Ovarian Stimulation Protocols for the Practicing Gynecologist



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CHAPTER

Ideal Stimulation Protocols for Intrauterine Insemination Cycles

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ABSTRACT

Intrauterine insemination (IUI) is the first step in the fertility treatment pathway for many infertile couples. IUI cycles require personalization and individualization to enhance success rates. Such individualization necessitates a detailed understanding of reproductive endocrinology, patient characteristics, and the specific goals of treatment. When compared to in vitro fertilization (IVF), IUI cycles offer lower success rates but are significantly less expensive.

The various parameters to be optimized include the precycle assessment, ultrasound to assess the uterus and ovaries, hormonal evaluation to ensure normal endocrinological function, and tailor-making the choice of ovarian stimulation agents and protocols for best results. Published evidence, systematic reviews, and meta-analyses recommend stimulation with letrozole, gonadotropins, or a combination of both for best results over natural cycle IUI. The clinical pregnancy rates, live birth rates, and cost effectiveness of the protocols are examined with the supporting recently published evidence regarding the same.

INTRODUCTION

It is estimated that 8–12% of couples worldwide suffer from infertility. The condition is plagued by several myths, but the wider accessibility of assisted reproductive services has made the situation easier as compared to a few decades ago. Besides trying with timed intercourse and natural cycles, intrauterine insemination (IUI) remains a first step that clinicians can offer couples trying to conceive.[1,2]

Intrauterine insemination cycles require a substantial amount of personalization and individualization to enhance success rates since the procedure is inherently one that is associated with a low degree of success. Such individualization necessitates a detailed understanding of reproductive endocrinology, patient characteristics, and the specific goals of treatment. When compared to in vitro fertilization (IVF), IUI cycles offer lower success rates but are significantly less expensive and less invasive from the couple's point of view.[3,4]

In this chapter, we review the published evidence to date regarding the key components, considerations, and protocols involved in ovarian stimulation for IUI cycles.

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INTRAUTERINE INSEMINATION BASICS

Intrauterine insemination is a common assisted reproductive technology (ART) technique used to treat various forms of infertility. It involves placing sperm directly into a woman's uterus, specifically during her ovulation period, thereby enhancing the chances of sperm reaching the egg and achieving natural fertilization. Stimulation protocols are a crucial step in the process as they enhance the number and quality of eggs available for ovulation and improve the likelihood of conception when compared to natural cycles.[5]

Optimizing Intrauterine Insemination Success Rates

Success with IUI may depend on a variety of known and unknown factors including paternal age and body mass index (BMI), the total motile sperm count (TMSC), fraction of sperm with rapidly progressive motility, sperm morphology, maternal age and BMI, causative factors for female infertility, endometrial thickness, number of mature follicles, and duration of infertility, in addition to protocol specific variables.[6,7]

Precycle Couple Assessment

Before initiating an IUI cycle, a thorough evaluation of the couple by the treating clinician is essential. This includes the following:

- *Medical history:* Assessing both partners for any underlying conditions that could affect fertility, such as polycystic ovary syndrome (PCOS), endometriosis, or male factor infertility.
- *Clinical examination of both partners:* A basic physical evaluation of both partners is necessary to rule out the various factors responsible for infertility—the presence of more than one factor is common and decreases success rates with treatment. Addressing and correcting them before offering IUI is prudent.
- *Hormonal profile:* Evaluating serum hormone levels, e.g., follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin, estradiol, progesterone, and anti-Müllerian hormone, to determine the ovarian reserve and function. Subtle endocrinological issues are more common than thought, and the time spent correcting them is rewarded with much-improved success rates.
- *Ultrasound assessment:* Conducting a transvaginal ultrasound to evaluate ovarian morphology, endometrial lining, and the presence of any cysts or abnormalities. This is also repeated on the 2nd or 3rd day of the cycle with due consideration to the patient's social and religious beliefs. Such assessment, also referred to as a baseline scan, is required to individualize the starting gonadotropin dosage.

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- *Tubal patency:* A test for tubal patency such as the hysterosalpingography (HSG) or saline infusion sonosalpingography (HyCoSy) is a basic prerequisite since IUI cycles rely on natural fertilization and the presence of patent functioning fallopian tubes.
- *Semen analysis:* Performing a comprehensive semen analysis to assess sperm count, motility, morphology, and abnormal forms is essential so that corrective steps may be taken to address any issues before the IUI cycle begins.
- *Infection screen of both partners:* This includes VDRL, human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) testing which may be missed in a busy clinical practice and should be documented prior to subjecting the couple to IUI.

GOALS OF STIMULATION PROTOCOLS

The primary goals of stimulation protocols in IUI cycles include:

- Inducing the development of multiple follicles to increase the likelihood of fertilization
- Timing insemination accurately to coincide with ovulation
- Minimizing the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies

Stimulation Protocols

Stimulation protocols used for IUI cycles can be broadly categorized based on the medications used.

Clomiphene Citrate

Clomiphene citrate (CC) is often the first-line medication for ovarian stimulation in IUI cycles, especially widely used even today among the older generation of practitioners. It works by blocking estrogen receptors, leading to increased release of gonadotropins from the pituitary gland. The chemical structure of clomiphene is detailed in **Figure 1**.

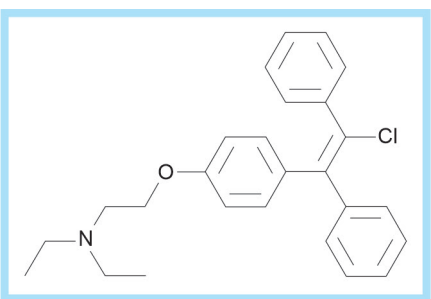

Fig. 1: Chemical structure of clomiphene.

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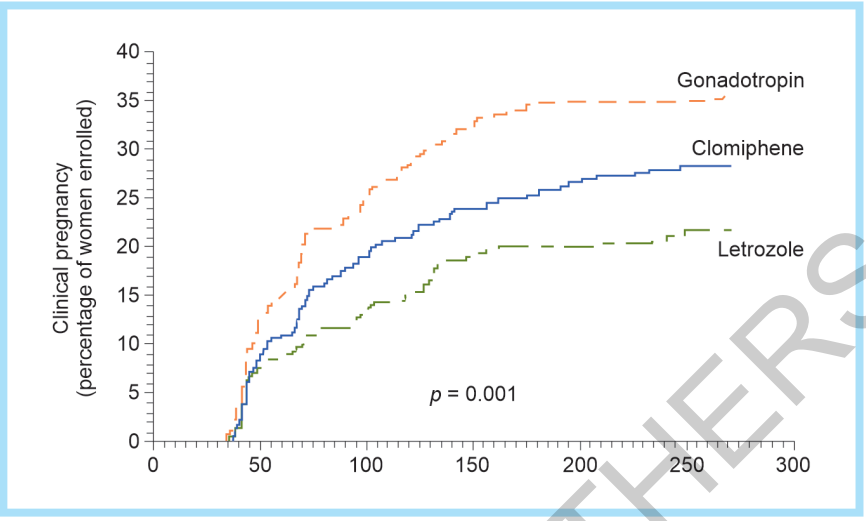

Fig. 2: Clinical pregnancy rates with clomiphene in unexplained infertility.[8]

It is typically used in a dosage of 50–100 mg/day being administered for 5 days, starting on cycle day 2/3. Serial ultrasound monitoring is essential to assess follicular development. The goal is to achieve one to two mature follicles. Clomiphene is considered a good starting oral ovulogen in cases of unexplained infertility. **Figure 2** depicts the findings of one clinical trial comparing clomiphene versus letrozole (LE) in women with unexplained infertility.[8]

Letrozole

Letrozole is an aromatase inhibitor and is another option for inducing ovulation. It has gained popularity due to a lower risk of multiple pregnancies compared to CC and is recommended by the European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) as the first-choice oral ovulogen in women with PCOS.[9]

Letrozole is used in a dose of 2.5–7.5 mg/day for 5 days, starting on cycle day 2/3 of the cycle. Ultrasound monitoring is usually employed to track follicle growth. LE preferentially causes monofollicular development and decreases the chances of multiple pregnancies. It is also associated with better endometrial thickness since it does not have antiestrogenic effects like clomiphene. The chemical structure of LE is depicted in **Figure 3**.

Gonadotropins

In cases where patients do not respond to oral agents or have specific indications (e.g., advanced age and poor ovarian reserve), gonadotropins

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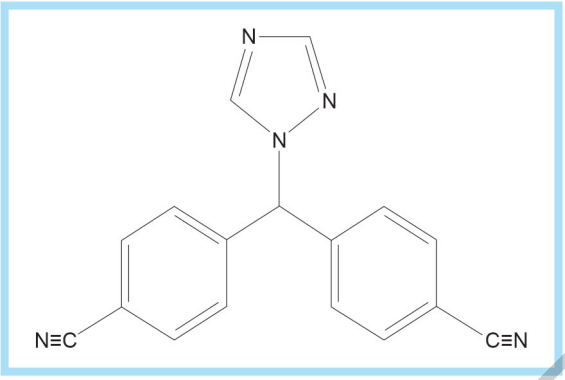

Fig. 3: Chemical structure of letrozole.

(FSH and hMG) may be used. The starting dose typically ranges from 75 to 150 IU/day, based on individual response, with adjustments made during the cycle. These are available as intramuscular or subcutaneous injections and are primarily of two types: (1) Highly purified urinary preparations (HP-hMG) and (2) recombinant preparations (recFSH).

The starting dosage may be based on sliding scales which are available and take into account the age, weight, and ovarian reserve of the woman. Further doses are adjusted based on the patient's response observed through ultrasound and hormone levels. Recent studies have evidenced the superiority of ovarian stimulation with injectable gonadotropins over oral ovulogens.[10]

Frequent monitoring through ultrasounds and serum estradiol levels is vital to avoiding OHSS and ensuring appropriate follicular growth. This is performed on alternate days initially and later may be more frequent, i.e., daily when closer to the time of ovulation triggering. IUI cycles that rely on pure gonadotropin stimulation may not be very cost effective, and the incidence of OHSS and multiple pregnancies may be higher.

Combinations

Many practitioners in various parts of the world resort to combinations of ovarian stimulation agents which include CC with gonadotropins or LE with gonadotropins. In these protocols, the oral ovulogen is started on day 2/3 of the cycle and the gonadotropin is added from day 7/8 onward.

The advantages of this approach are a lower cost of cycle as regards ovarian stimulation drugs, lower incidence of OHSS and multiple pregnancies, and being more patient-friendly since less intensive monitoring may be required. This approach also optimizes follicular and endometrial growth while significantly reducing costs to the patient.[11]

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OVULATION TRIGGERING

Human chorionic gonadotropin (hCG) is the most commonly used ovulation trigger in a dose of 5,000 or 10,000 IU and is administered as an intramuscular or subcutaneous injection. In some cases, a gonadotropin-releasing hormone (GnRH) agonist (e.g., triptorelin or leuprolide) may be employed, especially in women who are at a high risk for OHSS.

This is usually performed when the leading follicle diameter reaches 22–23 mm in an oral ovulogen cycle and 1–2 mm earlier when gonadotropins are being employed for ovarian stimulation. In all cases, an endometrial thickness >7 mm most closely correlates with higher implantation and clinical pregnancy rates, so this is the aim of the attending clinician.

TIMING OF INSEMINATION

The timing of IUI is critical for success. Insemination is usually performed 24–42 hours after the trigger injection of hCG. Ovulation is known to occur approximately 36 hours after the trigger shot; therefore, it is vital that the insemination be performed around this time. The oocytes released have a maximal fertilization potential for about 12 hours which also makes the timing of insemination important.

PUBLISHED LITERATURE COMPARING PROTOCOLS

Dias et al. performed a randomized controlled trial with 341 IUI cycles from January 2016 to November 2020. The stimulation protocols used clomiphene, LE, and gonadotropins. The clinical pregnancy rate per cycle was 8.5% and the live birth rate (LBR) was 5.3%.[4]

Wang et al. published their data on 3,984 cycles in 1,862 couples who underwent IUI between July 2006 and July 2017. The clinical pregnancy rate was significantly higher in ovarian stimulation cycles than in natural cycles (21.2% vs. 11.6%, respectively; $p < 0.01$). The clinical pregnancy rate in the group administered LE + hMG was the highest when compared with the other groups, namely LE alone, clomiphene alone, clomiphene + hMG, and hMG alone.[12]

As regards cost-effectiveness of the different stimulation options available, van Eekelen et al. published their data in 2021 which identified that the agent with the lowest cumulative LBR over four IUI-OS cycles conducted within 1 year was CC (29.4%), followed by LE (32.0%) and gonadotropins (34.5%). The average costs per four cycles were €362, €434, and €1809, respectively. **Figure 4** depicts the cost-effectiveness curves for the various agents.[13]

In 2016, a single university center published its data on 5,109 couples undergoing 8,893 IUI treatment cycles. They specifically addressed clinical pregnancy rates, miscarriage rates, and LBRs as well in their analysis. In ovulatory women without ovarian stimulation, the LBR was 7.6%.

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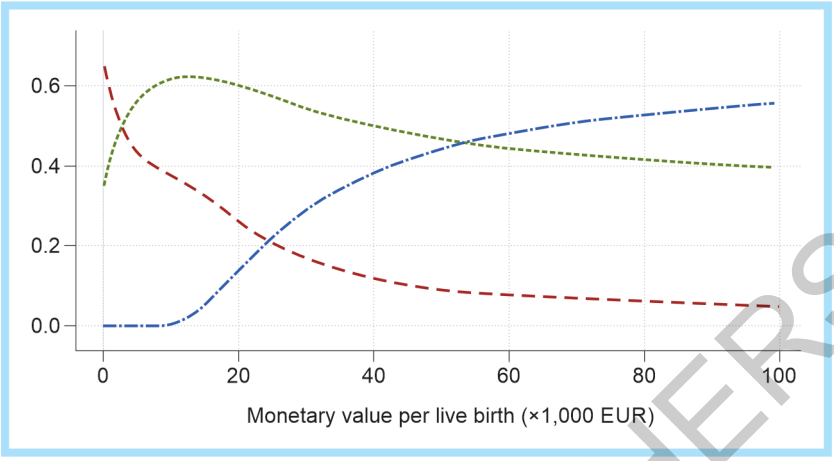

Fig. 4: Cost-effectiveness for agents for ovarian stimulation in IUI cycles. Red indicates clomiphene, green indicates letrozole, and blue indicates gonadotropins). (IUI: intrauterine insemination)

Stimulation with clomiphene citrate, LE, human menopausal gonadotropin, CC, or LE combined with hMG achieved LBRs of 6.1, 5, 7.9, 8, and 12.2%, respectively.

Letrozole combined with hMG achieved a significantly improved LBR compared with no stimulation. hMG stimulation was associated with a higher rate of twins (7.4%) than no stimulation (0%; $p < 0.01$). In anovulatory women, ovarian stimulation with CC, LE, hMG, CC or LE combined with hMG achieved LBRs of 11.3, 5.1, 11.8, 12.6, and 13.6%, respectively.[14]

Table 1 depicts the statistical data from the 8,893 cycles while **Figures 5A to C** demonstrate the clinical pregnancy rates, miscarriage rates, and LBRs associated with the stimulation protocols employed.

Danhof et al.'s Meta-analysis Published in 2020[15]

Danhof et al. identified 26 studies with 5,316 women. The relative risk (RR) for live birth/ongoing pregnancy comparing CC IUI to natural cycle IUI was 1.05. LE IUI versus natural cycle IUI showed RR of 1.15. Gonadotropin IUI versus natural cycle IUI had an RR of 1.46.

The RR comparing gonadotropins to CC was 1.39, LE versus CC was 1.09, and comparing LE to gonadotropins was 0.79. The RR for multiple pregnancy rates in gonadotropins versus CC was 1.42, LE versus CC was 0.97, and LE versus gonadotropins was 0.29.

They concluded that IUI with gonadotropins ranked highest on live birth/ongoing pregnancy rates, but women undergoing this treatment protocol were also at risk for multiple pregnancies with high complication rates.[15]

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TABLE 1: Statistical data from 8,893 IUI treatment cycles.[14]

	NC (n = 2,591)	*CC (n = 2,246)*	*LE (n = 264)*	*hMG (n = 559)*	*CC + hMG (n = 980)*	*LE + hMG (n = 197)*	*p-value*
Ovulatory women pregnancies (%)	241 (9.3)	196 (8.7)	20 (7.6)	55 (9.8)	101 (10.3)	33 (16.8)‡	0.004
Miscarriages (%)	35 (14.5)	46 (23.5)	5 (25)	8 (14.5)	15 (14.9)	8 (24.2)	0.13
Twin pregnancies (%)	0 (0)	8 (4.1)†	(0)	3 (7.3)†	9 (8.9)‡	2 (6.1)*	0.001
Ectopic pregnancies (%)	10 (4.2)	12 (6.1)	2 (10)	3 (5.5)	8 (7.9)	1 (3.0)	0.66
Live births (%)	196 (7.6)	138 (6.1)	13 (5.0)	44 (7.9)	78 (8)	24 (12.2)‡	0.01
	CC (n = 515)	*LE (n = 79)*	*hMG (n = 85)*	*CC + hMG (n = 1,025)*	*LE + hMG (n = 350)*	*p-value*	
Anovulatory women pregnancies (%)	78 (15.2)	7 (8.9)	13 (15.3)	169 (16.5)	62 (17.6)	0.38	
Miscarriages (%)	18 (23.1)	2 (28.6)	2 (15.4)	26 (15.4)	14 (22.6)	0.5	
Twin pregnancies (%)	3 (3.8)	0 (0)	0 (0)	8 (4.7)	3 (4.8)	0.9	
Ectopic pregnancies (%)	2 (2.6)	1 (11.1)	1 (7.7)	14 (8.3)	0 (0)	0.07	
Live births (%)	58 (11.3)	4 (5.1)	10 (11.8)	129 (12.6)	48 (13.6)	0.28	

(CC: clomiphene citrate; hMG: human menopausal gonadotropin; NC: natural cycle)
*$p < 0.05$.
†$p < 0.01$.
‡$p < 0.001$.
The *p*-value indicates a statistically significant difference compared with the NC group.

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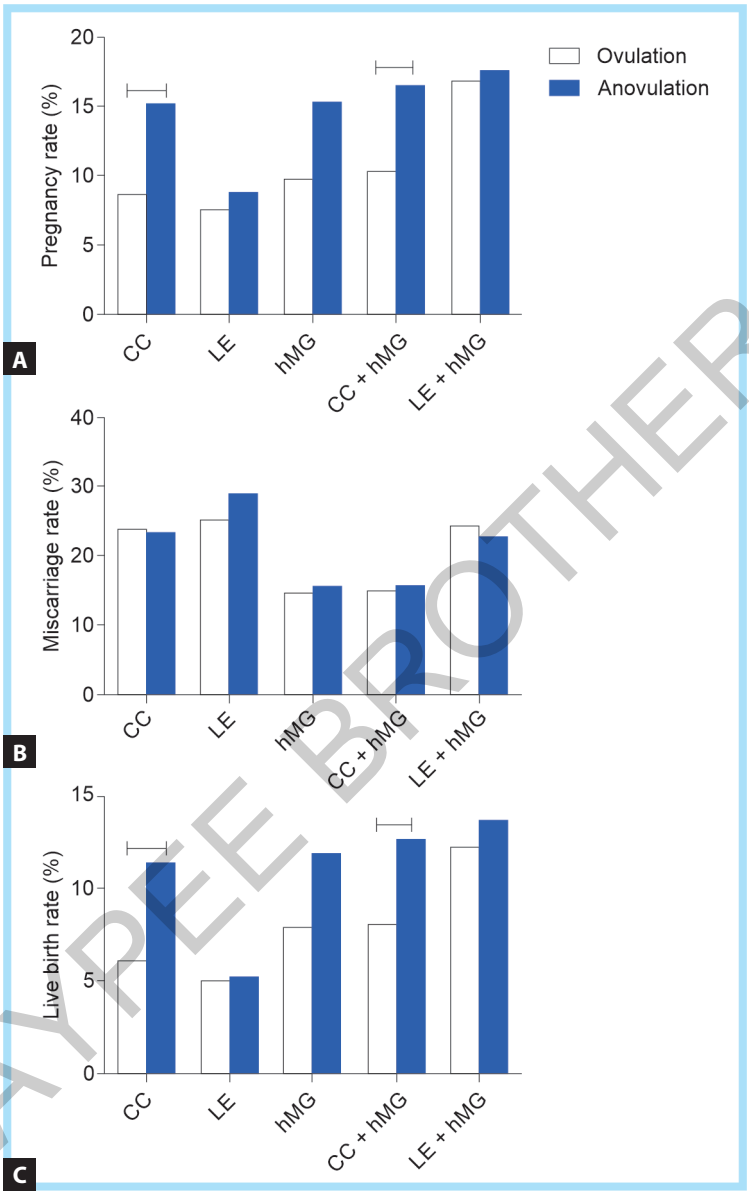

Figs. 5A to C: CPR, miscarriage rates, and LBR in 8,893 IUI cycles.[14] (CC: clomiphene citrate; CPR: clinical pregnancy rate; hMG: human menopausal gonadotropin; IUI: intrauterine insemination; LBR: live birth rate)

FIIX Study[16]

The FIIX study is a multicenter, open label, parallel, and pragmatic noninferiority randomized controlled trial of 580 couples with unexplained infertility comparing four cycles of IUI-OS with CC and one completed cycle

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of IVF. The two arms will compare four cycles of IUI followed by two cycles of IVF versus two cycles of IVF. The trial is ongoing, and the results are expected to be published in the forthcoming months. **Figure 6** depicts the study protocol.

Systematic Review and Meta-analysis Published 2022

Seven of 22 eligible RCTs with 2,495 couples, of which 2,411 had unexplained infertility, were included. Six RCTs ($n = 1,511$) compared gonadotropins with CC and one ($n = 900$) compared gonadotropins, LE, and CC. Moderate-certainty evidence showed that gonadotropins enhanced the LBR compared to CC [6 RCTs, 2,058 women, RR 1.30 and 95% confidence interval (CI) 1.12–1.51]. Gonadotropins may also increase the multiple pregnancy rate compared to CC.

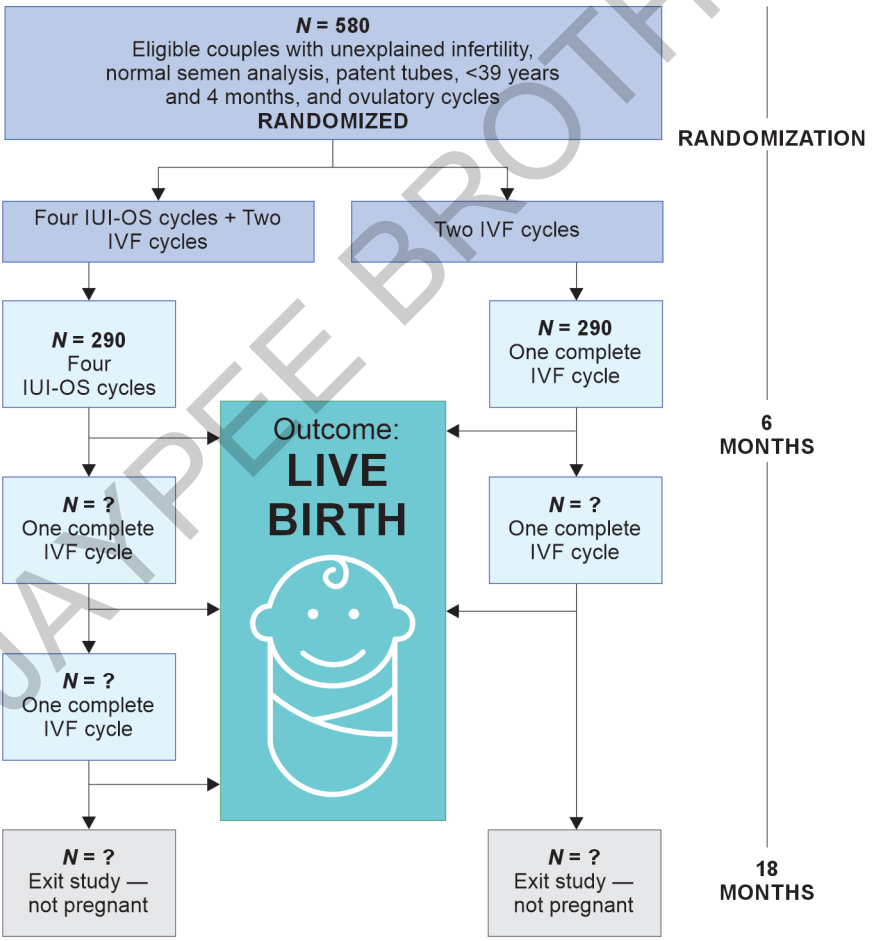

Fig. 6: FIIX study protocol. (IUI-OS: intrauterine insemination-ovarian stimulation; IVF: in vitro fertilization)

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A low starting dose of gonadotropins (≤75 IU) is associated with increased LBRs compared to CC (5 RCTs, 1,457 women, RR 1.26, and 95% CI 1.05–1.51). For multiple pregnancies, analyses showed inconclusive findings between gonadotropins and CC.

Moderate certainty evidence showed that gonadotropins reduced the time to conception, leading to a live birth when compared to CC (6 RCTs, 2,058 women, HR 1.37, and 95% CI 1.15–1.63).[10]

CONSIDERATIONS FOR STIMULATION PROTOCOLS

Infertility treatments are a unique example where one size never fits all, and there is no ideal stimulation protocol. Each of the various protocols described have its own advantages and disadvantages. Individualization and personalization of gonadotropin dosages and tweaking are highly recommended for best results and for enhancing the success rates in IUI cycles. Scientific literature still does not have solid conclusions that define the best method and the real influence of each one on the IUI outcome.[5]

- *Patient-specific factors:* Individual patient characteristics, such as age, ovarian reserve, and the underlying cause of infertility, should guide the choice of stimulation protocol.
- *Risk of OHSS:* Monitoring for signs of OHSS is essential, especially in patients using gonadotropins. Adjustments to the dosage and protocol may be necessary based on ovarian response. Fine tuning and monitoring are of paramount importance.
- *Multiple pregnancies:* The risk of multiple pregnancies increases with stimulation medications. This should be discussed with the couple before beginning stimulation, and monitoring should aim to limit the number of mature follicles.
- *Luteal phase support:* Providing luteal phase support with progesterone supplementation after IUI can enhance the chances of implantation and clinical pregnancy rates.

CONCLUSION

Intrauterine insemination is a valuable treatment option for couples experiencing infertility. Ideal stimulation protocols involve a careful balance of medication choices, monitoring, and timing to optimize outcomes while minimizing risks. Individualization of treatment based on patient characteristics and responses is key to success in IUI cycles.

By continually assessing, evaluating, and adjusting drug dosages and protocols, healthcare providers can improve the chances of conception and help couples achieve their dream of parenthood. Further research into the efficacy of various stimulation protocols will continue to refine and enhance IUI outcomes, making it a more effective option for those facing infertility challenges.

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Ovarian Stimulation Protocols for the Practicing Gynecologist



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ISBN 978-1-917851-06-0

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