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Evaluation of Pregnancy Rate in IUI Cycles of Unexplained Infertile Patients for whom hCG Day Coitus is Recommended

Açıklanamayan İnfertil Hastaların IUI Sikluslarında hCG Günü Önerilen Koitusun Gebelik Oranına Etkisi

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ABSTRACT

Objective: Aim of this study is to investigate whether the recommended coitus on the day of hCG affects pregnancy and live birth rates by increasing intrauterine sperm count in IUI cycles of unexplained infertile patients with male subfertility. **Material and Methods:** 300 patients data is collected retrospectively from the files of the Ali Kemal Belviranlı Maternity and Children's Hospital İnfertility Clinic between 2018 and 2020. Patients with unexplained infertility in the 18-35 age group whose antral follicle count were within normal limits, FSH value <10 U/L and proven tubal patency by HSG were included in the study. In male partners, total motile sperm count (TMS) between 5X106 and 15X106 were considered as male subfertility. All patients were induced with gonadotropins before IUI. Chi-square test of independence were conducted to determine the relationship between the coitus status of the participants and pregnancy outcomes. **Results:** We have seen from the retrospectively reviewed patient files that while 152 of 297 patients were recommended only IUI, 145 of them were offered coitus on the day of hCG. 8 patients with 29 pregnancies that resulted in delivery applied coit on the day of hCG together with IUI and 21 patients did not apply coitus on hCG day. It was determined that recommended coitus on hCG trigger day in adition to IUI does not improve live birth rates (p>0,05) with male subfertility patients. **Conclusion:** Although it is a conventional recommendation to suggest coitus with insemination, we concluded that coitus does not improve pregnancy outcomes with male subfertility.

Keywords: Coitus; intrauterin insemination; male subfertility

ÖZET

Amaç: Bu çalışmanın amacı, erkek subfertilitesi olan açıklanamayan infertil hastaların IUI sikluslarında hCG gününde önerilen koitusun intrauterin sperm sayısını artırarak gebelik ve canlı doğum oranlarını etkileyip etkilemediğini araştırmaktır. **Gereç ve Yöntemler:** Ali Kemal Belviranlı Kadın Doğum ve Çocuk Hastanesi İnfertilite Kliniği dosyalarından 2018-2020 yılları arasında 300 hasta verisi retrospektif olarak toplandı. 18-35 yaş grubunda açıklanamayan infertilitesi olan, antral folikül sayısı normal sınırlarda olan, FSH değeri <10 U/L ve HSG ile kanıtlanmış tüp açıklığı olan hastalar çalışmaya dahil edildi. Erkek partnerlerde total hareketli sperm sayısının (TMS) 5X106 ile 15X106 arasında olması erkek subfertilitesi olarak kabul edildi. Tüm hastalara IUI öncesinde gonadotropinler uygulandı. Katılımcıların koitus durumu ile gebelik sonuçları arasındaki ilişkiyi belirlemek için ki-kare bağımsızlık testi yapıldı. **Bulgular:** Retrospektif olarak incelenen hasta dosyalarından 297 hastanın 152'sine sadece IUI önerilirken, 145'ine IUI ' a ek olarak hCG gününde koitus önerildiği tespit edildi. Doğumla sonuçlanan 29 gebelikten 8 hastaya IUI ile birlikte hCG yapıldığı gün koitus uygulandığı ve 21 hastaya sadece IUI uygulandığı tespit edildi. Erkek subfertilite hastalarında IUI'ye ek olarak hCG tetik gününde önerilen cinsel birleşmenin canlı doğum oranlarını iyileştirmediği (p>0,05) belirlendi. **Sonuç:** İnseminasyonla birlikte koitus önerilmesi geleneksel bir öneri olmasına rağmen, erkek subfertilitesi olan açıklanamaya infertil hastaların gonadotropinlerle indüklenmiş IUI sikluslarında Hcg günüde önerilen koitusun canlı doğum sonuçlarını iyileştirmediği sonucuna vardık.

Anahtar Kelimeler: Koitus; intrauterin inseminasyon; erkek subfertilitesi

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Fertility is the capacity to produce clinical pregnancy.[1] On the other hand, infertility is the inability of a couple to achieve pregnancy within one year despite adequate and regular sexual intercourse. This period is one year for women under age of 35 and 6 months for women over the age of 35.[2] Around 186 million people worldwide suffer from infertility.[3] The strongest significant factor in female infertility is female age. Lifestyle and environmental factors also play an active role.[4] Approximately 40% of infertile couples have a male factor infertility and 50% have female factor infertility.[5] Among the most common causes of infertility are unovulatory cycles, tubal factor and male factor. The remainder is unexplained infertility. In some studies, it has been stated that unexplained infertility may be associated with older age.[6] Treatment methods include monitoring, diet, ovulation induction, and intrauterine insemination (IUI), assisted reproductive techniques (IVF, ICSI).[7]

Intrauterine insemination with ovulation induction (IUI-OI) is the first-line treatment for couples with unexplained infertility.[8] Although the success rate is low, it is a method that can be used in suitable patients due to its easy application and low cost. It aims to increase pregnancy rates by increasing the number of dominant follicles per cycle obtained by increasing serum levels of follicle stimulating hormone (FSH).[9] The success rate of IUI has a wide range of outcomes with respect to causes of infertility, age and other variables such as follicular stimulation and cycle characteristics.[10,11] Semen characteristics are widely used to predict the outcome of insemination. It has been suggested that some parameters such as sperm motility, sperm morphology and total motile sperm count (TMS) are prognostic indicators of pregnancy rate.[12] Many studies have shown that the total number of motile sperm inseminated is associated with increased fertility.1[3] Silverberg et al. showed that increasing the TMS count using two IUIs per cycle resulted in increased pregnancy rates.[14] Several researchers have also observed that the second ejaculate from normozoospermia men increases the TMS count when added to the first ejaculate.[15,16]

The aim of this study is to investigate whether the recommended coitus on the day of human chorionic gonadotropin (hCG) day affects pregnancy and live birth rates by increasing intrauterine sperm count in unexplained infertile patients with male subfertility.

MATERIAL AND METHODS

The study was performed under the principles of Helsinki Declaration, following the approval of the Ethics Committee of Konya Chamber of Commerce Karatay Medical University (2022/008) numbered and 29.12.2022 dated, datas are collected retrospectively from the Ali Kemal Belviranlı Maternity and Children's Hospital İnfertility clinic between 2018 and 2020. In our study 300 female patient files with unexplained infertility and male subfertility husbands were investigated. Pregnancy data of 3 patients could not be obtained, they were not included in the study. We performed the study with 297 patients. Patients with unexplained infertility who had at least one year of infertility problems in the 18-35 years age group whose basal antral follicle count and AMH (antimullerian hormone) values were within normal limits, FSH value <10 U/L and proven tubal patency by hysterosalphingography (HSG) were included in the study. Patients with recurrent IUI cycles, comorbidities, known infertility reasons, tubal occlusion, endometrioma/endometriosis, policystic ovary syndrom (PCOS) ,body mass index (BMI) >30kg/m^2 were not included in the study. Husbands whose TMS count on spermiogram values between $5x10^6$ and $15x10^6$ were considered to have male subfertility.

The patients' age, antral follicle count, AMH and basal hormone values were taken as dermographic data. The information was obtained from the hospital files of the patients. Unexplained infertility status was taken into account in the patients. We have seen from the retrospectively reviewed patient files that while n=152 of 297 patients were applied only IUI, n=145 of them were offered coitus on the day of hCG in addition to IUI. We aimed to investigate recommended coitus on the day of hCG affects pregnancy and live birth rates by increasing intrauterine sperm count in unexplained infertile patients with male subfertility.

Initial infertility tests (hormone analysis, semen analysis, full gynecological examination, HSG) were performed for all couples. After undergoing ultra-

sonography (USG) investigation and measuring basal hormon levels on the second day of menstruel cycle, patients underwent ovarian stimulation with gonadotropin therapy treated with appropriate doses of 75-150 IU menotropin (Menopur, Ferring, Sweeden) or 75-150 IU recFSH (Gonal f, Merck Serono, Germany) according to their body mass index (BMI). Ultrasonography measurements (endometrial thickness and follicular size) were made transvaginally by Mindray dc transvaginal ultrasound. Dominant follicle size was 17 mm or more 250 micrograms of recombinant hCG (Ovitrelle, Ares Serono, Turkey) was used to induce ovulation. Insemination was performed 36 hours after hCG administration. All patients were asked to come with congested urine for the insemination procedure. Spermiograms were evaluated according to World Health Organization (WHO) standards (sperm count >20x10^6 /ml, total sperm count >40x10^6/ml, progressive motility >50%, normal morphology (>30% WHO criteria, >14% Kruger Strict criteria).[17] Samples were collected by masturbation before IUI procedure. Semen samples were prepared with swim-up technique two hours before insemination. Using an artificial insemination catheter (Wallace, Smith Medical International Ltd, UK) was slowly injected into the intrauterine cavity. The patients were rested for 10-15 minutes after the procedure. Luteal phase support was given with 400 mg vaginal micronized progesterone for two weeks. Serum beta hCG level was measured on the 12th day. Clinical pregnancy was defined as to see fetal cardiac activity on transvaginal ultrasonography 2-3 weeks after a positive pregnancy test. Patients who were found to be pregnant were followed up those who gave birth at 24 weeks and less than 500 g were recorded as abortion, and those others were recorded as live births.

SPSS 25 was used in the statistical analyzes carried out within the scope of this research. Chi-square test of independence were conducted to determine the relationship between the coitus status of the participants and pregnancy outcomes. Descriptive statistics were used to show the data on the demographic information of the patients. Since the pregnancy groups were not numerically balanced, analyzes were carried out using non-parametric tests.

RESULTS

Among the 297 patients who participated in the study, n=36 (12.1%) were clinically positive pregnancy, n=7 (2.3%) had abortion, n=29 (9.7%) had a live birth. The age of the patients included in the study was 18-35 years and the mean was 28.4 years. Among the basal hormone values measured on the second day of menstruation, the FSH average is 6,67 U/L, luteinizing hormone (LH) average is 5.45 U/L, E2 average is 43.8 ng/L. Mean AMH values, AFC and TMS count of the husbands were 2,5±1,12 ng/mL, n=8±3,2 and 10±1,4x10^6 respectively. Mean demographic parameters and cycle characteristics of the patients are shown in Table 1. The patients were started on gonadotropin doses varying between 75-150 IU depending on the antral follicle number and BMI. Rec FSH adminsterded 193 patients, menotropin was administered to 94 patients, and combined recFSH+menotropin was administered to 10 patients. There is no a significant difference between the types of gonadotropins used and live birth (p=0.487). The relationship between gonadotropin types and live birth is shown in Table 2.

TABLE 1: Demographic and clinical characteristics of the patients.

Characteristics		Mean±(SD) or n(%)
Age(year)		28.41±4.34
FSH(U/L)		6,67±2,18
LH(U/L)		5,45±2,96
E2(ng/L)		43,85±16,98
AMH (ng/mL)		2,5±1,12
AFC (number)		8±3,2
TMS (number,10^6)		10±1,4
Cycle Duration (day)		8.81±2.29
Gonadotropin	rFSH	193 (65%)
	Menotropin	94 (31.6%)
	Combined (rFSH+Menotropin)	10(3,4%)
Gonadotropin Dose(IU)		81.65±5.99
Total Drug Dose (IU)		776.31±438.13
Endometrium thickness (mm)		14.44±5.40
Follicle Size (mm)		17.79±2.21

FSH: Follicle stimulating hormone, LH: Luteinizing hormone, E2: Estradiol, rFSH: recombinant FSH, IU: internationale unit, U: unit, L: liter, ng:nanogram, AMH: antimullerian hormone, TMS: total motil sperm, mm: milimeter, SD: Standard Deviation.

TABLE 2: Gonadotropin types and its relationship with pregnancy outcomes.

Drug Type	Live birth (n=29)	Abort (n=7)	No pregnancy (n=263)	p value
rFSH(IU)	18	6	169	0.487
HMG(IU)	11	1	83	
Gonadotropin combined (rFSH and HMG)	0	0	10	

rFSH: Recombinant follicle stimulating hormone, HMG: Human menapausal gonadotropin, IU: Internationale unit.

It was determined that 8 patients with 29 pregnancies that resulted in delivery applied coit on the day of hCG together with IUI and 21 patients did not. It was determined that coitus with hCG trigger day time was not associated with live birth rates ($p>0.05$). We also found that it did not increase the abortion rate. The relationship between coitus and pregnancy outcomes is shown in Table 3.

DICUSSION

Unexplained infertile patient population is a group for which no correctable cause can be found. In our study, we investigated whether coitus in addition to IUI increases the live birth rate by increasing the number of intracavitary sperm in the IUI cycles of unexplained infertile patients with male subfertility. As a result of our study, we found that this conventional recommendation does not improve live birth rates.

Timing of IUI close to ovulation and delivery of the optimum motile sperm fraction are important factors in achieving the highest pregnancy rates (PRs) per cycle. TMS inseminated number has been stated as the most predictive index of conception in IUI cycles. In the study conducted by Haiyan Lin et al., with 5363 IUI cycles they found better outcome with post-wash TMS >22.32 million.[18] It has been reported that at least 1 million TMS for insemination is a requirement for conception after IUI.[19] In addition to improving the TMS count, intercourse on the hCG day improves fertilization in women who ovulate earlier than expected after hCG administration. Studies on the frequency of intercourse in natural cycles show that it is possible to conceive as a result of intercourse 5 days before ovulation, but it is less likely 1 day after ovulation.[20]

When we look at the literature, we see that it is one of the rare studies on this subject. In our study, both groups (recommended coitus and not recommended coitus) clinical pregnancy rate was 12.1%, while the live birth rate was 9.7%. This rate is higher than the 9.8% pregnancy rate reported by Reindollar et al. (Fastt) in 503 patients with unexplained infertility.[21] We found that in addition to intrauterine insemination in patients with male subfertility coitus on hCG day did not affect live birth rates. However al. Huang, F. J et al., found that in infertile couples with a normal sperminogram; IUI with a small number of alimented motile sperm, timed intercourse significantly increases pregnancy rates compared to IUI alone.[22]

TABLE 3: The relationship between coitus and pregnancy outcomes.

		Pregnancy resulted with labor		Abortus		Non-Pregnant		
Coitus		n	%	n	%	n	%	p
	Yes	8	27.6	2	28.6	79	30.3	974*
	None	21	72.4	5	71.4	182	69.7	

Note. n=number of participants, * Chi-square Test of Independence

According to the Van Voorhis and friends with levels of TMS exceeding 10 million for IUI, no further improvement in conception rates was noted. In addition, when the average TMS was above 30 million, Van Voorhis and friends noted higher pregnancy rates when controlled ovarian hyperstimulation was used in conjunction with the IUI cycle as compared with natural cycle IUI.[23] But the result of our study did not support the study of Van Voorhis et al. although we used controlled ovarian hyperstimulation in conjunction with the IUI in patients with male subfertility according to WHO spermiogram parameters; coitus did not increase pregnancy rates in our study.

In the study of Fu-jen Huang et al. investigating the effect of coitus on the success of IUI, 101 couples were treated with IUI alone, and 100 couples were treated with both IUI and timed intercourse within a 12-18 hour period.[24] It was determined that timed intercourse increased pregnancy rates in the group with motile sperm count $<40\times10^6$ (27.7% vs 10.5%, p= 0.023) (25.7% vs. 22.7%, p= 0.671). In infertile couples with normal spermiogram but motile sperm count is $<40x10^6$, timed intercourse significantly increases pregnancy rates compared to IUI alone. This alternative treatment seems to be a practical, simple and inexpensive supplement that increases the pregnancy rate in patients undergoing ovulation induction and intrauterine insemination program according to Fu-jen Huang et al.

However, Uzun Batak et al., when comparing the two groups, it was concluded that coitus did not increase pregnancy rates.[24] In this study, 297 patients with unexplained infertility with normal motility spermiogram were evaluated. Among the patients who underwent ovulation induction with gonadotropin, 171 were named group 1, in which sexual intercourse was recommended after IUI, and 126 patients, in which sexual intercourse was recommended 72 hours after IUI named as group 2. Pregnancy (13.5%, 11.9%), clinical pregnancy (11.7%, 8.7%), live birth (9.4%, 6.3%) rates between group 1 and group 2 are respectively. In group 1 pregnancy, clinical pregnancy, live birth rate parameters was higher in group 2, but it was not statistically significant (p>0.05). Miscarriage rates (2.3%, 2.4%) were similar but not statistically significant (p>0.05). This revealed that offering sexual intercourse in the unexplained infertile group with normal motile spermiogram number did not statistically benefit the number of pregnancies, clinical pregnancies and live births and also did not increase the miscarriage rates.

The limitation of our study was that it was retrospective study and infertility periods could not be accessed from file records. Additionally, calculating the TMS count, which has the highest correlation with pregnancy, could contribute to the literature.

CONCLUSION

Although recommending coitus with insemination is a traditional recommendation, we conclude that coitus recommended on the hCG day does not improve live birth outcomes in gonadotropin-induced IUI cycles of unexplained infertile patients with male subfertility.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Dilay Gök Korucu;* ***Design:*** *Dilay Gök Korucu;* ***Control/Supervision:*** *Dilay Gök Korucu;* ***Data Collection and/or Processing:*** *Latife Nevin Pehlivanlar Dar, Oğuzhan Günenc;* ***Analysis and/or Interpretation:*** *Latife Nevin Pehlivanlar Dar, Oğuzhan Günenc;* ***Writing the Article:*** *Dilay Gök Korucu.*

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