

## Intrauterine Insemination, IVF/ICSI

### Intrauterin İnseminasyon, IVF/ICSI

Çağlar ÇETİN

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#### ABSTRACT

Infertility is defined as the inability to conceive after one year despite regular intercourse. The need for treatment and treatment option are determined by the evaluation process that starts after this stage. Treatment mainly includes ovarian stimulation followed by timed intercourse, intrauterine insemination (IUI), and in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI). Choosing the appropriate patient and appropriate treatment method is critical here and is based on many factors. Maternal age and infertility etiology are the main determinants of treatment selection. As important as it is to think about IVF/ICSI selection quickly in patients over 38 years of age, it is equally important to switch to assisted reproductive techniques without waiting in the presence of very low sperm parameters. An inappropriate indication will fail even if the treatment is done in the best way. Appropriate patient selection and giving enough time to the patient in the treatment stages will increase success. In the presented article, IUI and IVF/ICSI patient selection criteria will be evaluated according to the causes of infertility. Here, the order in which the patient will be evaluated and the steps to be taken on the way to IVF/ICSI in the treatment of staged infertility will be evaluated in detail and descriptively.

**Keywords:** Infertility; intrauterine insemination; in vitro fertilization; treatment.

#### ÖZ

İnfertilite düzenli ilişkiye rağmen bir yılın sonunda gebe kalamama olarak tanımlanmaktadır. Bu aşamadan sonra başlayan değerlendirme süreci ile tedavi ihtiyacı ve tedavi seçeneği belirlenmektedir. Tedavi temel olarak over stimülasyonunu takiben zamanlı ilişki, intrauterin inseminasyon (IUI) ve in vitro fertilizasyon (IVF)/intracitoplazmik sperm enjeksiyonunu (intracytoplasmic sperm injection, ICSI)'nu içermektedir. Burada uygun hasta ve uygun tedavi yönteminin seçilmesi kritiktir ve birçok faktöre bağlıdır. Anne yaşı ve infertilite etiolojisi tedavi seçiminde ana belirteçlerdir. 38 yaş üzeri hastada hızla IVF/ICSI seçimi hakkında düşünmek ne kadar önemli ise çok düşük sperm parametreleri varlığında beklemeden yardımcı üreme tekniklerine geçmek de o kadar önemlidir. Uygun olmayan endikasyon tedavi en iyi şekilde bile yapılsa başarısız olacaktır. Uygun hasta seçimi ve tedavi aşamalarında hastaya yeterli süre verilmesi başarıyı artıracaktır. Sunulan makalede infertilite nedenlerine göre IUI ve IVF/ICSI hasta seçim kriterleri değerlendirilecektir. Burada hasta değerlendirmesinin hangi sıra ile yapılacağı ve basamaklı infertilite tedavisinde IVF/ICSI'ya giden yolda geçilmesi gereken basamaklar detaylı ve açıklayıcı olarak değerlendirilecektir.

**Anahtar kelimeler:** İnfertilite; intrauterin inseminasyon; in vitro fertilizasyon; tedavi.

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## INTRODUCTION

Infertility is defined as the inability to achieve pregnancy despite one year of regular and unprotected intercourse (1,2). It results from male factors in approximately 30-40%, female factors in 30-40%, unexplained in 10-15%, and multifactorial conditions in 10-15% of the patients. Treatment options for the active management of infertility include ovulation induction, intrauterine insemination (IUI), and in vitro fertilization (IVF). The choice of treatment option is exactly based on many factors such as the woman's age, the cause of infertility, ovarian reserve, and duration of infertility. However, several critical factors such as accessibility, effectiveness, cost, safety, and risks of treatment may also affect the choice of treatment option.

### Intrauterine Insemination Today

The IUI is a simple, inexpensive, non-invasive, and safe treatment option for the management of infertility in eligible couples. The basic principle of IUI ensures that morphologically and genetically normal sperms with less DNA damage and more intact cell membrane are isolated with appropriate and simple sperm preparation techniques to reach the oocyte. IUI is mainly recommended for male factors, unexplained infertility, stage I-II endometriosis, and cervical factor (3). The National Institute for Health and Care Excellence (NICE) guideline in 2013 does not recommend IUI for male factor, unexplained infertility, and stage I-II endometriosis, which are the most common indications for IUI unless there are religious, cultural, and social prohibitions for IVF. They recommend direct IVF if not able to achieve pregnancy with expectant management after two years. However, this recommendation in the guideline for the more global use of IVF which is a more expensive, invasive, and difficult method is based on the results of only two studies (4,5). As a result, infertile couples with a good prognosis benefit from IUI would be clearly determined to avoid unnecessary IVF applications.

### Intrauterine Insemination for Whom? How to Decide?

Hunault et al. (6) first performed model validation in 2004 to select patients with a good prognosis for IUI. This model is based on female age, duration of infertility, primary/secondary infertility, and motile sperm count. It aims to determine the couple's chances of spontaneous pregnancy within one year. A new model system was also created by the collaborative effort for clinical evaluation in reproductive medicine (CECERM) group (<https://www.freya.nl/probability.php>) in 2007 and proposed as suitable for patients with both patent tubes, an infertility duration of >1 year, female age of <38, ovulatory females, and without severe male factors (7). The score for the chance of spontaneous pregnancy in a year according to this model is calculated by using the female age, infertility duration, primary/secondary infertility, and motile sperm count. Patients are eligible for IUI if the score is >30% in both models. In general, the literature suggests that the success of IUI is higher in patients with a young age, good ovarian reserve, short duration of infertility, and secondary infertility. A descriptive prospective validation study included 1,079 subfertile couples who underwent 4,244 cycles of IUI in seven fertility centers, was found that the ongoing pregnancy rate for IUI was 6.6% per cycle (8). According

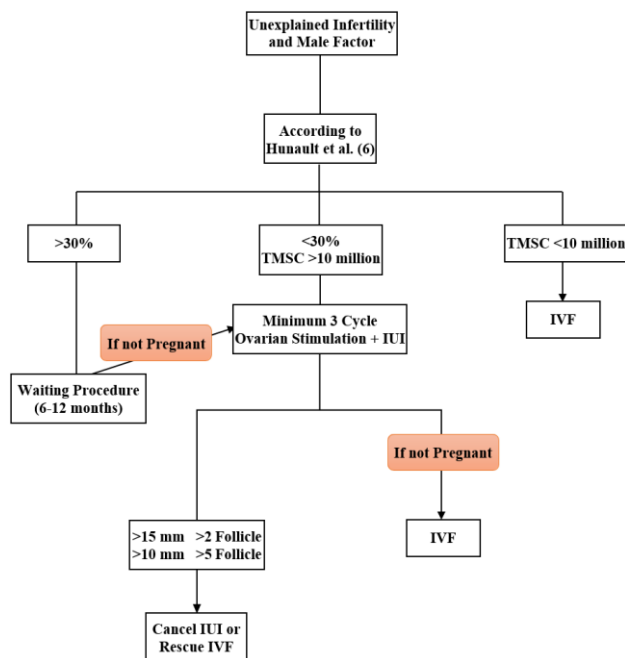
to the scoring system of this study, patient with a score <5 has the highest chance of pregnancy, and the pregnancy chance of this group is >12%. The scores based on female age were identified as 7 for 20-25 years, 9 for 26-31 years, 10 for 32-35 years, 11 for 36-39 years, and 12 for >40 years. The scores based on the duration of infertility were identified as 0 for 1-2 years, 1 for 2-5 years, 2 for 5-7 years, and 3 for 7-13 years. Scores based on the etiology of infertility were identified as 0 for unexplained, -3 for cervical, and 1 for male factors. Scores based on the stimulation protocol were 0 for none, -2 for clomiphene, and -2 for human menopausal gonadotropin (hMG) or follicle stimulating hormone (FSH). Lastly, scores based on the number of cycles were identified as 1 for 1, 2 for 2, 3 for 3, 4 for 4, and 5 for 5-13.

### Natural or Stimulated Intrauterine Insemination?

A meta-analysis including 26 studies reporting on 5316 women compared the effectiveness and safety of IUI with clomiphene citrate (CC), letrozole, or gonadotrophins with each other and with IUI in a natural cycle (9). This meta-analysis indicated that gonadotropin-stimulated IUI cycles have higher pregnancy rates with high complication rates such as multiple pregnancies. Therefore, they recommended the use of strict cancellation criteria to avoid high multiple pregnancy rates. A Cochrane review in 2020 including 15 trials with 2068 women evaluated live birth rates in the unexplained infertile group by IUI treatment with or without ovarian stimulation compared to timed intercourse or expectant management with or without ovarian stimulation or IUI with ovarian stimulation compared to IUI in a natural cycle (10). Despite insufficient data, they showed that in couples with a low prediction score of natural conception, IUI in a natural cycle probably results in a higher cumulative live birth rate when compared to timed intercourse with ovarian stimulation. IUI with ovarian stimulation may result in a higher cumulative live birth rate compared to IUI in a natural cycle. IUI with ovarian stimulation probably results in a higher cumulative live birth rate compared to expectant management without ovarian stimulation. As a result, IUI with ovarian stimulation seems to have the highest cumulative live birth rate among these approaches. Three randomized controlled trials comparing IUI with ovarian stimulation vs IVF indicated similar live birth rates with 3-6 IUI with ovarian stimulation and 1-2 IVF treatments. The point highlighted in these studies was to increase the cancel rate against the high risk of multiple pregnancies (7-25%) in gonadotropin-stimulated IUI cycles when compared to IVF treatment with single embryo transfer (11-13). A Cochrane review including 27 randomized controlled trials (RCTs) with 4,349 couples evaluated the effectiveness and safety of different approaches (expectant management, ovarian stimulation, IUI, ovarian stimulation-IUI, and IVF/intracytoplasmic sperm injection, ICSI) in couples with unexplained infertility. It showed that IUI with ovarian stimulation improves pregnancy rates but it may also increase the incidence of multiple pregnancies. It highlighted that the use of strict cancellation criteria may prevent the increase in the incidence of multiple pregnancies. However, in this meta-analysis, the increase in the cost of IUI through the use of gonadotropins was not evaluated (14). IUI should

be canceled to prevent the possibility of increased multiple pregnancies in when >2 follicles with >15 mm or >5 follicles with >10 mm have occurred.

A retrospective observational study including 319 105 IVF and 30 669 IUI cycles compared to IUI vs IVF in terms of success rates, associated risks, and cost-effectiveness (15). They concluded that the success rate of IUI is almost similar to IVF and IUI is related to the lower risk of maternal and neonatal complications and lower cost. In 2015, a Cochrane review compared IVF to other treatment modalities (expectant management, IUI of ovulation induction-IUI) in terms of pregnancy rates in unexplained infertility (16). It found that there is no difference between IVF and ovulation induction-IUI in terms of live birth rate in patients who had not received any treatment before. In the light of literature, it still seems to be suitable for the use of IUI treatment for eligible patients before IVF treatment (17).



**Figure 1.** Decision making approach for IUI vs IVF  
TMSC: total motile sperm count, IUI: intrauterine insemination, IVF: in vitro fertilization

**What Do the Guides Say?**

The NICE guideline in 2013 does not recommend IUI for male factor, unexplained infertility, and stage I-II endometriosis, which are the most common indications for IUI unless there are religious, cultural, and social prohibitions for IVF. They recommend direct IVF if not being able to achieve pregnancy with expectant management after two years. The Canadian guideline in 2019 suggests that based on the female age and the duration of infertility, expectant management recommends in couples with unexplained infertility (18). Otherwise, IVF can be considered as either the first-line treatment choice or after 3 cycles of ovulation induction-IUI if not achieving pregnancy. It also highlighted the increase in the risk of multiple pregnancies in gonadotropin-stimulated IUIs. Likewise, the American Society for Reproductive Medicine (ASRM) guideline in 2020 recommends IVF treatment if not achieving pregnancy with 3-4 cycles of

ovulation induction-IUI. ASRM does not recommend gonadotropin-stimulated IUIs because there is no superiority of gonadotropins to oral agents in terms of success and it is related to the increase in the risk of multiple pregnancies and higher cost (19). On the other hand, ASRM stated that IVF could be considered as a first-line treatment to decrease the time to achieve pregnancy if the woman's age is >38 because IVF has higher pregnancy rates in this age group.

**When should In Vitro Fertilization be the First Choice?**

Although a systematic review included eight RCTs compared the efficacy of ovarian stimulation-IUI and IVF in couples with unexplained infertility. They concluded that regardless of previous treatment history, there was no difference in live birth rates if the female age was <38 but it also demonstrated that the live birth rate in women over 38 age was two times higher in IVF (20). An RCT compared the results of immediate IVF and two cycles of ovulation induction-IUI (oral agents and gonadotropin) in women aged 38-42 years with unexplained infertility (21). The results of this study showed higher pregnancy rates with fewer treatment cycles in the immediate IVF group. In the light of literature, IVF can be considered as the first-line treatment for older women because of the increase in the risk of aneuploidy related to advanced female age, higher pregnancy rates of IVF, and the decrease in time to achieve pregnancy. While total motile sperm count (TMSC) is one of the most important predictors to determine the success of IUI treatment, IVF can also be considered as first-line treatment in patients with TMSC <10 million and severe male factors although there is no clear threshold value determined in the studies (22).

**CONCLUSION**

Infertility treatment is a field of treatment that requires specialist training on the subject. Especially in IVF/ICSI applications, it is essential not to make mistakes in standard laboratory techniques as well as patient selection. The correlation between laboratory and clinical follow-up will increase success. Appropriate patient selection and giving enough time to the patient in the treatment stages will increase success.

**Key facts:**

- Couples with a good prognosis for IUI treatment can be determined by using prognostic models.
- Ovarian stimulation-IUI would be suitable in couples with a good prognosis.
- There is no superiority of the use of gonadotropins to the use of oral agents for ovarian stimulation in terms of success rate during IUI treatment. However, the use of gonadotropins for ovarian stimulation during IUI treatment is associated with an increase in cost and risk of multiple pregnancies.
- The strict cancellation policy should be used to reduce the risk of multiple pregnancies related to ovarian stimulation-IUI cycles.
- IVF treatment can be considered if not achieving pregnancy with 2-3 cycles of ovarian stimulation-IUI.
- IVF can be considered as the first-line treatment in the following situations including women over 38 age, TMSC <10 million, and severe male factors.

**Ethics Committee Approval:** Since our study was a review, ethics committee approval was not required.

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