Iranian Journal of Reproductive Medicine Vol.7. No.4. pp: 169-173, Autumn 2009

The effect of administrating indomethacin or hyoscine before embryo transfer on ART outcome (a pilot study)

Farnaz Sohrabvand[1] M.D., Fedyeh Haghollahi[1] M.Sc., Masoomeh Maasomi[1] B.Sc., Leila Asgarpoor[1] M.D. , Mamak Shariat[2] M.D., Mahtab Hamedani[1] Ph.D.

1 Department of Infertility, Vali-e-Asr Reproductive Health Research Center, Vali-e-Asr Hospital,Tehran University of Medical Sciences, Tehran, Iran.
2 Mother and Child Health Research Center, Vali-e-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Received: 26 April 2009; accepted: 16 November 2009

Abstract

Background: In spite of the great progress in assisted reproductive techniques (ART), and although good quality embryos are transferred, pregnancy rates have remained around 30%-35% due to low implantation rates.

Objective: The aim of this study was to assess and compare the effects of administrating indomethacin or hyoscine suppositories prior to embryo transfer on the pregnancy rate in ART cycles.

Materials and Methods: This double-blind clinical trial was performed in Vali-e-Asr Hospital as a pilot study from August 2005 through December 2006 on 66 infertile women in ART cycles. Controlled ovarian hyperstimulation was done using recombinant FSH (Gonal-F) with a long GnRH analogue protocol. After obtaining written consent, the subjects were randomly allocated into three equal groups (n=22). Groups A and B received indomethacin and hyoscine rectal suppositories, respectively 30 minutes before embryo transfer and group C was the control group. Data were analyzed by $\chi 2$, t-test, ANOVA, and Kruskall Wallis tests.

Results: Overall pregnancy rate was 31% (n=21) with 13.6% (n=3) in group A, 45.5% (n=10), and 36% (n=8) in groups B and C respectively, which shows that pregnancy rate is significantly higher in the group using hyoscine compared to the other two groups (p=0.04). Uterine muscle cramps were experienced by 3 women (13.6%) in group C while none were reported by women in groups A or B, which shows a significant difference ($p<0.04$).

Conclusion: It seems that compared to indomethacin, hyoscine administration 30 minutes prior to embryo transfer can significantly increase pregnancy rates by reducing uterine and cervical muscle spasm.

Key words: *Embryo transfer, Hyoscine, Indomethacin, Pregnancy rate, ART.*

Introduction

Assisted reproductive techniques (ART) are now a major part of the armamentarium of the infertility specialists. In the past two decades, continued refinements in technology have increased the probability of success with these technologies and made them widely available (1).

Several factors can affect the success of IVF (such as age, infertility diagnosis, past reproductive-obstetrical history). The most important procedure-related factor affecting success are the number of oocytes retrieved and the number of high quality embryos derived from them in the laboratory (2). In spite of the great progress

Corresponding Author:
Farnaz Sohrabvand, Department of Infertility, Vali-e-Asr Reproductive Health Research Center, Vali-e-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran.
E-mail: fsohrabvand@yahoo.com

[Downloaded from ijrm.ir on 2026-11-13]

in reproductive techniques, a large number of ART treatment cycles are unsuccessful, and although most patients have at least 2 or 3 good quality embryos for transfer, but only 30%-35% of these patients become pregnant, which is usually due to low implantation rates (2). The role of uterine receptivity in infertility has remained unknown, due to the lack of knowledge about the basic mechanisms of controlling endometrial receptivity (1). Much researches have been performed in this field in order to improve the quality of embryo transfer, such as improvements in the type of catheter used, slow extraction of the catheter from the uterus, prevention of bleeding, depth of embryo transfer, not using a tenaculum, removal of cervical mucus, rinsing the cervical canal with culture medium prior to embryo transfer, transfer of embroyo under sonographic guidance, administration of antibiotics and bed rest after transfer (3, 4). Among the factors which significantly affect endometrial receptivity, is the absence of uterine contractions at the time of embryo transfer (5, 6). In a nonpregnant uterus, uterine contractions play an important role in human reproduction. Studies show that fertility rate can be increased by suitable stimulation or by reducing uterine contractions (7, 8). In order to reduce uterine contractions or cramps after embryo transfer it is recommended that the transfer to be done with the least trauma. With a difficult ET, in a study (9) strong random uterine contractions and fundocervicaluterine contractions were seen. In another study, the same group reported that a tenaculum applied to the cervix during mock ET resulted in increased uterine contractions (10). Prostaglandin (PG) which is synthesized from arachidonic acid by cyclooxygenase (COX), stimulates uterine contractions and may adversely affect outcome of ET. In this respect, treatment by uterine relaxants or NSAID drugs should be considered. NSAIDs block the action of COX and inhibit the production of PGs and theoretically should have beneficial effect on uterine contractions and pregnancy rate (11).

Also it has been shown that some NSAIDs like low-dose acetylsalicylic acid (aspirin) irreversibly inhibits the cyclo-oxygenase enzyme in platelets, thus, preventing the synthesis of thromboxane (12) which causes vasoconstriction and platelet aggregation. By this mechanism, low-dose aspirin may enhance uterine blood flow and tissue perfusion and thus improve endometrial receptivity for implantation. Recently some prostaglandin inhibitors such as indomethacin have been evaluated in this respect but the results are controversial. In a study by Bernabeu *et al* on oocyte recipients who had received indomethacin before transfer, there was no significant effect on implantation rates (13).

In order to induce relaxation in uterus and cervix, other drugs such as hyoscine can be taken into consideration. Hyoscine is an anti-muscarinic drug, which limits the muscarinic effects of acetylcholine on autonomic factors; one of these effects is reduction of cervical spasm (14). Sirohiwal *et al* (2004) showed that hyoscine suppository use can significantly reduce the duration of stage 1 delivery by reducing cervical resistance (15). Since there are no available data on effect of hyoscine or similar group of drugs on ART outcome, this study was performed with the aim to assess and compare the effects of administrating indomethacin and hyoscine suppositories prior to embryo transfer on the rate of pregnancy in ART cycles.

Materials and methods

This double-blind clinical trial (pilot study) was performed on 352 patients who attended Vali-e-Asr Hospital from August 2005 to December 2006. Sixty six cases, for whom ART was recommended by an infertility specialist due to tubal factors, ovulation disorders, or severe male factor, were put on their first ART cycle. All patients had a third day FSH serum level of < 10 IU/L. Controlled ovarian hyperstimulation was done using recombinant FSH (Gonal-F, Merck Serono, Switzerland) with a long GnRH analogue protocol. Ovum extraction was done 36-38 hours after HCG administration which was given when at least two 18 mm follicles were detected. After microinjection and embryo formation, the study group was randomly divided into three groups (N=22). Group A and group B received indomethacin (10mg, Tolid Daru, Iran) and hyoscine (100mg, Tolid Daru, Iran) rectal suppository respectively, half an hour prior to embryo transfer. Group C did not use any form of medication which is the conventional method used (control group). Embryo transfer was done using the Wallace catheter without sonographic control. The patients were asked about their feeling of lower abdominal pain which was considered as having or lacking cramps. All three groups rested for half an hour after embryo transfer and were then discharged. Patients suffering from systemic diseases or endometriosis were excluded. Information including, age, duration and cause of

[Downloaded from ijrm.ir on 2026-11-13]

infertility (primary, secondary), history of ART, endometrial thickness, number of oocytes and embryos transferred, and type of catheter, depth of transfer, presence of cramps after embryo transfer were recorded in the questionnaire.

Statistical analysis:

Data was entered into SPSS version 14 computer software and subsequently analyzed. Success rates were compared using T tests, chi-square, Fisher, Kruskall Wallis and paired regression tests.

Results

Out of the 66 subjects under study, 21(31%) became pregnant. Pregnancy rate was 13.6% (n=3), 45.5% (n=10), and 36% (n=8) in groups A, B, and C, respectively (Table I). Mean age of the study group and their partners was 29.12±4.9 and 33.24±6.6 years respectively. Of the couples, 77% had primary infertility, 59% of which were due to male factor. Duration of infertility was 6.33±3.61 years. A significant statistical difference was not detected in the three groups under study regarding quantitative variables such as age of women, age of their partners, duration of infertility or qualitative data such as type and cause of infertility (Table II). Mean endometrial thickness was 10.09±1.47mm, 9.82±2.1mm and 9.68±2.07mm in groups A, B, and C, respectively and statistical analysis did not show a significant difference ($p>0.7$).

Also there was no significant statistical difference between endometrical thickness and pregnancy rate in the group under study or in the three groups separately. The number of embryos transferred was between 2-3. Three embryos were transferred in 12 (54.5%), 8 (36%) and 19 (86%) patients in group A, B, and C, respectively, which was significantly higher in the control group ($p<0.003$).

After embryo transfer, uterine muscle cramps were reported by 3 women (13.6%) in group C but no women in groups A or B, which shows a significant difference ($p<0.04$). The relationship between all variables and outcome of pregnancy was studied using binary regression analysis which showed that hyoscine increases the rate of pregnancy considerably.

Table I. Comparison of outcomes of the three groups under study.

Outcome	Control group	Hyoscine group	Indomethacin group	p-value
No.(%) βhCG+	8 (%36)	10 (%45.5)	3 (%13.6)	<0.04*
Abdominal muscle cramps No.(%)	3 (%13.6)	0	0	0.04*

* Kruskall- wallis

Table II. Demographic characteristics of three groups under study.

Group characteristics	Control (Group C N=22)	Indomethacin (Group A N=22)	Hyoscine (Group B N=22)	Total N=66	p-value
Age of women (years, mean±SD)	26.68±4.58	30.59±5.05	30.09±4.29	29.12±4.90	NS**
Age of men (years mean±SD)	30.86±4.02	33.09±8.85	35.77±5.49	6.66±33.24	NS**
Type of infertility No.(%)					
Primary	18(%82)	16(%73)	17(%77)	51(%77)	NS*
Secondary	4(%18)	6(%27)	5(%23)	15(%23)	
Duration of infertility (years)	6.18±3.37	6.11±3.71	6.70±3.86	6.33±3.61	NS**
Cause of infertility No.(%)					
Male	16(%73)	11(%50)	12(%54.5)	39(%59)	NS*
Female	3(%13.6)	7(%31)	8(%36)	18(%27)	
Both	3(%13.6)	3(%13.6)	0	6(%9)	
Unexplained	0	1(%4.5)	2(%9)	3(%4.5)	

*Kruskall Wallis **ANOVA

[Downloaded from ijrm.ir on 2026-11-13]

Discussion

Assisted reproductive techniques, have been a milestone in the armamentarium of infertility treatments since 1978 i.e. the birth of the first child conceived by IVF (1). In spite of the great progress in ART, success rate (clinical pregnancy rate) has not increased significantly (2). Factors affecting pregnancy mostly include embryo quality, endometrial receptivity, and taking all important measures in embryo transfer techniques. Even when transfer is performed with utmost care and without inducing trauma, it can cause endometrial reaction which may lead to an inflammatory response and affect ART outcome. Endometrial receptivity is one of the factors in which information is lacking (2). The current study shows that, as compared to the control group, indomethacin and hyoscine both reduce uterine cramps ($p=0.04$). The results of the present study show that pregnancy rate is signifgicantly higher in the hyoscine as compared to the indomethacin or control groups ($p<0.04$). In other words, by eliminating uterine cramps, hyoscine can cause an increase in pregnancy rate, whereas indomethacin only reduces uterine cramps and pain but does not have a clearly positive effect on pregnancy rate. Lesny *et al* (2004) studied junctional zone contractions in uterine muscle cells through the real time ultrasound and has demonstrated more subtle contractions, in which peristaltic-like movements are confined to the endometrium and the immediately adjacent myometrium in the uterus during IVF-ICSI in ovum donation cycles. The lack of histological evidence for contractile tissue within the endometrium is a sign which shows that probably the origin of these contractions is within the junctional zone (subendometrial layer) of the myometrium (16). Seven days after the onset of ovarian stimulation, cervico-fundal, fundo-cervical, and dispersed uterine spasms were observed in all patients. In this study, junctional zone activity was more intense throughout the IVF cycle as compared to normal cycles, but with similar direction, which may be due to the widely different hormonal levels. High junctional zone activity and the resulting high endometrial stimulation, may negatively affect endometrial receptivity and embryo implantation (17). Fanchin *et al* (1998) also showed a direct relationship between uterine contractions during embryo transfer and low pregnancy rates (6). In the same field, many pharmacological factors have been used to reduce uterine contractions. Moon *et al* (2004) studied the effect of administring 10mg beta-cyclodextrin piroxicam, one and two hours prior to embryo transfer. Their results showed that pregnancy rate was higher (46.8%) in experimental group than the control group (27.6%) (18). The results of the study by Bernabeu *et al* (2006) showed that indomethacin does not have a significant role in pregnancy rate (12). Also, Tervit *et al* (1980) showed that in donor-recipient cycles, pregnancy rate is not affected by indomethacin administration in the recipient (19). The results of this study showed that the administration of hyoscine 30 minutes prior to embryo transfer can positively affect pregnancy rate as compared to the control group, with no medication. According to this study, indomethacin does not affect pregnancy rate in spite of reducing uterine cramps. Although theoretically NSAIDs inhibit COX and thromboxane in platelets and therefore increase blood flow by preventing aggregation, it seems that they can probably have deleterious effects on inflammatory events which are necessary for implantation. Instead, the beneficial effects of hyoscine may probably be due to its physiological anticholinergic effects as explained before.

In spite of our findings, since this study was performed on a limited number of patients and since other numerous factors are involved in this process, we recommend that more precise studies be performed on a wider scale in order to obtain more accurate results.

Conclusion

It seems that hyoscine administration, 30 minutes prior to embryo transfer can significantly increase pregnancy rates by reducing uterine and cervical muscle spasm.

Acknowledgement

This study was approved and financially supported by the Deputy of Research of Tehran University of Medical Sciences. We would like to greatly thank all authorities and colleagues of the contributing centers including the Gynecology and Infertility Clinics and IVF laboratory of Vali-e-Asr Hospital for their help and support.

References

1. Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. *Lancet* 1978; 2: 366.
2. Gardner DK, Weissman A, Howles CM, Shoham Z. Textbook of assisted Reproductive techniques laboratory

[Downloaded from ijrm.ir on 2026-11-13]

and clinical perspectives. Second edition.Taylor & Francis 2004; 543: 579.
3. Sallam HN. Embryo transfer- Can the technique affect the results? The 4th World Congress on controversies in Obstetrics, Gynecology & Infertility. Oren Publisher Ltd.International Proceedings Division 2003;324-334.
4. Masao J, Tsuneo O, Mitsutoshi I, Nakamura Akiliko, Hiroshi H. Measurement of endometrial tissue blood flow: a novel way to assess uterine receptivity for implantation. *Fertil Steril* 2001; 76: 1168-1174.
5. Schild R, Knobloch C, Dorn C, Fimmers R, Hansmann M. Endometrial receptivity in an in vitro fertilization program as assessd by spiral artery blood flow, endometrial thickness, endometrial volume, and uterine artery blood flow. *Fertil Steril* 2001; 75: 361-366.
6. Fanchin R, Roghini C, Olivennes F, Taylor S, Ziegler D, Frydman R. Uterine contraction at the time of embryo transfer alter pregnancy rates after in vitro fertilization. *Hum Reprod* 1998; 13: 1968-1978.
7. Caldwell N, Gardner R. The selective effects of Indomethacin on contractile responses of the isolated rat uterus. *Endocr Res* 1986; 12: 255-267.
8. Grbovice L, Jovanovic A, Tulic I. Indomethacin reduces contraction of isolated nonpregnant human uterine artery induced by prostaglandin F2 alpha. *Hum Reprod* 1996; 11: 1998-2002.
9. Fanchin R, Ayoubi JM, Righini C, Olivennes F, SchonauerLM, Frydman R. Uterine contractility decreases at the time of blastocyst transfers. *Hum Reprod* 2001; 16: 1115-1119.
10. Fanchin R, Ayoubi JM, Olivennes F, Righini C, deZiegler D, Frydman R. Hormonal influence on the uterine contractility during ovarian stimulation. *Hum Reprod* 2000; 1: 90-100.
11. Grimes DA, Hubacher D, Lopez LM, Schulz KF. Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use. *Cochrane Database Syst Rev* 2006, 18: CD006034.
12. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* 1971; 231:232–235.
13. Bernabeu R, Roca M, Torres A, Ten J. Indomethacin effect on implantation rates in oocyte recipients. *Human Reprod* 2006; 21:364-369.
14. Burke LM, Davenport AT, Russell GB, Deaton JL. Predictors of success after embryo transfer, experience from a single provider. *Am J Obstet Gynecol* 2000; 182:1001-1004.
15. Sirohiwal D, Dahiya K, DE M. Efficacy of Hyoscine-N-butyl bromide (Buscopan) suppositories as a cervical spasmolytic agent in labour. *Aust N Z J Obstet Gynaecol* 2005;45:128-129.
16. Lesny P, Killick SR. The junctional zone of the uterus and its contractions. *BJOG* 2004;111:1182-1189.
17. Marikinti K, Brinsden PR.The presence of blood in the transfer catheter negatively influences outcome at embryo transfer. *Human Reproduction* 2005; 20:2029-2030.
18. Moon HS, Park SH, Lee JO, Kim KS, Joo BS. Treatment with piroxicam before embryo transfer increases the pregnancy rate after in vitro fertilization and embryo transfer. *Fertil Steril* 2004; 82:816-820.
19. Tervit HR, Cooper MW, Goold PG, Haszard GM. Non-surgical embryo transfer in cattle. *Theriogenology* 1980; 13: 63-71.

[Downloaded from ijrm.ir on 2026-11-13]

[Downloaded from ijrm.ir on 2026-11-13]