Uterine Peristalsis in Women With Repeated IVF Failures: Possible Therapeutic Effect of Hyoscine Bromide

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Abstract

Background: Uterine peristalsis, which is influenced by hormonal and cholinergic effects, may have a role in successful implantation and continuing pregnancy.

Cases: We encountered abnormal uterine peristalsis in three women who had had repeated in vitro fertilization (IVF) treatment failures. They subsequently had successful pregnancies when hyoscine bromide was administered at the time of embryo transfer.

Conclusion: It is possible that decreasing uterine peristalsis with use of an anticholinergic agent during IVF treatment facilitates retention of embryos and increases the probability of successful pregnancy.

Résumé

Contexte : Le péristaltisme utérin, lequel est influencé par des effets hormonaux et cholinergiques, pourrait jouer un rôle dans la réussite de l'implantation et de la poursuite de la grossesse.

Cas : Nous avons constaté un péristaltisme utérin anormal chez trois femmes qui avaient subi des échecs à répétition dans le cadre d'un traitement de fécondation *in vitro* (FIV). Elles ont par la suite connu une grossesse réussie lorsqu'on leur a administré du bromure d'hyoscine au moment du transfert d'embryon.

Conclusion : Il est possible que l'atténuation du péristaltisme utérin au moyen d'un agent anticholinergique au cours du traitement de FIV facilite la rétention des embryons et entraîne la hausse de la probabilité de réussite de la grossesse.

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INTRODUCTION

Uterine peristalsis may play a role in the ability to conceive[1–6]; unusual patterns of peristalsis have been observed in women with endometriosis and infertility.[7,8] Uterine peristalsis is under the influence of hormones,[9] and its activity can be suppressed by anticholinergic agents.[10] We report the identification of unusual uterine peristalsis in three infertile women who subsequently had successful pregnancies with in vitro fertilization (IVF) treatment combined with administration of an anticholinergic agent.

THE CASES

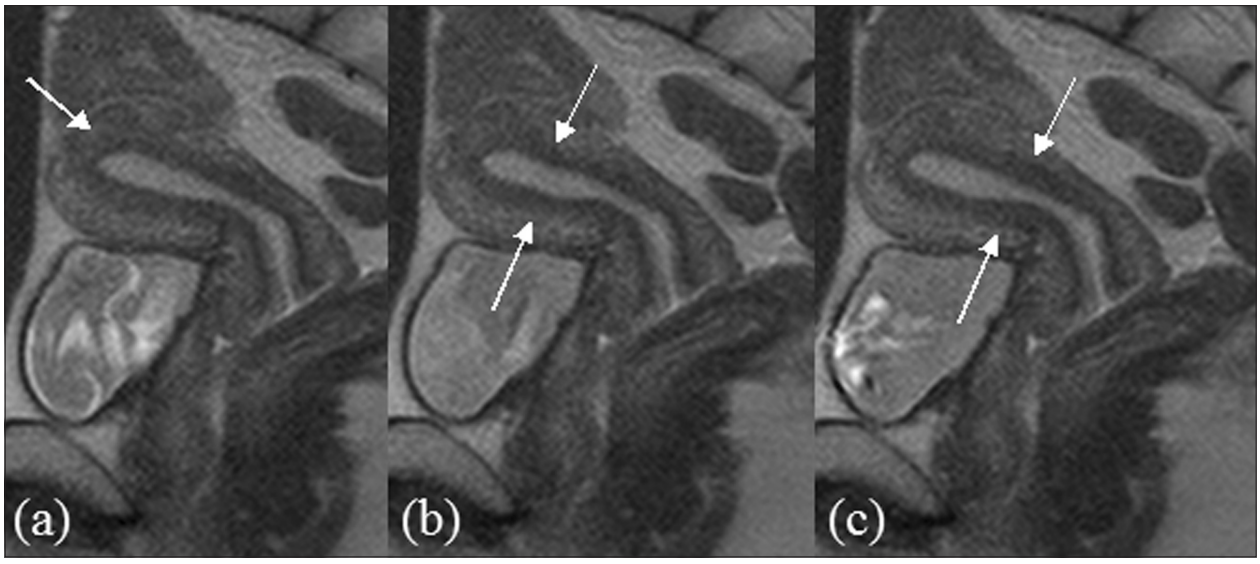
Case One

A 30-year-old woman had a six-year history of unexplained infertility. She had previously undergone six cycles of IVF and multiple embryo transfers without success. In the first IVF cycle, three embryos (two 8-cell and one 4-cell, all of good quality) were transferred. Pregnancy did not occur, and in the subsequent cycle three frozen-thawed embryos (two 5-cell and one 4-cell embryo, of good to medium quality) were transferred. Again, pregnancy did not occur, and in the next IVF cycle a two-step consecutive transfer of a frozen-thawed embryo (4-cell good quality) and two blastocysts was performed.

Subsequently, we transferred two frozen-thawed embryos (5-cell good quality and 5-cell poor quality) but without success. Sperm concentration and sperm quality were normal in all treatment cycles. Four additional cycles of IVF with blastocyst transfer also failed.

After obtaining written informed consent, we performed a uterine peristalsis study as previously described.[11–13] As

A serial image taken from 60 HASTE images in Case 2. Thickest and/or darkest areas within the junctional zone are indicated by arrows. These areas move from fundus to cervix with distortion of the endometrial configuration. (a) Thickest area of junctional zone at the fundus. The endometrial outline is made concave by contraction at the fundus. (b) Darkest area of junctional zone has moved to the middle of the uterine corpus. The endometrial cavity is compressed at those points. (c) Thickest and darkest areas within the junctional zone have moved to the uterine cervix.



usual, it was performed in the late follicular phase of a natural cycle when the dominant follicle was ≥ 18 mm in diameter. The study consisted of acquisition of cine MR images using a 1.5-T magnet unit (Symphony; Siemens Medical Systems, Erlangen, Germany) every three seconds over three minutes, and repeated after five minutes. The images were analyzed using an original computer assisted program.[14]

The first cine MRI was performed on day 13 of a 27-day cycle, and we identified peristaltic waves passing from the fundus to the cervix seven times in three minutes. In the second scan, the number of peristaltic waves was the same, but the direction was mixed (cervical–fundal and fundal–cervical). We administered hyoscine butylbromide 20 mg intramuscularly (Buscopan, Nippon Boehringer Ingelheim, Hyogo, Japan), and the uterine peristalsis study was repeated five minutes later. On this occasion, peristalsis was identified four times in three minutes, with fundal–cervical direction.

Subsequently, the patient underwent another IVF treatment with injection of hyoscine butylbromide prior to embryo transfer. We transferred two 8-cell embryos of good quality and two blastocysts. The patient conceived, but unfortunately the pregnancy was ectopic, and she underwent a right salpingectomy. A year later, she underwent another IVF treatment cycle and had a frozen-thawed blastocyst transfer with hyoscine injection just before transfer. The patient conceived with an intrauterine pregnancy and subsequently delivered a healthy boy weighing 2900 g.

Case Two

This 34-year-old woman had an eight-year history of unexplained infertility and had undergone four failed IVF treatment cycles elsewhere.

We performed a uterine peristalsis study. The first preovulatory MR scan on cycle day 12 of a 29-day cycle identified uterine peristalsis six times in three minutes, and in the second scan it was identified eight times in three minutes. The direction of peristalsis was fundal-cervical on both occasions (Figure). In a subsequent IVF treatment cycle with hyoscine injection, we transferred two high-quality 4-cell embryos. An intrauterine pregnancy was achieved, but the patient subsequently miscarried. In a subsequent IVF cycle with hyoscine administration, two high-quality 4-cell embryos were transferred, resulting in pregnancy and subsequent delivery of a healthy girl weighing 3152 g.

Case Three

This 33-year-old woman had a five-year history of unexplained infertility, with several failed IVF treatment cycles. In the first and second IVF cycles, we had transferred one good quality 8-cell embryo, and three smaller embryos (a 4-cell, a 3-cell, and a 2-cell) respectively. In the next treatment cycle, three frozen-thawed embryos (one 6-cell, and two 4-cell) were transferred, and in the cycle after that two

frozen-thawed embryos (both 6-cell) were transferred without success.

The uterine peristalsis study done on day 15 of a 30-day cycle showed fundal–cervical waves two times in three minutes during the first and second MR scans. In the subsequent IVF treatment cycle, with hyoscine administration, a two-step embryo transfer (a 5-cell embryo and a 3-cell embryo, followed two days later by a blastocyst) was performed. The patient conceived and subsequently delivered a healthy boy weighing 3620 g.

DISCUSSION

Our cine MR studies demonstrated that the direction of uterine peristalsis in the follicular phase is from fundus to cervix, with a frequency of two to six times in three minutes. In the periovulatory phase, it propagates in the opposite direction, from cervix to fundus, with a frequency of 3.5 ± 0.6 times per minute.[3,15–18] In the luteal phase, the frequency of peristalsis decreases, relaxing the uterus.[3,15–17]

Ijland et al. reported that periovulatory fundal–cervical peristalsis was most frequently observed in women who never conceived.[1] They also found active uterine peristalsis in the mid-luteal phase among 46% of women who never conceived compared with 11% in those who subsequently conceived.[1]

We studied uterine peristalsis in three women with long-standing unexplained infertility and repeated IVF failures. In contrast to the usual periovulatory cervical–fundal direction of uterine peristalsis, these women had had peristaltic waves in the opposite direction. Fundal–cervical waves may impair sperm transport, and expel an embryo from the uterine cavity. Administration of hyoscine bromide in the patient described in Case 1 decreased the frequency of uterine peristalsis, mitigating these deleterious effects. Pierzynski et al. reported that administration of an oxytocin antagonist also decreased uterine contractility.[19] As a result, the embryo is retained in the uterine cavity. Franchin et al. found that a low frequency of peristaltic waves at the time of embryo transfer was related to successful implantation and pregnancy.[5]

Hyoscine is an anticholinergic drug that is well absorbed after oral or parenteral administration. Animal studies have shown that it is not teratogenic (unpublished data, Nippon Boehringer Ingelheim). The duration of effect is about 40 minutes after an intramuscular injection, but its metabolites remain in the body for a few hours.[20]

Administration of hyoscine in our patients appeared to be beneficial. It suggests a possible role of this agent in the treatment of infertility. A randomized controlled trial to evaluate the efficacy of hyoscine on the pregnancy rate is clearly needed.

Our report has some limitations. Although previous reports have shown the effects of estradiol, oxytocin, progesterone, and other substances on uterine contractility,[21–23] we did not assess hormone concentrations. We did not conduct the uterine peristalsis studies at the time of embryo transfer, which may have shown a different pattern from the study done in the late preovulatory phase. In addition, we do not have information about the reproducibility of uterine peristaltic studies. Finally, subtle differences in embryo quality might have accounted for the different outcomes of IVF treatment with and without hyoscine treatment.

CONCLUSION

This preliminary report suggests that women with repeated IVF failures might have abnormal uterine peristalsis. It is possible that decreasing peristalsis by administration of hyoscine increases the chance of embryo retention, implantation, and successful pregnancy. Further study in a large number of patients is needed.

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