Unexplained Infertility, the Controversial Matter in Management of Infertile Couples

30% of infertile couples worldwide are diagnosed with unexplained or idiopathic infertility and the problem is defined as the lack of an obvious cause for a couple's infertility and the females' inability to get pregnant after at least 12 cycles of unprotected intercourse or after six cycles in women above 35 years of age for whom all the standard evaluations are normal. The veracity of 'unexplained infertility' term has been challenged by many clinicians and researchers; they emphasize that the assignment of this title to an infertile couple is much dependent on the quantity, quality and nature of the applied diagnostic tests (1, 2).

According to the ESHRE guidelines, necessary tests for unexplained infertility are semen analysis, assessment of ovulation and the luteal phase, and assessment of tubal patency by hysterosalpingogram or laparoscopy. However, there are controversial opinions about the value of endometrial biopsy, ovarian reserve (AMH, AFC), post-coital test and serum prolactin levels.

Our inability to find the causes of couples' infertility does not mean that there is no cause for the disorder. Extensive research should be conducted on other possible causes of failed conception such as ovarian and testicular dysfunctions, sperm and oocyte quality, fallopian transport defects, endometrial receptivity, implantation failures, and endometriosis (3, 4).

Management of infertile couples with idiopathic cause needs individualized treatment. Several key variables including age, infertility history, treatment history, costs, and risks should be considered in selection of the suitable treatment plan.

The rate of spontaneous conception in these couples is more than the couples with defined causes of infertility and several studies have reported that the rate of spontaneous pregnancy was 13-15% during the first year of attempt which increased to 35% during the next two years of attempt. Moreover, the rate could reach 80% in younger couples during the following three years of unprotected intercourse without any adjuvant therapy. The rate of spontaneous pregnancy drastically declines with infertility duration of more than 3 years and in women over 30 years of age. There are several mathematical models such as Hunault's prognostic model to estimate the rate of spontaneous pregnancy. Therefore, when the chance of spontaneous conception for a couple is so high, no further fertility treatment is needed and the best plan for them would be expectant management (1, 3, 5).

However, the main problem for treatment in these couples is disagreement of physicians on the management of unexplained subfertility. Many of infertility specialists are unaware of latest protocols and procedures approved by ESHRE, ASRM and other societies for managing unexplained infertility. Several other factors including lack of strong evidence, couples impatience for completion of standard protocols and dominance of ART treatment compared to other options in infertility clinics lead to diversity of clinical practice regarding unexplained infertility.

Failure in implementation of standard practice for treatment of unexplained infertility leads to overtreatment in most of cases. This practice is mainly accompanied with misdiagnosis and undiagnosis of eligible cases for expectant management (5).

Several expensive, time-consuming and risky therapies of Assisted Reproductive Technology (ART) bring about complications in infertility clinics. For many couples, ART will not increase the chance of pregnancy. It will be favorable for infertile couples and specialists that the first-line treatment would be simple, low-cost and noninvasive (5).

The guideline of National Institute for Health and Care Excellence (NICE) on fertility suggests some treatment options regarding the above criteria for management of unexplained infertility. The age of women and infertility duration are important factors in offering specific therapy to a couple. Expectant management for 2 years is the best choice for good prognosis when the woman's age is less than 30. This includes active medical intervention which requires the females to be aware of their ovulation time and the best period for unprotected intercourse. The main advantage of expectant management is avoiding multiple gestations which are accompanied with obstetric and prenatal complications, postnatal disability and the considerable burden on healthcare system can not be neglected in this regard. If the long period of expectant management cannot lead to pregnancy, ovulation induction by clomiphene and letrozole is not effective for these couples. Also insemination cycles without ovarian stimulation (COH) will have little benefit for them. COH/IUI (3-4 cycles) are effective in women under 35, but COH/IUI increase the risk of multiple gestations. However, COH/IUI is ineffective for couples with long duration of infertility (4).

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Couples over 35 and couples with long duration of infertility are suitable candidates for IVF. In comparison with COH/IUI, IVF shortens time to pregnancy and reduces the risk of multiple pregnancies. Failed fertilization is reported in 8.4%-22.7% of IVF cycles for couples with unexplained infertility; therefore, many clinics offer routine ICSI for these couples. It may result in an increase in the costs for each take home baby. However, several studies suggested split IVF/ICSI would be the best option for these couples since its cumulative pregnancy rates are higher than conventional IVF and the costs are less than those in ICSI (2).

Prognosis of unexplained infertility and its response to above procedures is quite agreeable. However, some problems such as the limited number of these options and high dependence of specialist and couples on ART should not let the physicians offer additional expensive and experimental tests which waste the golden time of couples for pregnancy without any effective results. Through doing more research on reproductive biology and increasing our knowledge of gametogenesis, fertilization, embryo development, implantation and fetus-uterus crosstalk, more effective treatment options in future for infertile couples specially the ones with unexplained infertility would be provided.

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