatment which can cost approximately US Dollar 33,000 – 41,000 in UK, US and Canada. Total ART treatment costs as percentage of total healthcare expenditures in 2003 were 0.06% in US **(Connolly M. P et al 2010).**

The funding structure for IVF/ART is highly variable among different nations. In US there is no federal government assistance exists for IVF. Many other countries provide full or partial coverage thru government insurance. In Malaysia there are over 40 IVF centres available and the cost is expensive i.e. RM 12,000 – 18,000 per cycle. Thus, we need to counselled and tailored treatment specifically for each patient, based on the above factors.

This aim for this retrospective and prospective study is to evaluate the treatment and outcome of patients with unexplained infertility treated in our infertility clinic, in order to find an optimum method in treating such cases.

2.0 LITERATURE REVIEW

2.1 Aetiology of Infertility

The causes of infertility can be divided into male factor (35%), female factor (50%) and unexplained infertility (15%). Of the female factor, it is further divided into ovulatory disorders, tubal factors, uterine factor and endometriosis associated infertility.

A retrospective audit by **De M et al, 2005** followed up the management and outcome of patients referred to a specialist infertility clinic for 4 years duration. 179 couples were included in the study. Results showed the causes of infertility were unexplained infertility (17.5%), tubal factor (27%), anovulation Infertility (21%), male factor (17.5%), multi-factorial (8%), endometriosis (3%) and congenital factors (3%).

In another study by **Wilkes S. et al, 2009** did a population based study in UK primary care looking into the epidemiology and management of infertility. They aim to describe the incidence, prevalence, referral patterns and outcomes of infertile couples. The diagnoses of infertility are unexplained infertility (38%), ovulation dysfunction (25%), semen disorder (25%) and tubal factor (18%).

Male factor infertility is not a rare problem. It affects 1 in 20 men. The aetiologies of male factor infertility are disorders of spermatogenesis, duct obstruction, accessory gland disorders, disorders of sperm and vesicular fluids, sexual dysfunction and psychological and environmental factors. Despite these, in the majority of cases, the cause of male infertility is unknown. Recent studies are now focusing of epigenetic factors causing male factor infertility **(Dada R et al, 2012).**

IUI may be considered as the first line treatment in male infertility. If pregnancy is not achieved after 3-6 cycles of IUI, IVF can be proposed **(Tournaye H. et al, 2012)**

Ovulatory disorder is the principal cause of female infertility, contributing about 1/5th of all infertile couple (**Ashalatha S et al, 2000).** Ovulation disorders can be divided into 3 groups

based on WHO Classification of Ovulatory Disorders. The treatment would depend on the group of disease.

WHO Group 1 Ovulation Disorder showed a hypogonadotrophic hypogonadism e.g. Kallman syndrome. Patients in this group would responds to treatment with injections of gonadotrophin releasing hormone (GnRH) or gonadotrophin formulation containing leiutenizing hormone (LH).

WHO Group 2 Ovulation Disorder is also known as hypothalamic pituitary dysfunction. Example is Polycystic Ovarian Syndrome (PCOS), which has a prevalence rate of 4-18%. Women in this group can be treated using ovulation induction agents such as clomiphene citrate, metformin and gonadotrophins.

Meanwhile, women in Group 3 Ovulation Disorders which is also known as hypergonadotrophic anovulation or ovarian failure, has very low chance to conceive spontaneously. IVF with oocyte donation remains the mainstay treatment for these women.

Tubal factor infertility causes 14% of cases of infertility, with pelvic inflammatory disease (PID) being the most common cause. Other causes include septic abortion, ruptured appendix, pelvic surgery and ectopic pregnancy. 75% of cases of tubal disease involved the distal part and 25% of cases are of proximal part.

Patients with proximal tubal blockage can be offered selective salphingography and tubal catheterization under x-ray. This may improve pregnancy rate. However if the procedure failed, patient can be considered for tubo-cornual anastomosis, which can increase pregnancy rate up to 50% if done by trained surgeon.

Patients with distal tubal blockage, can be offered microsurgical approach using magnification. The pregnancy rate would depends on the degree of the disease; pregnancy rate is higher in couples with mild peri-tubal adhesion compared to patients with gross hydrosalphinx. In couple with moderate to severe tubal disease, we should offer IVF.

Uterine factor causes 15% of couples with infertility. Fibroid is the most common cause of uterine factor related infertility, and others are endometrial polyp, intrauterine adhesions and structural abnormalities.

The interference of fibroid on infertility is largely depends on their location. Submucosal fibroid would interfere with implantation, and thus should be removed regardless of the size and structure. intramural fibroid distorting the endometrial cavity can reduce conception rate and can be removed. There is no evidence to support the removal of subserosal fibroid in asymptomatic women. Myomectomy can be done hysteroscopically or abdominally (**Gambadauro P et al, 2012).**

Endometriosis which is characterised by presence of glandular epithelial and stromal cells in the extra uterine environment, affects 10-15% of women in the reproductive age. The disease affects several parts in the women reproductive system i.e. ovarian function, oocycte retrieval, embryo development and the endocrine system involved in the reproductive process and results in infertility and pregnancy loss **(Stilley J A et al, 2012).**

Endometriosis is classified using the **American Fertility Society (AFS) system of Classification** and the management would depends on the stages of endometriosis. In minimal to mild endometriosis, medical treatment do not enhance pregnancy rate. Ovarian hyperstimulation and intrauterine insemination (IUI) is more effective than no treatment. Surgical ablation have not been shown to improve fertility.

In moderate to severe endometriosis, studies have not shown that medical treatment either alone or with surgery improves fertility. On the other hand, surgical management (which include cystectomy or drainage of cyst) can be beneficial at this stage.

Unexplained infertility is diagnosed when standard investigations which include semen fluid analysis (SFA), tubal patency tests and ovulation assessment, failed to identify any abnormalities or provide a diagnosis.

Most centres would investigate these couples extensively in an effort to find the cause for their failure of conception. In a prospective study of 114 women diagnosed with unexplained infertility, done by **Bonneau C et al, 2012** showed that laparoscopy revealed pelvic pathology in 95 patients. Thus diagnostic laparoscopy should be strongly considered in unexplained infertility workup should not be underestimated

Fatini C et al, 2012 tried to demonstrates the relationship between inherited thrombophilia and unexplained infertility thus suggesting the contribution of genetic components in modulating unexplained infertility, behind anovulation, male and tubal factor. Another recent development is seen in **Kokcu A et al, 2012** made a synthesis and review of literature looking into possible roles of various immunological factors in recurrent miscarriages and unexplained infertility.

Haxton M J et al, 1987 has showed that there is no evidence that the approach of doing extensive research is superior to waiting for spontaneous conception which is concurred with solid epidemiological evidence.

2.2 Investigations of Infertility

The general consensus is that infertile couple should be investigated as soon as they seek medical attention. However the decision on detail and urgent investigations will vary depending on several factors such as duration of infertility and maternal age **(Obstetrics, Gynaecology and Reproductive Medicine 2007).**

According to the guideline, both husband and wife should be directly involved in the management of their infertility problems. Thus it is generally agreed that both couple need to be seen together, which is describe as couple centred management, as decisions taken on each other's partner will affect both of them **(NICE Clinical Guidelines 2004)**.

For investigations and management of infertility, physician would generally adhere to the **Royal College of Obstetricians and Gynaecologists Evidence-based Clinical Guidelines on Initial Investigations and Management of the infertile couple (1999).**

Detailed history need to be taken from both husband and wife, including menstrual history, sexual history, past medical illness and past surgical history, family history and social history.

Drug history including drug abuse on both partners should also be elicited. Environmental factors and occupation of the patients can also affect infertility. **(Quick Guideline in Management of Infertility in USM 2011)**

Clinical evaluation of the infertile couple should include 5 categories: Seminal Fluid Analysis (SFA), Post coital test, Assessment of ovulation, uterine and tubal evaluation and Laparoscopy (**Balasch et al, 2000**). Of these, SFA, mid luteal phase progesterone and tubal patency evaluation comprises the initial basic patient work up (**Crosignani and Rubin 2000)**. And in patients with unexplained infertility, all the results expected to be normal.

RCOG suggested that male partner should have two SFA done during the initial investigations. A single SFA will be able to identify almost 90% of men with true semen abnormalities. However, if abnormalities detected, a second confirmatory test after 3 months would increase its specificity.

For semen collection, the RCOG suggested abstinence for 2-3 days prior to the test. The male partner is suggested to produce the sample by masturbation and not by coitus interruptus. They are advised to use a wide mouth sterile plastic specimen cup and not to use condom when collecting the specimen. When delivering the specimen, they are to bring the specimen to the laboratory as quickly as possible and to keep at body temperature.

Medical practitioners are advised to use the same laboratory, as different ones might have different criteria. Although many laboratory would adhere to WHO values for normal SFA.

Normal semen volume is 2-5ml. Liquefication time is within 30 minutes. Semen concentration should be > 20 million/ml, with semen motility of > 50%, semen morphology > 30% normal forms and WBC < 1 million/ml.

The ovarian reserve is assessed the remaining population of primordial and resting follicles **(Gougeon et al, 1986).** There are several methods in evaluating the ovarian reserve such as serum FSH and LH, oestradiol (E2) levels, progesterone levels, Inhibin B, antral follicle count and serum Anti- Mullerian Hormone (AMH) however, only antral follicle count and early follicular phase FSH are the most common test and used in this study to assess ovarian reserve.

Assessing ovulation is part of investigations in couples with infertility. Women with regular menstrual cycle are generally ovulating. There are several methods used in assessing ovulation, such as basal body temperature, urinary measurement of LH surge, mid luteal phase serum progesterone and ultrasound scan. However, only these last two are generally used.

Assessing tubal patency is part of investigations for patients with infertility. There are 2 most common ways to assess for tubal patency; hysterosalphingogram (HSG) and laparoscopic dye insufflation test. To choose which test to perform for each particular patient, the RCOG recommended the use of HSG in low risk couples and laparoscopy if pelvic assessment is indicated or if HSG shows tubal damage. Other tests include hystero-contrast-sonography, selective salphingography or fertiloscopy and falloposcopy.

Couples with unexplained infertility would have normal results shown on all the above investigations.

2.3 Management of Unexplained Infertility

It is generally accepted that unexplained infertility can be managed either by expectant management (EM), controlled ovulation hyperstimulation (COH) or controlled ovulation hyperstimulation + intrauterine insemination (COH+IUI) and in vitro fertilisation (IVF).

Although **Ray A et al, 2012** wrote an update and review of practice for unexplained infertility in the Reproductive Biomed Online Journal. The research team concluded that treatment for unexplained infertility is empirical and many different regimens have been used. The standard protocol has been to progress from low technology to high technology treatment options. However more multicentre RCT is needed to identify the best treatment option in unexplained infertility.

2.3.1 Expectant Management (EM)

Expectant management would substitute as medical practitioner giving general advice regarding lifestyle issues such as diet, exercise, smoking and sexual intercourse. Patients are advised to take folic acid 0.4mg daily as supplements to prevent neural tube defect.

Patients may be provided with appropriate evidence based information, verbal and written in a format they understand during consultation **(NICE Clinical Guidelines 2004).**

Period of expectant management are usually given for 6-12 months duration, and during this period they are no clinical visits or medical intervention done. They are either given date after specified time for assessment and further treatment, or sometimes advised to return back if they fail to conceive.

However, as expected, this type of management is not attractive and popular among patients and even medical practitioner, and they would thus resort to other methods most commonly controlled ovulation hyperstimulation (COH) and controlled ovulation hyperstimulation + intrauterine insemination (COH+IUI).

Previous studies have compared between expectant management (EM) and controlled Ovulation Hyperstimulation (COH) with intrauterine insemination (IUI) whether stimulated or

non-stimulated cycles. These studies have aimed to prove that in correct patient selection, expectant management is not inferior to other available treatment.

Example of such study is a famous study by **Bhattacharya S et al in 2008** which compared the effectiveness of clomiphene citrate and unstimulated intrauterine insemination with expectant management for the treatment of unexplained infertility. The result from the study showed that empirical clomiphene citrate and unstimulated intra uterine insemination are unlikely to offer superior live birth rates, when compared to expectant management.

Other studies such as **Custers I M et al in 2011** has shown that in couples with unexplained infertility, initial expectant management (EM) for 6 months is considered cost saving without the risk of delay in achieving pregnancy or reduce pregnancy chance.

Interestingly, a study by **Eijkemans M J C et al, 2008** looked into pregnancy chances on couples in IVF/ICSI waiting list. The result showed that a chance for ongoing pregnancy without treatment while waiting for IVF/ICSI is below 10% but maybe as high as 25% within 1 year in selected patients, and more significantly in couples with unexplained infertility compared to other causes.

Woodsworth S et al, 2011 researched on whether clomiphene citrate and IUI are cost effective as first line treatment for unexplained infertility. 580 women across 5 Scottish hospitals were randomized to 3 groups: expectant management, clomiphene citrate or IUI for 6 months. The study found that empirical clomiphene citrate and unstimulated IUI do not offer superior live birth rates compared to expectant management, despite being more expensive. Another study by **Brandes M et al, 2011** also recommended that expectant management in couples with good pregnancy prognosis.

Based on evidence above, we evaluated the current treatment for unexplained infertility used in our centre (COH and COH+IUI) with expectant management in terms of pregnancy rate, and prove that expectant management is comparable to other known treatment modalities in the treatment of unexplained infertility.

2.3.2 Controlled Ovulation Hyperstimulation (COH)

Controlled ovulation hyperstimulation using clomiphene citrate has long been considered as the first line treatment for couples with unexplained infertility. COH aim is to produce multi follicular development and thus increases the pregnancy rate. There several type of ovulation induction agents and can be used either individually or in combination.

Clomiphene citrate was first successfully used as ovulation induction agent in 1961. It is the most commonly used drug in patients with WHO group 2 ovulation disorders and has been used empirically for patients with unexplained infertility.

Clomiphene citrate is a non-steroidal selective oestrogen receptor modulator which acts primarily by binding with oestrogen receptors at the hypothalamus. This competitive inhibition results in a perceived drop of circulating oestrogen to the hypothalamus, thus eventually lead to increase in gonadotropins secretion and subsequent induction of ovulation.

Treatment is usually started with the lowest dose which can achieve ovulation. Clomiphene citrate has shown to achieve ovulation rate for up to 80% per cycle with increase in of 20-25% per ovulatory cycle.

The reason for its popularity among patients and medical practitioners is because it is relatively cheap, requires minimal monitoring and the belief that it is able to correct subtle ovulatory dysfunction.

Patients should be informed regarding the risk of multiple pregnancy and potential risk of ovarian cancer. However, we weigh the risks, costs and benefit of this drug,

Patients who received clomiphene citrate 200mg to 250mg for 5 days for 3-4 cycles without response, are diagnosed to have clomiphene resistant. Other ovulation induction drugs are used when this occurred.

As mentioned above, study that compared between the effectiveness of clomiphene citrate when compared to expectant management in the treatment of unexplained infertility has shown that there is no significant difference between the two treatment modalities in terms of pregnancy rate and live birth rate **(Bhattacharya S et al, 2008)**

Several studies have been performed over the years, comparing between clomiphene citrate and other types of ovulation induction agents such as aromatase inhibitors for example letrazole and anastrazole. So far, there are no known studies that compare between clomiphene citrate and gonadotrophins in controlled ovulation hyperstimulation.

Letrazole is a 3rd generation selective aromatase inhibitor. Letrazole inhibit peripheral oestrogen production thus stimulating the release of FSH. It is has been used as ovulation induction agents since late 1990s and used in clomiphene-resistant anovulatory patients.

NICE Guideline Development Group did not recommended the use of aromatase inhibitors cannot be in women with unexplained infertility as there are ongoing trial on its safety.

A randomised controlled trial was conducted at Ain Shams University Hospital and Dar Al Hekma Hospital for 2 years duration by **Ibrahim M I et al, 2012** comparing between letrazole and clomiphene citrate for superovulation in couple with unexplained infertility. There were several outcomes measured in this study such as number of mature follicles, serum oestradiol level, endometrial receptivity, day of hCG injection and clinical pregnancy including the side effects from each treatment group. The study concluded that letrazole has beneficial effect on the endometrium, thus may improve implantation rate and pregnancy rate.

Badaway A et al, 2009 has shown that there is no significant difference between clomiphene citrate and letrazole, in terms of live birth rate, but no significant difference in clinical pregnancy and multiple pregnancy.

2.3.3 Controlled Ovulation Hyperstimulation + Intrauterine Insemination (COH+IUI)

Intrauterine insemination has been known to enhance pregnancy rate by three-folds even without controlled ovulation hyperstimulation **(Hughes E G et al, 1997)**. IUI is a well-known method for assisted reproductive technique. It is a therapeutic treatment. There is a wide variation in indications, protocol of ovarian hyperstimulation, semen preparation, timing and technique for insemination.

IUI is indicated in patients with unexplained infertility, prolonged subfertility, cervical factor infertility, Stage I/II endometriosis and patient with single fallopian tube. IUI is contra indicated in patients with ovarian failure, significant male factor infertility, significant tubal adhesions, tubal dysfunction and significant uterine abnormality.

Controlled Ovulation Hyperstimulation in IUI can be given using clomiphene citrate, gonadotrophins or sequential therapy.

Currently there are various FSH containing products available. FSH containing gonadotrophin can be divided into 4 groups: human menopausal gonadotrophin (hMG) containing both FSH and LH, Urinary FSH (uFSH), highly purified urinary FSH (uFSH-HP) and recombinant FSH (rFSH).

The human recombinant FSH which is most commonly used in the study is produced from Chinese hamster ovary cell line transfected with genes for the α and β subunits of FSH. It has subtle differences with the native molecule in its glycosylation and sialation.

hCG, which has similar structural and biological similarity to LH, is used in combination with exogenous gonadotrohin which causes LH surge, and thus induce ovulation once follicle development reaches maturity. There are different types of hCG available, but the most commonly used in the study is recombinant hCG e.g. Ovidrel, Pregnil.

There are 2 regimes used using exogenous gonadotrophin, which are the Step-up Regime and the Step-down regime.

The Step-up regime is the most commonly used in the study. It begins with using a low dose exogenous gonadotrophin, 50-75 IU on Day 3-5 of menstrual cycle. It is designed to define the effective threshold of response. 4-7 days after stimulation, treatment response is measured using TVS and or serum oestradiol level.

Response is labelled as adequate response when there is increase in the growth of one or two follicles and or a moderate rise in serum oestradiol level. We need to increase the dose of exogenous gonadotrophin by 37.5-75 IU when there is inadequate response. The dose in maintained or increased as indicated. TVS is done to assess the number and size of follicles every 1-2 days. Most of the COH cycle would take 7-12 days.

Once the dominant follicle (DF) is more than 12 mm and the endometrial thickness is more than 10, hCG injection is given to induce ovulation. If there is signs of ovulation hyperstimulation (OHSS) or more than 3 follicles with 17mm size, or more than 4-5 follicles with 14mm size, hCG injection is withhold.

In contrast, the Step-down regime started with a higher dose (150-225iu) and the dose a gradually reduced. The aim is to promote continued development of the more sensitive dominant follicle only and withdraw its support from the less sensitive smaller follicles.

This type of regime is usually used after the response threshold has been established in one or more previous stimulation cycle.

Sequential treatment is a treatment regime that has been used in patients with clomiphene-resistant anovulatory cycle and in patients with unexplained infertility. The regime would be commenced with a standard course of clomiphene citrate using either 50 or 100 mg daily dose from Day 2- Day 6 cycles. This is followed by a low dose hMG/rFSH 75iu daily beginning on the last day of clomiphene citrate.

The monitoring of response from this treatment regime is similar to the exogenous gonadotrophin regime. The pregnancy rate is found to be almost similar to exogenous gonadotrophin, with an added advantage of using lower dose of gonadotrophin, shorter duration of gonadotrophin use and thus the cost is lower.

Sperm washing would allow selection of sperm with normal morphology, motility and absence of antibody, WBC and infectious organism. Preferred sperm preparations are the one yielding the largest population of highly motile cells without chemical or cellular component. The most commonly used methods are standard swim up regime and density gradient prep.

IUI is performed on the day when the postulated follicle will rupture, thus increases the chance to pregnancy. This is estimated 24 hours after spontaneous ovulation, 34-36 hours after hCG injection in induced ovulation.

The sperm must be available at least 1 hour before insemination for preparation. 0.5 - 3ml of washed or prepared sperm is introduced into the uterine cavity by means of a thin cannula. Post IUI procedure, patients are given progesterone tablet for luteal support.

2.3.3.1 Studies Compare between Clomiphene citrate and Gonadotrophins

Berker B et al, 2011 performed a randomized trial comparing the efficacy between recombinant FSH and clomiphene citrate for ovarian stimulation in couples with unexplained infertility and male subfertility undergoing IUI. 198 couples were treated with 100 mg/day clomiphene citrate for 5 days (93 patients) or recombinant FSH with starting dose of 75–100 IU daily (96 patients).

The main outcome measurement was on-going pregnancy rate (OPR). Continuous variables were compared with student's t test or Mann–Whitney U test according to distribution of each variable. Categorical variables were compared with Chi square test or Fisher's exact

test where appropriate. The study concluded that recombinant FSH is superior to clomiphene citrate for enabling multi-follicular development in COH+IUI cycles of unexplained and male infertility couples.

Nayar K D et al, 2008 conducted a study comparing the efficacy between clomiphene citrate and low dose recombinant FSH for ovarian hyperstimulation in IUI cycles for unexplained infertility and male subfertility. This prospective cohort study was done from January 2007 to September 2007. The outcome measured was: Clinical pregnancy rate, multiple pregnancies and spontaneous abortion. Results were analysed following the intention–to-treat principle.

Cumulative pregnancy rates (17.33% vs. 20.0%; relative risk [RR], 0.839; 95 % confidence interval [CI], 0.363 to 1.937) were similar between two groups. Spontaneous abortion rate and multiple pregnancy rate were similar between two groups. There is no significant difference of pregnancy rates ($p<0.68$), spontaneous abortion ($p<0.931$) and multiple pregnancies ($p<0.812$) between two groups ($p>0.05$).

The study concluded that in couples with primary unexplained or male subfertility participating in an IUI program, ovarian hyperstimulation can be achieved by CC or rFSH. No significant difference in pregnancy rates between CC and rFSH was observed.

2.3.3.2 Studies Compare between Doses of Gonadotrohpins

A prospective study were done by **Streda R et al in 2012** trying to compare between different starting gonadotrophin doses for ovulation induction in combination with IUI. The patients were divided into 50, 75 and 100 IU group based on patients' response to clomiphene citrate treatment. The results showed that all treatment regimes were effective for ovulation induction. They reported on the case of multiple pregnancy, but not on the incidence of OHSS.

2.3.3.3 Studies Compare between Stimulated and Unstimulated IUI

Goverde A J et al, 2005 compared between natural and mild hyperstimulation cycles for IUI, their effects on pregnancy and multiple pregnancy. Pregnancy outcome of 310 natural and 334 mildly hyperstimulated cycles for IUI in 171 couples with unexplained or mild male factor subfertility was analysed on a patient level with random coefficient models.

Results showed that the pregnancy rates were similar; 35% and 39.8% per couple in the natural and mildly hyperstimulated cycles respectively (p-value = 0.60). Multiple pregnancies, all twin pregnancies, were conceived significantly more frequently in the mild hyperstimulation group (27% of the pregnancies) than in the natural cycle group (4% of the pregnancies) (p-value = 0.01).

The application of a mild hyperstimulation protocol as an alternative to a standard hyperstimulation protocol for IUI does not result in higher pregnancy rates than IUI in the natural cycle, while at the same time multiple pregnancies cannot be avoided.

2.3.3.4 Studies Compare between Stimulated IUI using Clomiphene citrate and Gonadotrophin

A randomized clinical trial of clomiphene citrate versus low dose recombinant FSH for ovarian hyperstimulation in IUI cycles for unexplained and male subfertility was performed by **Dankert T et al, 2007**. Couples with primary unexplained or male subfertility were randomized to receive clomiphene citrate or recombinant FSH for ovarian hyperstimulation. Cumulative pregnancy rates and live birth rates were primary outcomes.

27 pregnancies were observed in the clomiphene citrate group (38%) and 23 in the recombinant FSH group (34.3%). The live birth rate was 28.2% (20/71) and 26.9% (18/67) for clomiphene citrate and recombinant FSH, respectively. Overall, the live birth rates per cycle were 10% for clomiphene citrate-stimulated and 8.7% for recombinant FSH stimulated cycles. In couples with primary unexplained or male subfertility participating in an IUI program, ovarian hyperstimulation can be achieved by clomiphene citrate or recombinant

FSH. No significant difference in live birth rates between clomiphene citrate and recombinant FSH was observed.

3.0 OBJECTIVES

3.1 General Objective

To evaluate the outcome of various types of management of unexplained infertility

3.2 Specific objectives

1. To determine the demographics of couples with unexplained infertility in Hospital USM
2. To determine the pregnancy rate among patients with unexplained infertility, who received expectant management, controlled ovarian hyperstimulation and controlled ovarian hyperstimulation with intrauterine insemination
3. To evaluate the ovarian response and the endometrial receptivity among patients receiving stimulated cycles

4.0 METHODOLOGY

This is an audit to evaluate the outcome of various methods of management given to patients with unexplained infertility in the Infertility Clinic, Hospital USM. It is a retrospective and prospective cohort study, which was performed over three years duration from 1st December 2010 until 30th November 2013.

4.1 REFERENCE POPULATION

Patients with infertility in Hospital USM

4.2 SOURCE POPULATION

All patients who were diagnosed to have unexplained infertility, attending the Infertility Clinic in Hospital USM, between 1st December 2010 until 30th November 2013.

4.3 RESEARCH ETHICAL ADHERENCE

The audit was conducted after being presented to and approved by the Human Research Ethics Committee of USM (HREC). The letter of approval from the HREC is as in Appendix 1. The permission to review the case notes of the patients was obtained from the Director Hospital of Hospital USM and the patients via phone calls.

4.4 PATIENTS SELECTION AND PRE-ASSESSMENT

There were two ways of patients' recruitment into the study; the first cohort of patients was those who had attended the Infertility Clinic between 1st December 2010 until 31st December 2012 and the second cohort of patients were recruited from those attending the Infertility Clinic from 1st January 2013 until 31st December 2013.

4.4.1 Patient selection for the 1st cohort of patients (1st December 2010-31st December 2012)

For this cohort of patient, the list of the infertility patients was obtained from the Infertility list of attendance. The case notes of the patients were reviewed to select only those who were diagnosed to have unexplained infertility.

Phone calls were made to these patients to obtain their consent for their case notes reviewed to obtain the clinical information.

The management which was given was reviewed, together with the outcome of the management.

4.4.2 Patient selection for the 2nd cohort of patient (1st January- 31st December 2013)

A prospective study was performed on the second cohort of patients. The diagnosis of unexplained infertility was made when all the results for the baseline investigations for infertility (as stated in 4.4.3) was made. Informed consent to participate in the study was obtained from the patients.

The patients were subsequently counseled for treatment, either to receive expectant management, controlled ovarian hyperstimulation (COH) without intrauterine insemination (IUI); COH alone, or COH with IUI; COH + IUI. The choice of treatment given was based on the overall patient's demographic data, which looked into the age of the patient and the duration of infertility. The selection of treatment was made by the consultant in charge of the patient and patient's decision after full counseling.

4.4.2.1 Expectant management group

Patients who were given the expectant management were given a 3-monthly follow-up to review if they were pregnant, until a maximum of 12 months. The time when they managed to get pregnant was documented.