

## Unexplained Subfertility

Fakhera Feroz-Zaidi\*

Clinician Scientist UCL Gower Street, University College London, United Kingdom

\*Corresponding author: Fakhera Feroz-Zaidi, Clinician Scientist UCL Gower Street, University College London, United Kingdom, Tel: 447772966307; E-mail: fah4@doctors.org.uk

Received date: 15 February, 2015; Accepted date: 24 March, 2015; Published date: 26 March, 2015

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**Keywords:** Unexplained sub fertility; Infertility

### Introduction

Subfertility is said to be idiopathic or unexplained when a couple does not conceive and no definite cause of subfertility can be diagnosed after a complete evaluation. Up to 25% of patients who present themselves for investigation in a reproductive medicine clinic are diagnosed with unexplained subfertility. It is a multifactorial disorder of reproduction. Many are based on the disruption of biological process that are crucial to the functioning of a normal endometrium, for example lesions in the molecular repertoire that are crucial to implantation, luteal phase defect and microscopic endometriosis. In the absence of a correctable abnormality, the default therapy for unexplained subfertility is empiric.

Several key events are necessary for conception to occur. A mature egg must be released from the ovary. The egg must be picked up by a fallopian tube and then fertilised by sperm. The embryo must be transported to the uterus by the fallopian tubes. Finally the embryo must implant into the uterine lining and develop. Subfertility results when a problem develops in one or more of the steps in this process. Subfertility is defined as one year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycles. Infertility (or sterility) refers to the absolute inability to conceive and monthly fecundity rates (MFR) is the probability of achievement of pregnancy within one menstrual cycle [1]. The average monthly fecundity rate in humans is only 20%. The major factor affecting the individual spontaneous pregnancy prospect is the time of unwanted non-conception, which determines the grading of subfertility [2]. Most of the pregnancies occur in the first six cycles (80%). After that, serious subfertility must be assumed in every second couple (10%). Five percent of the couples are definitive infertile with a nearly zero chance of becoming spontaneously pregnant in the future. With age, cumulative probabilities of conception decline because heterogeneity in fecundity increases due to a higher proportion of infertile couples [1,2].

Secondary subfertility is defined as the inability to become pregnant, or to carry a pregnancy to live birth, following the birth of one or more biological children [3].

Subfertility is said to be idiopathic or unexplained when a couple does not conceive and no definite cause of subfertility can be diagnosed after a complete evaluation. Up to 25% of patients who present themselves for investigation in a reproductive medicine clinic are diagnosed with unexplained subfertility. The diagnosis is usually made after investigations show normal semen parameters, ovulatory concentration of serum progesterone in the mid-luteal phase, tubal patency and a normal uterine cavity [4].

It is important to emphasise to couples with a diagnosis of unexplained subfertility that they have only had essential, simple fertility tests that do not always assess function. For example, despite showing tubal patency, normal transport of eggs and sperm in tubes has not been evaluated as no test for this is available. Although a woman may have an ovulatory concentration of serum progesterone and this indicates formation of corpus luteum, it does not necessarily mean an egg has been released nor that an egg has been picked up in the fallopian tubes. Even for women who ovulate, there is no information about oocyte quality and consequent embryo quality after fertilisation. Despite normal semen parameters, the sperm may fail one of the steps needed to fertilise the oocyte.

It remains unclear whether the basic subfertility assessment should also test for antisperm antibodies, adequate cervical mucus production, timely development of secretory phase endometrial responses, presence of adhesions and evidence of pelvic endometriosis. At present, even the most sophisticated diagnostic assessment cannot reveal all of the possible abnormalities. Therefore, unexplained subfertility appears to represent either the lower extreme of the normal distribution of fertility or it arises from a defect in fecundity, which cannot be detected by the routine infertility evaluation [4].

### Epidemiology of Unexplained Subfertility

The average incidence of unexplained subfertility has been reported to be approximately 25%; the incidence varies from 0% to 37% [5,6]. It has been clearly demonstrated that the chance of conception in such couples is most closely related to the duration of their infertility, the age of the female partner and whether the infertility is primary or secondary. It is agreed that an eventual pregnancy rate of 60-70% will be achieved after 3 years of follow up with no specific treatment [2,4]. The decision as to whether it is appropriate to treat a couple for unexplained subfertility or to wait for spontaneous pregnancy is dictated largely by the duration of subfertility, the woman's age and the couple's wishes. A woman over 35 should be advised to start treatment earlier than a younger woman. The spontaneous monthly fecundity rate declines with increasing duration of unexplained subfertility. After 3 years, the spontaneous pregnancy in untreated couples with unexplained subfertility falls to 40%, after 5 years to 20% [1].

Couples with unexplained subfertility suffer from both diminished and delayed fecundity, compared with the 20% to 25% that would be expected in normal fertile couples. In a review of unexplained infertility studies, the average cycle fecundity in the untreated control groups was 1.8% in 11 non-randomized studies and 3.8% in six randomized studies [7].

## Possible Causes of Unexplained Subfertility

The underlying basis for infertility in patients with unexplained subfertility is not known. In some of these women, an “endometrial factor” may be involved in the infertility and there may be a primary derangement in the expression of the endometrial genes crucial to implantation [8]. In addition, the human endometrium is the end organ for the signal derived from the hypothalamic-pituitary-ovarian axis. Therefore, the aetiological factor(s) causing infertility may secondarily cause an alteration in the molecular repertoire of the endometrial receptivity [8]. In either case, such aberrations may be specific and thus may allow diagnosis of infertility. At the present time, only limited information exists regarding the genes that account for endometrial receptivity in humans and whose aberrant expression is associated with infertility [8].

It is conceivable that various types of subfertility may primarily or secondarily affect the regulatory mechanisms involved in implantation and lead to lesions in the molecular repertoire required in this process [8].

Serological tests have identified the presence of anti-sperm antibodies in couples with unexplained subfertility, although a clear association between the presence of these antibodies and unexplained subfertility has yet to be established [8]. Antiphospholipid antibodies have also been linked but this is a difficult association to prove since assays for antiphospholipid antibodies other than anticardiolipin are not standardized [9].

Ongoing research into unexplained subfertility has now led to a greater number of theories for the cause and establishment of the disease. It is a multifactorial disorder of reproduction. Many are based on the disruption of biological process that are crucial to the functioning of a normal endometrium, for example lesions in the molecular repertoire that are crucial to implantation, luteal phase defect and microscopic endometriosis. Furthermore, sperm dysfunction and occult chlamydia infection have also been associated with unexplained subfertility [9].

## Management of Unexplained Subfertility

A lack of agreement exists regarding the diagnostic tests to be performed and their prognostic value as well as criteria of normality [9]. Variation in the way different investigators interpret their data, together with the difficulty in performing prospective randomized trials, have resulted in today's differences in opinion and practice among specialists. 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 [4].

In the absence of a correctable abnormality, the default therapy for unexplained subfertility is empiric. Expectant treatment is the option of choice for young patients with a short period of subfertility. The spontaneous pregnancy rate is very high (60%) in this group of

patients within 2 years, however for subfertility greater than 3 years duration and particularly if the female partner is older than 35 years, monthly fecundity rates in unexplained couples are 1% to 3% [9]. If the above measure fails to achieve pregnancy, intrauterine insemination (IUI), superovulation with oral or injectable medications, combinations of IUI with superovulation and assisted reproductive technologies (ARTs) could be performed [9-16].

## References

- Evers JL (2002) Female subfertility. *Lancet* 360: 151-159.
- Gnoth C, Godehardt E, Frank-Herrmann P, Friol K, Tigges J, et al. (2005) Definition and prevalence of subfertility and infertility. *Hum Reprod* 20: 1144-1147.
- www.who.int/reproductivehealth/topics/infertility/definitions/en/
- Hart R (2003) Unexplained infertility, endometriosis, and fibroids. *BMJ* 327: 721-724.
- Bhattacharya S, Hamilton M (2014) Management of Infertility for the MRCOG and Beyond, 3rd ed. Cambridge University Press 77-83.
- Collins J (2003) Stimulated intra-uterine insemination is not a natural choice for the treatment of unexplained subfertility. Current best evidence for the advanced treatment of unexplained subfertility. *Hum Reprod* 18: 907-912.
- Guzick DS, Sullivan MW, Adamson GD, Cedars MI, Falk RJ, et al. (1998) Efficacy of treatment for unexplained infertility. *Fertil Steril* 70: 207-213.
- Feroze-Zaidi F, Francis F, Smith SK, Brosens JJ (2007) Aberrant endometrial expression of serum-and glucocorticoid-inducible kinase-1 in women with unexplained infertility. *Reproductive Sciences* 14: 119A.
- Bhattacharya S, Hamilton M (2006) Management of Infertility for the MRCOG and Beyond, 2nd ed. RCOG Press 89-96.
- Aboulghar MA, Mansour RT, Serour GI, Al-Inany HG (2003) Diagnosis and management of unexplained infertility: an update. *Arch Gynecol Obstet* 267: 177-188.
- Ray A, Shah A, Gudi A, Homburg R (2012) Unexplained infertility: an update and review of practice *Reproductive BioMedicine Online* 24: 591-602.
- Arcaïni L, Bianchi S, Baglioni A, Marchini M, Tozzi L, et al. (1996) Superovulation and intrauterine insemination vs. super ovulation alone in the treatment of unexplained infertility. A randomized study. *J Reprod Med* 416: 1-14.
- Athallah N, Proctor M, Johnson N (2002) Oral versus injectable ovulation induction agents for unexplained sub fertility. *Cochrane Database Syst.*
- Bhattacharya S, Harrild K, Mollison J, Woodworth S, Tay C, et al. (2008) Clomiphene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial. *Br Med J* 337: a716.
- Biacchiardi CP, Revelli A, Gennarelli G, Rustichelli S, Moffa F, et al. (2004) Fallopian tube sperm perfusion versus intrauterine insemination in unexplained infertility: a randomized prospective crossover trial. *Fertil Steril* 81: 448-451.
- Chung CC, Fleming R, Jamieson ME, Yates RWS, Coutts JRT (1995) Randomized comparison of ovulation induction with and without intrauterine insemination in the treatment of unexplained infertility. *Hum Reprod* 10: 3139-3141.