Evaluation of the Effects of Misoprostol on Pregnancy Rates Among Infertile Couples Undergoing Ovulation Induction and Intrauterine Insemination

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Abstract

Objective: In an attempt to improve the conception rates, artificial insemination techniques with misoprostol in various forms have been reported. The positive effect of vaginal misoprostol leading to an improved clinical pregnancy rate is not clearly understood. The known effects of prostaglandin E on increasing myometrial contractility and potential relaxation of tubal isthmus may all facilitate fertilization potential. We intended to investigate here the effects of misoprostol on pregnancy rates and the outcome of intrauterine insemination.

Materials and Methods: All patients (age, ≤35 years), whose data on male and female diagnosis was available, were included in the study. The data of 34 cycles, determined as the control group, with either unexplained infertility or ovulatory dysfunction, having undergone therapeutic insemination in an effort to establish pregnancy were retrospectively studied. Prospectively, 33 cycles were randomized as the study group to ovulation induction followed by intrauterine insemination and vaginally administered 200 mg misoprostol at the time of insemination. Oral and injectable fertility drugs were administered. The cycles were monitored and endometrial thickness and follicular development were measured by transvaginal ultrasound. Both retrospective (control group) and prospective (study group) results were reviewed and analyzed and the pregnancy rates in intrauterine insemination recipients were compared.

Results: In a retrospective analysis involving 34 inseminations in the control group, five pregnancies were recorded for an overall pregnancy rate of 13% per insemination (or cycle). In the follow-up prospective study (n: 33), four pregnancies were recorded and the pregnancy rate for the intrauterine insemination-misoprostol study group was 11% per cycle. There were two abortions in the misoprostol group while only one recorded in the control group. There was no difference between the couples of the two groups regarding their age; duration, type and cause of infertility.

Conclusion: Because of the indefinite advantage and the higher miscarriage rates of misoprostol over pure cycles in our study, we cannot recommend presently the routine use of intravaginal misoprostol in intrauterine insemination cycles.

Keywords: misoprostol, intrauterine insemination, pregnancy rate

Özet

Ovülasyon İndüksiyonu ve İntrauterin İnseminasyon Uygulanan İnfertil Çiftlerde Misoprostolün Gebelik Oranları Üzerine Etkisi

Amaç: Son zamanlarda gebelik oranlarını artırmak amacıyla farklı formlarda misoprostol ile inseminasyon yöntemleri bildirilmiştir. Henüz olumlu etkisi kesinlik kazanmamış olmasıyla birlikte prostaglandin E'nin myometrial kontraktilite ve tubal istmik relaksasyon üzerine bilinen etkileri nedeniyle fertilizasyonu kolaylaştırabilir. Çalışmamızda bunların gerçekliliğini ispatlamayı ve misoprostolün gebelik oranları ve intrauterin inseminasyon sonuçları üzerine etkilerini araştırmayı planladık.

Materyal ve Metot: Yaşı 35 ve altındaki, kadın ve erkeğe ait infertilite verileri bulunan tüm olgular materyalimizi oluşturdu. Açıklanamayan infertilite ve ovülasyon disfonksiyonu nedeniyle inseminasyon yapılan toplam 34 siklus kontrol grubu olarak belirlendi ve verileri retrospektif olarak incelendi. Prospektif olarak da 33 siklusa, çalışma grubu olarak belirlendikten sonra, intrauterin inseminasyon yapıldı ve inseminasyon sırasında tüm olgulara 200 μg misoprostol intravaginal olarak uygulandı. Ovülasyon indüksiyonu oral ve parenteral yoldan uygulanan ilaçlarla yapıldı. Siklus boyunca endometrial kalınlık ve follikül gelişimi transvaginal ultrasonografi ile monitörize edildi. Retrospektif (kontrol grubu) ve prospektif (çalışma grubu) sonuçlar değerlendirildi ve gebelik oranları karşılaştırıldı.

Sonuçlar: Otuz dört inseminasyon içeren retrospektif analizde beş gebelik kaydedildi (inseminasyon veya siklus başına gebelik oranı: %13). Otuz üç siklus içeren takip grubunda ise dört gebelik oluştu (siklus başına gebelik oranı: %11). Kontrol gru-

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bunda bir düşük görülürken misoprostol grubunda iki gebelik düşük ile sonuçlandı. İki grup arasında yaş; infertilite süresi, tipi ve nedeni açısından fark yoktu.
Tartışma: Çalışmamızda, daha yüksek düşük oranları ve saf intrauterin inseminasyon sikluslarına göre üstünlüğünün belirsizliği nedeniyle, intravaginal misoprostolün rutin kullanımını mevcut veriler ışığında önermemekteyiz.

Anahtar sözcükler: misoprostol, intrauterin inseminasyon, gebelik oranı

Introduction

There is good evidence in the literature in favour of intrauterine insemination (IUI) as the most cost-effective treatment for unexplained and moderate male factor subfertility. Although it may take relatively more treatment cycles to achieve pregnancy, there are considerable advantages to the patient in terms of risk/benefit ratio and financial cost compared with IVF.

Involuntary subfertility is a common problem, affecting up to 15% of couples and the demand for its medical treatment is increasing. Various factors are known to influence the treatment outcome in IUI. These include: use of ovulation augmentation with clomiphene citrate, human menopausal gonadotropin (HMG) (1) or follicle stimulating hormone (FSH) (2); the method of sperm preparation; timing of ovulation and insemination (3-4); the number of preovulatory follicles (5-6); motile sperm count of semen used for insemination (7); and the number of inseminations per treatment cycle (8).

In an attempt to improve spontaneous conception rates, artificial insemination techniques with misoprostol in various forms have been reported (9). In a recent paper, Barroso et al. reported their experience with vaginal administration of misoprostol (200 µg) at the time of intrauterine insemination. The rationale for administering misoprostol vaginally was to enhance uterine contractility and isthmic tubal relaxation, affect luteal maintenance, enhance transport of spermatozoa, enhance spermatozoon-oocyte binding and induce immunosupression — all properties that may account for the fertility-enhancing effects of misoprostol (10-13).

The aim of the present study is to compare the pregnancy and miscarriage rates between IUI and IUI+misoprostol protocols. We tried to investigate the outcome of IUI with misoprostol and if there would be any clinical advantage in its routine use at our Reproductive Unit.

Materials and Methods

The study was performed in the Reproductive Unit of Istanbul Medical Faculty between February, 2003 and July, 2003. All patients 35 years or younger, whose data on male and female diagnosis was available, were included in the study. The data of 34 cycles, determined as the control group, with either unexplained infertility or ovulatory dysfunction, having undergone therapeutic insemination in an effort to establish pregnancy were retrospectively studied. Thirtythree (n: 33) cycles followed prospectively were determined as the study group and ovulation induction followed by IUI and vaginally administered 200 mg misoprotol at the time of insemination was conducted. The indication for IUI treatment was unexplained infertility (where history, physical examination, semen analysis, laboratory assessment of ovulation and tubal patency were normal). Male factor was defined as: (i) a sperm count of $<20x10^6$/ml; (ii) normal forms < 30% (WHO); (iii) or progressive motility (grade A+B) < 30% before sperm preparation. The study couples had at least 1 year of infertility and had undergone a basic infertility evaluation consisting of anamnesis, FSH, LH, E2, prolactin and thyroid hormone concentrations, ultrasonography and semen analysis. Tubal patency was confirmed by hysterosalpingography. The inclusion criteria were: infertility history of >1 year, female age <35 years, normal patent tubes, no previous IUI or other assisted reproduction techniques (in order to avoid a selection bias). All women in the study underwent ovarian stimulation using clomiphene citrate of a fixed regime protocol, CC (Gonaphene®), 100 mg/day was given during 5 consecutive days, starting on day 3 of the cycle. The gonadotropin group was stimulated starting on day 3 with 75 or 150 IU/day using follitropin alpha (rFSH) (Gonal F®, Serono) or HMG (Humegon®, Organon or Pergonal®, Serono). Ovarian and endometrial responses were monitored by vaginal ultrasonography and 10.000 IU of HCG (Pregnyl®, Organon or Profasi®, Serono) was administered when at least one follicle was >18 mm in mean diameter. Evidence of ovulation was recorded ultrasonographically on the day of IUI: an irregularly shaped follicle with marked reduction in size, with or without fluid in the periovulatory area. Intrauterine insemination was performed 36 h after administration of HCG using an intrauterine catheter with a 1- or 2-ml syringe. The catheter was gently passed through the cervical canal and the sperm suspension expelled into the uterine cavity with insemination volumes ranging from 0.5 to 2 ml. A 200 µg misoprostol (Cytotec®) tablet was administered vaginally just after completing IUI. Women remained supine for 15-20 min after IUI. If menstruation was delayed after IUI, a urinary pregnancy test was performed. All pregnancies were confirmed by ultrasonography. The luteal phase was routinely supported pharmacologically in our study by oral micronized progesterone (Progestan®)100 mg/8 h for 15 days following insemination. Semen was collected by masturbation into a sterile jar after at least 3 days' sexual abstinence. After liquefaction and initial sperm analysis, the standard swim-up or Percoll gradient technique was used for preparation. Briefly, in the swim-up technique the sperm sample was centrifuged at 500 G for 15 min, the supernatant discarded and the pellet diluted in 2.5 ml of medium and re-centrifuged. After removing the supernatant the final pellet was gently covered with medium and incubated for 1 h at 37°C in an incubator. In the Percoll technique, semen was layered onto a discontinuous Percoll gradient (40%, 90%; Pharmacia, Bio Process Technology AB, Uppsala, Sweden) containing

Medi-Cult® medium and centrifuged at 500 G for 20 min. The lowest (90%) fraction was then suspended in 6 ml of medium and recentrifuged (500 G for 10 min). The remaining pellet was diluted in 0.5–1 ml of medium and incubated as in the swim-up technique.

The statistical analysis was performed by means of χ^2, Fisher's exact test, Mann–Whitney and Student t-test following the standard criteria of applicability. Each parameter was tested by means of the odds ratio (OR) and its 95% confidence interval (CI). Statistical significance limit was defined as p: 0.05. The variables selected for the initial analysis were pregnancy rate (PR), miscarriage rate (MR), female age, sperm concentration and progressive motility (grade A+B) after preparation, number of preovulatory follicles (>16 mm in diameter) and thickness of the endometrium.

Results

Totally 67 IUI cycles were included in the analysis. The mean age of women was 27.17 ± 3.18 years (range 20–34). Both groups were similar regarding the main demographic characteristics. Overall, there were no statistically significant differences between the two groups in relation to mean age, mean baseline FSH, mean baseline LH, E2 and number of ampules used. In our study, most IUI parturients were nulliparous (91%). In the presence of normal sperm and patent tubes we offered IUI as first-line treatment and rejected IUI to women >35 years old.

Sperm concentration and progressive motility (grade A+B) after preparation were not predictive of IUI success. This is obviously due to pretreatment sperm screening and exclusion of couples with a progressively motile sperm count after preparation of less than $1x10^6$/ml. The median value of sperm concentration and the percentage of progressive motility (grade A+B) after preparation was $17x10^6$/ml (range <10–$200x10^6$/ml) and 89% (range 30–100%), respectively and the normal morphology was 53.4% (range 30–95%).

No significant difference was noted between the study and the control group regarding age, gravidity, parity, duration of infertility, cycle day of insemination and the use of luteal progesterone support.

In all cases, ovarian stimulation was combined with IUI and the most commonly used stimulation protocols were clomiphene citrate (CC) alone (61%) or gonadotropins alone (39%). We used FSH in doses >75 IU daily for patients <30 years and 150 IU daily for patients over 30 years. The mean ampule number of FSH was 9.9 per cycle. At present there is no clear evidence in the literature to enable us to conclude whether clomiphene citrate or gonadotropins are superior for ovarian stimulation, with some studies promoting gonadotropins and others reporting no difference in pregnancy rates. The pregnancy rate of the gonadotropin (HMG)-stimulated misoprostol cycle was greater than that of CC group but the difference was of borderline significance, probably due to the limited size of the series. Significantly more transvaginal scans were performed in the gonadotropin group compared with the clomiphene group. The mean (± SD) cycle day of treatment was 14.3±3.4 in the gonadotropin group and 13.2±2.4 in the clomiphene citrate group.

The combined mean pregnancy rate for all IUI cycle types was 12% per cycle. Although the pregnancy rate of the study group was smaller (11% (4/33)) than that of the control group (13% (5/34)), the difference was not statistically significant. The miscarriage rate was higher in the IUI-misoprostol group: 50% (2/4) versus 20% (1/5) in the control group.
The median number of preovulatory follicles (>16 mm in diameter) on the HCG day was 2 (range 1–5) and the median endometrial thickness was 8.3 mm (range 5–14 mm). The endometrial thickness was significantly higher (mean: 9.7 mm, range: 6-14 mm) in the gonadotropin group compared with the CC group (mean: 7.1 mm, range: 5-9 mm); being not related to the treatment outcome.

All pregnancies resulted from monofollicular cycles and follicles ≤20 mm.

Compared with pure cycles, among the 33 cases using misoprostol, no patient discomfort related to the drug was reported. There was no case of ovarian hyperstimulation syndrome (OHSS) among gonadotropin stimulated patients.

Discussion

The combined mean pregnancy rate for all IUI cycle types was 12% per cycle. Although the pregnancy rate of the study group was smaller than that of the control group, the difference was not statistically significant. The miscarriage rate was higher in the IUI-misoprostol group: 50% (2/4) versus 20% (1/5) in the control group but the miscarriage cases were insufficient in number for a statistical analysis. In other words our study showed no statistically significant difference in the pregnancy rate with the use of misoprostol in IUI.

Intrauterine insemination is a simpler, less invasive and cheaper first-line treatment than IVF for subfertility, resulting in an acceptable pregnancy rate (PR) of 12–20% per cycle (14-15). Despite the high success rates of new treatment options, it would be cost-effective to consider less-demanding treatments for subfertile couples before undergoing the more expensive and more invasive IVF treatment (16). IUI in combination with controlled ovarian hyperstimulation (COH) in unexplained infertility is clearly associated with acceptable pregnancy rates, which is reflected by the fact that most units stated that they would offer this as the first-line treatment in appropriate cases. In general, the results reported by our unit are consistent with those reported in the literature, with most centers achieving pregnancy rates of 12-20% per cycle. Adopting an initial protocol of three cycles of IUI will allow almost 30% of patients to avoid IVF (17). Although success rates may not be as good as for idiopathic infertility, the most recent Cochrane review (18) reported that IUI with COH significantly increased the probability of pregnancy by a combined odds ratio of 6.0 com-

pared with timed intercourse alone. In a meta-analysis carried out by Peterson et al. (1994), the average pregnancy rate per cycle for unexplained infertility, using HMG/IUI, was 18%. A decreased fertilization rate has been suggested to be the cause of failure to conceive among women with unexplained infertility, which possibly can be overcome by superovulation therapy associated with an increased number of fertilizable oocytes in IUI (19). Recently the most refined of these, intrauterine insemination, alone or in combination with COH, has been the focus of substantial research.

Misoprostol is a commercially available synthetic prostaglandin that is structurally related to PGE1 and was used initially to prevent peptic ulcer disease induced by chronic ingestion of nonsteroidal antiinflammatory drugs (20). It has also been used extensively as an oral and intravaginal abortifacient, and most recently, as a medical aid to evacuate early pregnancy failures in humans (21-22). Misoprostol has also been used as a safe and inexpensive medication for cervical ripening and labour induction in human pregnancies (23). Due to the reported safety, widespread commercial availability and relative similarity of misoprostol to PGE, the usefulness of vaginally placed misoprostol as an adjunctive therapy at the time of IUI was investigated; and its tolerability and effects on clinical pregnancy rates were assessed. The positive effect of vaginal misoprostol leading to an improved clinical pregnancy rate is not clearly understood. As mentioned in previous trials, the known effects of PGE on increasing myometrial contractility, potential relaxation of tubal isthmus, improved spermatozoon–oocyte binding/penetration and attenuation of the female immune response to spermatozoa may all facilitate fertilization potential. The precise physiological mechanism(s) of how misoprostol leads to improved clinical pregnancy rates requires further research.

We have read with interest the paper published by Barroso et al, 2001, investigating in a prospective design whether IUI with misoprostol (prostaglandin E1) (200 μg) provided a higher probability of pregnancy. In their study, the authors observed a significant pregnancy rate in the IUI-misoprostol group and concluded that misoprostol application in stimulated cycles under intrauterine insemination beneficially effects the pregnancy outcome. Brown et al. found that misoprostol (400 μg) when placed vaginally at the time of intrauterine insemination improves pregnancy rates. Our study showed no statistically significant difference in the pregnancy rate with the use of misoprostol in IUI. We think that the small size of the study and the retrospective control group may bias the results and may provide a distorted view of our study, but our retrospective control group had clearly defined criteria for patient inclusion and the results reported by our unit were consistent with those reported in the literature.

Presently we have suspended in our clinic the clinical use of intravaginal misoprostol in intrauterine insemination because of the higher miscarriage rates and the indefinite advantage of misoprostol over pure cycles determined in this study. Until the reason for this difference is explained and the uncertainty solved we cannot recommend currently its use in routine IUI cycles.

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