

Progesterone Supplement and Luteal Phase Deficiency in Unifollicular Intrauterine Insemination Cycles

Unifoliküler İntrauterin İnseminasyon Sikluslarında Luteal Faz Defekti ve Progesteron Desteği

Intrauterin İnseminasyonda Progesteron Etkisi / Progesterone Supplement in Intrauterine Insemination

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Özet

Amaç: Intrauterin inseminasyon, diğer yardımcı üreme teknikleriyle karşılaştırıldığında, basit olması ve düşük maliyeti nedeniyle sıklıkla kulanılmaktadır. Mevcut araştırmada intrauterin inseminasyonda progesteron desteğinin faydasını ve luteal faz defektinin unifoliküler sikluslarda da görülebileceğini vurgulamayı amaçladık. Gereç ve Yöntem: Aralık 2011 ve Aralık 2012 arasında kliniğimizde sebebi belirlenemeyen infertilite tanısı alan ve intra uterin inseminasyon planlanan 278 hasta prospektif randomize kontrollü araştırmaya dahil edildi. Bulgular: Gebelik yakalama ve devam ettirme oranları açısından her iki grup karşılaştırıldığında progesteron destek tedavisi istatistiksel olarak anlamlı bulundu; (p< 0.05), %33.66'ya karşı %12.22. Tartışma: Progesteron desteği, luteal faz defekti olsun veya olmasın, gebelik oranları üzerinde olumlu etkiye sahiptir ve genel kanının aksine luteal faz defekti unifoliküler sikluslarda da görülebilmektedir.

Anahtar Kelimeler

Intrauterin İnseminasyon; Progesteron; Luteal Faz; Unifoliküler

Abstract

Aim: Intrauterine insemination is a widely used technique with advantages of being a simple and less invasive method with a lower cost when compared to other assisted reproductive techniques. In the present prospective randomized controlled study we aim to prove that progesterone supplementation is a beneficial factor in pregnancies achieved with intra uterine insemination and also we want to emphasise that luteal phase deficiency does not always occur in multifollicular cycles but can be seen in unifollicular cycles as well. Material and Method: Patients diagnosed with unexplained infertility between December 2011 and December 2012 were admitted to the study group. 278 IUI cycles with COH using recombinant FSH induction were recorded. Results: The effect of progesterone supplement on achieving pregnancy was statistically significant (p<0.05) with a rate of 33.66% when compared to the non-receiving group that had a rate of 12.22%. Discussion: Progesterone supplementation, either in defective luteal phase or not has a chance of improving pregnancy rates in general and contrary to the notion that luteal phase deficiency mainly occurs in multifollicular cycles, it can be seen in unifollicular patients as well.

Keywords

Intrauterine Insemination; Progesterone; Luteal Phase; Unifollicular

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Introduction

Intrauterine insemination (IUI) is a widely used technique with the benefits of being a simple and less invasive method with a lower cost in comparison to other assisted reproductive techniques (ART). Patient selection criteria, presence of various female infertility factors, differences in methods used for ovulation induction and management along with the number of cycles and variations in sperm parameters all affect success rates of the procedure.

Embryonic implantation occurs in the luteal phase, and a normal luteal phase is characterized by a normal hormonal environment, normal progesterone (P) secretion by the corpus luteum, and an adequate endometrial secretory transformation [1]. Luteal phase deficiency can be described as corpus luteum's deficiency in preparing an adequate endometrial maturity. Therefore corpus luteum's progesterone secretion is critical in achieving pregnancy and its healthy progression as long as trophoblastic cells are capable of adequate hormone synthesis and secretion [2]. Corpus luteum function is dependent on luteinizing hormone (LH) stimulation, and LH is dependent on gonadotropin releasing hormone (GnRH) secretion [2-3].

Different from natural cycles, controlled ovarian hyperstimulation (COH) often results in multifollicular development with higher steroid serum concentrations. LH serum level concentrations are usually low in GnRH agonist COH protocols due to prolonged suppression of hypothalamic GnRH secretion which also continues to compromise hypopituitaric LH secretion even after the stimulation phase, leading to the suggestion that higher serum steroid concentrations might have an adverse affect on LH secretion via said feedback mechanisms, which in turn results with premature luteolysis leading to corpus luteum deficiency and defective P secretion especially in multifollicular cycles [2]. In cycles with multifollicular growth, an advanced endometrium in the early luteal phase was observed in almost 50% of all patients [4].

In general it is widely accepted that luteal phase deficiency mostly occurs in multifollicular cycles by COH rather than natural cycles that tend to be unifollicular.

In the present prospective randomized controlled study we aim to prove that progesterone supplementation is a beneficial factor in pregnancies achieved with intra uterine insemination.

Material and Method

All authors listed state that the protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken.

All data were recorded in specific study forms and computer assigned randomization depending on odd/even number sequence for receiving or omitting progesteron supplement at admittance was performed.

All patients were required to fill and sign a specific informed consent form detailing the procedure

Patients diagnosed with unexplained infertility in our clinic from December 2011 to December 2012 were included in the study group. 278 IUI cycles with COH using recombinant follicule stimulating hormone (FSH) induction were recorded.

Patients that were unable to conceive while having regular ovulatory mensturations, normal hysterosalphingography (HSG) results with bilateral open tubal passage and a normal sperm analysis were considered as unexplained infertility.

Those with previous ovarian surgery, endocrine disorders (thyroid disfunctions, hyperprolactinema, polycystic ovarian syndrome), obese patients (body mass index above 30) were excluded from the study group and 87 cycles, that were multifollicular, were excluded from the study group as well but continued on receiving progesterone, (multifollicular cycles were specifically excluded from the study group in order to show if luteal phase deficiency occurs also in unifollicular cycles).

Ninety IUI cycles did not receive progesterone supplement of which 11 pregnancies were achieved while on the other hand 101 cycles received progesterone supplement of which 34 pregnancies were achieved.

All patients were evaluated by ultrasonography (USG) and basal hormone levels on the 2nd day of the cycle before administering 75 IU of recombinant FSH daily and reevaluated on the 7th day with USG. Multifollicular cycles were excluded from the study group and after confirming a single follicule of at least 21-22 mm in diameter, choriongonadotropine 250 µg was administered to assure ovulation followed by intra uterine insemination exactly 36 hours later. Twenty four hours after IUI, 100 mg progesterone supplement of thrice a day orally was initiated.

Since there is no single definitive method for defining luteal phase deficiency, laboratory tests measuring P levels at midluteal phase (day 21) before the IUI cycle were obtained nonetheless to support diagnosis.

Patients who had serum progesterone levels of < 6.0 ng/ml on day 21 before the IUI cycle were designated to have luteal phase deficiency.

As an ethical precaution, patients with low P levels that were designated by the computer to "not receive" progesterone were omitted from the study group but continued on standard IUI protocol receiving P supplement. So in a way, comparison was made between both unifollicular groups; one with luteal phase deficiency (101 patients) and one with no deficiency (90 patients) according to day 21 progesterone levels.

Pregnancy was confirmed 12 days after IUI by serum βhCG levels, and progesterone supplement was continued until 12th week.

Multifollicular cycles continued on their IUI protocol but their data was not included in the study.

The primary outcome measures were pregnancy and live birth. Efficacy of progesterone supplementation according to comparison of pregnancy and live birth rates between treatment and control groups were performed by Mann-Whitney U test. A P value of < 0.05 was considered to be statistically significant and considered as proof of progesterone treatment as a beneficial option in achieving and continuing a healthy pregnancy (Table 1).

Results

Eleven pregnancies were achieved in 90 patients that did not receive progesterone supplement resulting in a pregnancy rate of 12.22% while on the other hand 101 patients received progesterone supplement of which 34 pregnancies were achieved resulting in a pregnancy rate of 33.66%. Live birth rate was 97.05% for the progesterone receiving group with one case of

Table 1. Pregnancy Outcome and Rates

	Number of Cycles	Number of Pregnancies	Pregnancy Rate [%]*	Number of Live Birth	Live Birth Rate [%]	Mean BMI	Mean day 21 P levels (ng/ml)
Received Progesterone	101	34	33.66*	33	97.05	21.41±4.36	4.41±1.01
Not received Progesterone	90	11	12.22*	11	100	26.21±2.11	8.38±1.20

*Mann-Whitney U Test comparing the data between the groups which received or not received progesterone therapy, P=.05

an anencephalic fetus terminated at 12th week of gestation. Live birth rate was 100% for the other group. The effect of progesterone supplement on achieving pregnancy was statistically significant (P = .05) with a rate of 33.66% when compared to the non-receiving group that had a rate of 12.22% [Table 1].

Conclusion

Naturally one or two dominant follicules are usually enough for the phyisiological feedback mechanism to function properly in a healthy woman but various ovulation induction protocols tend to produce multifollicules resulting in higher concentrations of serum estradiol (E) and progesterone levels thus inhibiting FSH and LH secretion causing very low levels of LH synthesis and secretion. Inhibin A is also known to have an effect in this, along with high E and P levels.

Lower LH presence is the reason for corpus luteum deficiency leading to progesterone deficiency and a shorter luteal phase, all of which is in general described as the luteal phase deficiency.

Patients with luteal phase deficiency are known to have fewer progesterone receptors on the nuclei of endometrial glandular cells therefore this previously mentioned inadequate endometrial structure is either because of these fewer receptors or low levels of progesterone [5-6].

In light of these evidences describing the physiological mechanisms leading to lower progesterone levels, the simple solution of providing the decreased progesterone led us to research the subject and deem if it is truly a beneficial treatment option.

Though Erdem, Hamilton and various other authors are supporting progesterone supplementation, authors like Keenan, Moghissi and Ebrahimi are against it [7-8]; [9-10].

According to our study results we are in favor of progesterone supplementation.

In the material and methods section we mentioned that specifically unifollicular cycles were chosen for the study group and since progesterone usage is the only known treatment for luteal phase deficiency, the outcome of the study shows that pregnancy rates were statistically better in the progesterone receiving group hence leading us to reason that luteal phase deficiency is indirectly proven to be an occurence in both groups, meaning also that day 21 progesterone levels is not a definitive method in diagnosis and finally since both groups are unifollicular this points out that luteal phase defeciency is not dependent on the number of follicules in a cycle.

There is also a debate on the way progesterone is administered. While Erdem et al. suggests daily vaginal usage of 90 mg progesterone gel, Ebrahimi et al. used daily vaginal usage of 400 mg of progesterone pessaries [8,10]. In our study group we preferred 100 mg of progesterone tablets orally thrice a day. The way progesterone is used is another study subject on the assumption of its benefit on improving pregnancy rates.

In conclusion, even though there are many different results obtained from various ovulation induction protocols, larger study groups involving multiple centers are still needed in this research subject to solidify a worldwide treatment protocol to be used in assisted reproductive techniques.

Competing interests

The authors declare that they have no competing interests.

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