Current Management of Unexplained Infertility

Essay

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Abstract

Unexplained infertility is still a somewhat nebulous diagnosis of exclusion that is made when a couple is involuntarily infertile and no abnormalities are revealed by a standard infertility evaluation.This diagnosis is made with the evidence of ovulation, adequate sperm production , and fallopian tube patency.

The age of the female and duration of infertility are important variables that affect the prognosis for pregnancy in unexplained infertility .There is a dramatic decline in the likelihood of pregnancy after three years of infertility and in the late 30s of age.This appears to be due to diminished ovarian reserve,oocyte aging, and embryo quality.

Key Words :

Anti sperm antibodies – Post coital test .

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A.S.A	Anti sperm antibodies
AACEP	Agonist /antagonist conversion with estrogen priming.
CASA	Cumputer assisted semen analysis
GIFT	Gamet intra fallopian transfer
HOS	Hypo osmotic swelling test
ICSI	Intra cytoplasmic sperm injection
IUI	Intrauterine insemination
IVF	In vitro fertilization
OPR	Ongoing pregnancy rate
PCT	Post coital test
PGD	Preimplantation genetic diagnosis
RCTs	Randomized controlled trials
ROC	Receiver operating characteristic
ROS	Reactive oxygen species
SM	Strict morphology
SPA	Sperm penetration assay
UI	Unexplained infertility
WHO	World Health Organization
ZIFT	Zygot intrafallopian transfer

Introduction

Infertitly is defined as the inability to conceive during one year of unprotected intercourse,and an infertility investigation is usually initiated after one year of involuntary infertility. Because the diagnosis of unexplained infertility ideally includes only couples with real subtle defects in reproductive function,that are not identified by conventional infertiliyty investigations,many investigators use a longer duration of involuntary infertility such as 2 or 3 years to diagnose unexplained infertility (Kim and Hornstein 1997).

Between 40-65% of couples given this label will conceive spontaneously over the following three years and it has been suggested that treatment should be deferred until the couple has been trying to conceive for at least three years, as before this time therapy doesnot confer any benefit over the natural chance of conception, unexplained infertility is a diagnosis of exclusion that is made when a couple is involuntarily infertile, and no abnormalities are revealed by a standared infertility evaluation.(ESHRE, 2004).It is important to seek agreement on which diagnostic tests are required before making this diagnosis. Missing information about reproductive processes is an important barrier to conception and live birth among infertile couples.(ESHRE,2004).

In the absence of a correctable cause, the therapy for unexplained infertility is, by default empiric,with the aim of increasing the probability of pregnancy and reducing the interval required for conception. The treatment options for unexplained infertility are several and the treatment results are promising.Expectant management can be recommended if the woman is under 28-30 years of age and the infertility duration is less than 2-3 years. In vitro fertilization (IVF) has revolutionized the treatment of infertile couples, as well as profoundly increasing the basic understanding of human reproduction. (IVF) can be used as both a diagnostic and a therapeutic tool in couples with unexplained infertility. The pregnancy rates with IVF are good, at 40% per treatment cycle. In addition, the outcome of pregnancies among women with unexplained infertility is generally comparable to that of spontaneous and other pregnancies using assisted reproductive technologies.(Isaksson ,2004).

Unexplained infertility(U.I):

Definition:

Infertility:

Is defined as the inability of a couple to conceive after one year of sexual intercourse without the use of any contraceptive method (Speroff et.al.,2004). Infertility is said to be **unexplained** when a couple doesn't conceive and no definite cause of infertility can be diagnosed after a complete standerd evaluation (Aboulghar, 2002).

Incidence:

The incidence of infertile population diagnosed with unexplained infertility ranges from 10% - 15% and using normal findings on more invasive diagnostic techniques as laparoscopy as a criterion, the prevalence may be less than 10% (Crosignani et al., 1993 and Speroff, 2005).

Diagnosis of UI:

Unexplained infertility refers to a diagnosis made in couples in whom standerd investigations including semen analysis , tests of ovulation and tubal patency are normal(Siristatidis,2008**)** .

Prior diagnostic tests should be examined critically.In some situations, such tests may need to be repeated.This may be true if significant time has passed, if there are discrepancies between tests, or if the results are unclear.However, the impulse to repeat multiple tests should be tempered by good judgment. A false positive result may expose the patient to potentially harmful and ultimately useless interventions. Moreover, interpretation of diagnostic infertility test results must be balanced with the knowledge that the ability of many components of the standard infertility tests to discriminate between infertile and fertile patients is not consistently evident. In a small case-control study comparing fertile patients undergoing tubal ligation with infertile patients, two-thirds of fertile patients were found to have an abnormality of at least one

infertility test.In a study of a large sample of infertile women, the prevalence of out-of-phase endometrial biopsies among the infertile women was not different than that in a matched group of fertile women.Additional tests beyond the standard evaluation have not, in general, proven to be useful.Tests that are poor or inconsistent predictors of subsequent pregnancy include the postcoital test, screening for chlamydia /mycoplasma / ureaplasma, varicocele identification, immunologic testing, tests of sperm function, identification of antisperm antibodies, and assessment of antiphospholipid antibodies (Cedars' 2005).

It has been suggested that the term UI is unsustainable, as conditions such as endometriosis,tubal infertility,premature ovarian aging and immunological infertility tend to be misdiagnosed as UI. In this debate, the view that although scientifically unsatisfying, the diagnosis of UI is sustainable from a clinical and practical perspective . Given our present treatment options,further investigations leading to a more accurate diagnosis is unlikely to change our management in these cases . Scientific curiosity must take second place to a more pragmatic approach, which takes into account the clinical and financial costs of making a more accurate diagnosis **(**Siristatidis,2008**)**.

Possible and previously proposed aetiologies of unexplained infertility:

The femal partner's age and the duration of unexplained infertility are important variables regarding to the possible aetiologies of unexplained infertility and determining the chance of still getting pregnant naturally in subfertility and unexplained infertility.

Female partner's age:

The woman's most fertile years are between 15 and 24 years of age after which fecundity declines steadily(Rosen et.al,2000).This steady fashion from the mid twenties until the late thirties or early forties, then after which a sharp decline occurs(Victor et.al,2002).The prevalence of infertility rises dramatically as age increase.The rate of pregnancy per IVF attempt also declines with advancing female age . an acceleration point has been found between the age of 36 and 38(Speroff et.al,2004).

Various mechanisms are involved in the age related.Decline of fertility (Gosden,1985),including progressive depletion of ovarian follicular store (Amir,2001), reduced follicular function (Hughes et.al,1990),poor oocyte quality (Mangal et.al,1999),diminished endometrial receptivity(Melclrum,1993).and reduced capillary permeability and blood flow in the uterus (Gosden,1995).Basal FSH concentration increases as menopause approaches (Kelin et.al,1996),presumably as a consequences of decreased inhibin production resulting from follicular depletion and diminished granulose cell formation(Hughes et.al,1990).probably by a similar mechanism , an elevated basal FSH concentration and abnormal clomiphene citrate challenge test are associated with low rates of pregnancy in IVF(Scott and Hofmann,1995).

The duration of unexplained infertility:

Infertility is defined as the inability to conceive after one year of unprotected regular intercourse, and an infertility investigation is usually initiated after 1 year of involuntary infertility. Acouple is diagnosed with unexplained if the results of this investigation are normal. Assigning this diagnosis after one year, however results in the inclusion of many fertile couples whose failure to conceive is due to chance alone. Kim and Hornstein,(1997) reported that 14% of fertile women did not become pregnant during 1 year of unprotected intercourse . He reached a conclusion that 6.6%of the fertile women required more than 2 years to do so.Because the diagnosis of

unexplained infertility should ideally include only couples with real but subtle defcts in reproductive function,many investigators use longer duration of involuntary infertility, as 2 to 3 years to diagnose unexplained infertility(Kim and Hornstein,1997).

Hull et. al, 1995 found that the main factor determining the likelihood of pregnancy in 196 couples with unexplained infertility was the duration of infertility. For couples with less than 3 years of infertility before the 24 months observation period, the cumulative pregnancy rate was 83% to 84%.However the rate was 56% after 3 to 5 years of infertility and decreased to 30% after 5 years.Collins and Row 1999 also found a dramatic decline in the likelihood of spontaneous pregnancy after 3 years of infertility among 470 couples with unexplained infertility.In couples with fewer than 3 years of infertility,the cumulative pregnancy rate was 45.6% after 2 years of observation.For couples with more 3 years of infertility, this rate was 27.5%.So these couples with more than 3 years of unexplained infertility are more likely to have subtle but real reproductive defects. After this period,the pregnancy rate decreases by 24%for every additiol year (Crosignani et.al,1993) and the chance of natural conception falls to decimal levels (Hull,1994).The pregnancy history of a couple also impacts on the time of conception and the chance for pregnancy.Kim and Hornstein,(1997)found that women planning a first pregnancy required more time for conception than those who had been pregnant before. For couples with unexplained infertility Collins and Row 1989 found that a history of pregnancy predicted a 1.8 times greater chance of a subsequent pregnancy. The cumulative pregnancy rate after 2 years was 33.1% for couples with primary infertility and 52.8% for couples with secondary infertility. Because the duration of infertility has such a powerful effect on the prognosis for pregnancy in couples with unexplained infertility , particular attention must be paid to the duration of infertility required by a study's diagnostic protocol . Comparison of results from different studies must be performed cautiously if one study population is defined by duration of infertility of more than 2 years(Kim and Hornstein,1997).Speroff et.al mentioned that pregnancy rate decreases not only with the increased duration of infertility but also with the increased duration of marriage due to frequent exposure to infection, uses of contraception, and decrease frequency of intercourse. (Speroff et.al,2004).

Table (1) summary of Possible aetiologies of unexplained infertility

Theory/clinical finding	Mechanism	Study
Pituitary and/or follicular dysfunction		
FSH elevation	Diminished ovarian reserved	Blacker et al., 1997
LH fall	Impaired follicular development	Omland et al., 2004
Poor ovulation	Impaired/short luteal phase	Harrison et al., 2000
Estrogen elevation	Altered folliculogenesis	Blacker et al., 1997, Leach et al., 1997
Abnormal prolactin	Absent mid-cycle prolactin rise and impaired oocyte development	Subramanian et al., 1997
Pituitary ovarian dysfunction	Impaired follicular development	Harrison et al., 2000
Impaired follicular development	Impaired ovulation and increased risk of LUF	Blacker et al., 1997 Omland et al., 1998
Gamete dysfunction oocyete dysfunction		
Decreased oocyte function	Reduced occyte quality	Blacker et al., 1997, Omland et al., 2004
Impaired oocyte transport	Impaired ovum pick-up and impaired tubal transport	Ahmed-Thabet, 2000, Omland et al., 1998.
Impaired oocyte-sperm interaction	Impaired fertilization	Blacker et al., 1997, Omland et al., 2004
Sperm dysfunction		
Impaired penetration of cervical mucus	Impaired fertilization	Hull et al., 1998
Impaired penetration of zona pellucida	Impaired fertilization	Takeuchi et al., 2000, Hull et al., 1998
Impaired penetration of ooplsmic membrane	Impaired fertilization	Takeuchi et al., 2000, Hull et al., 1998
Alterations in endometrial function		
Subclinical infection	Impaired implantation	Guzic et al., 1998.
Suboptimal expression of integrins and Pinopodes.	Impaired endometrial development and Switch in the window of implantation	Omland et al., 2004 Lessey et al., 1998
Immunological factors		
Elevated concentrations of ovarian anti bodies	Ovarian failure	Luborsky et al., 2000
Anti-spermatozoal antibodies	Impaired fertilization	Luborsky et al., 2000
Anti-cardiolipin antibodies	Increased uterine artery resistance	Battaglia et al., 1998

Evaluation of the male partner:

An infertility evaluation should be performed if a couple has not achieved conception after one year of unprotected intercourse. An evaluation should be performed earlier if male or female infertility risk factors exist and if the couple questions its fertility potential.The initial screening of the male should include a reproductive history and a physical examination performed by a urologist or a specialist in male fertility and two semen analysis . Additional procedures and testing may be used to elucidate problems discovered during the full evaluation.(Huyghe, et. al, 2008).

When couples seek assistance, an initial semen analysis remains the current standard for male evaluation.(Sasagawa et al,2001,Schoor et al,2002).

A diagnosis of male factor infertility is reached in only 40% of the affected males seeking assistance.(Guzick et.al.,2001,Menkveld et.al.,2001).

Laboratory evaluation:

The laboratory assessment of the male partner of an infertile couple is an important aspect of the overall investigation of that couple. The laboratory tests are designed essentially to determine whether (a) the semen samples contain adequate numbers of normal motile sperm, and the sperm are able (b) to migrate to the site of fertilization (Matson,1997)(sperm motility measured by both the percentage of motile sperm and the quality of movement ,called forward progression.Normal sperm motility should be at least 50% with a forward progression of 2.0 or higher “where 0 is no movement ,and 4.0 is excellent qualitative motion”)(Shama et.al., 2001)and (c) to fertilize oocytes. Within this framework, tests can be viewed as being either descriptive, in terms of describing the ejaculate and sperm, or assessing functional qualities of the sperm. Irrespective of the nature of the test, it must satisfy simple criteria, namely being reproducible and able to discriminate between the fertile and infertile populations reliably. (Matson,1997).

Routine semen analysis:

Although semen analysis is routinely used to evaluate the male partner in infertile couples, sperm measurements that discriminate between fertile and infertile men are not well defined.The classification-and-regression-tree analysis to estimate threshold values for subfertility and fertility with respect to the sperm concentration, motility, and morphology.An analysis of receiver-operating-characteristic curves to assess the relative value of these sperm measurements in discriminating between fertile and infertile men.The subfertile ranges were a sperm concentration of less than 13.5 x 10^6 per milliliter, less than 32 percent of sperm with motility, and less than 9 percent with normal morphologic features.The fertile ranges were a concentration of more than 48.0 x 10^6 per milliliter, greater than 63 percent motility, and greater than 12 percent normal morphologic features. Values between these ranges indicated indeterminate fertility. There was extensive overlap between the fertile and the infertile men within both the subfertile and the fertile ranges for all three measurements. Although each of the sperm measurements helped to distinguish between fertile and infertile men, none was a powerful discriminator. The percentage of sperm with normal morphologic features had the greatest discriminatory power.So the **conclusion** is**:** threshold values for sperm concentration, motility, and morphology can be used to classify men as subfertile, of indeterminate fertility, or fertile. None of the measures, however, are diagnostic of infertility.(Guzick, 2001).

Numerous authors have observed that sensitivity of the semen parameters is poor, indicating a large overlap in the distribution of these variables in the fertile and infertile groups (Menkveld et al., 2001).

A complete female fertility evaluation should be performed concurrently with that of the male to achieve successful and cost-effective outcomes.Accurate semen testing must include proper collection and analysis. Semen ideally should be collected after a 2 to 3 day sexual abstinence. A shorter abstinence period results in a lower sperm density, whereas a longer period may result in lower motility. If possible, the sample should be obtained by masturbation, avoiding the use of spermatotoxic lubricants.When interpreting results, it is important for the clinician to recognize the