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Original Article

Factors related to completeness of medical abortion with mifepristone and misoprostol

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Abstract

Background: Medical abortion that occurs in early pregnancy is generally safe and successful, but incomplete medical abortion can result in complications. This study aimed to examine factors related to completeness of medical abortion with mifepristone and misoprostol, and then to provide a new direction for research into establishing complete abortion with mifepristone and misoprostol.

Methods: Sixty-three patients with early pregnancy requesting medical abortion with mifepristone and misoprostol were selected. Immunohistochemistry was used to detect the expression and location of progesterone receptor, estrogen receptor, insulin-like growth factor-1, and vascular endothelial growth factor in chorionic villi among these women. Reverse transcriptase polymerase chain reaction was then used to determine the expression of insulin-like growth factor-1 and vascular endothelial growth factor mRNA.

Results: According to the outcome of medical abortion, the women were divided into either the incomplete medical abortion group ($n = 34$) or the complete medical abortion group ($n = 29$). Immunohistochemical analysis showed that progesterone receptor and estrogen receptor protein expression was not detected in chorionic villi in the two groups. However, compared with the complete abortion group, there was a marked decrease in the expression of insulin-like growth factor-1 and a significant increase in the expression of vascular endothelial growth factor ($p < 0.05$) in the incomplete abortion group. There was no significant difference in mRNA expression between the incomplete and complete abortion groups.

Conclusion: The expression of insulin-like growth factor 1 protein and vascular endothelial growth factor protein in chorionic villi may be related to the outcome of medical abortion with mifepristone and misoprostol.

Keywords: estrogen receptor; insulin-like growth factor 1; medical abortion; progesterone receptor; vascular endothelial growth factor

1. Introduction

Recently, medical termination has been the first choice for early pregnancy termination, and > 50% of the 53 million women with unwanted pregnancy worldwide requesting termination preferred medical abortion.[1] Mifepristone was the first approved medication for medical abortion. Actually, mifepristone in combination with misoprostol is safe and effective, has been used for more than 2 decades, and is available in 35 countries.[2] Mifepristone and misoprostol, in combination, generally demonstrate a high complete abortion rate of 92–99%.[3] However, the commonest causes of failure of this method are incomplete abortion (5%), excessive bleeding (3%), and ongoing pregnancy (1%).[4,5] Incomplete abortion commonly causes hemorrhage, infection, and abdominal pain, and has the potential for long-term emotional consequences. Furthermore, the risk of vaginal bleeding during medical abortion with mifepristone and misoprostol is increased in the early period of pregnancy.[6] Thus, it is important to find parameters to predict the

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success of medical treatment. Various clinical methods have been suggested for the evaluation of the outcome of medical abortion, such as endometrial thickness determined by ultrasound[7] and serum beta-human chorionic gonadotropin measurement.[8] However, none of these clinical factors are highly accurate or reliable.[8−11] At a molecular level, prolonged bleeding after medical abortion with mifepristone and misoprostol is associated with elevated expression levels of matrix metalloproteinase-9 (MMP-9) in villi and of tissue inhibitors of metalloproteinases-2 (TIMP-2) in the decidua.[12] However, no research has been carried out focusing on villi to study the success of medical abortion. Hence, we decided to explore factors in chorionic villi to relate the success of medical abortion with mifepristone and misoprostol.

Mifepristone functions as an antiprogesterone by competing with progesterone in the endometrium and decidua for receptor binding, thus terminating early pregnancy.[13] An array of novel progesterone receptor (PR)-regulated gene pathways and high expression of PR were found in the decidua of pregnant mice treated with mifepristone,[14] indicating that progesterone may play important roles in the regulation of endometrial decidualization, which can be blocked by mifepristone. However, only limited information is available about the effect of mifepristone in early gestational chorionic villi. One study reported that mifepristone impaired the production of human placental lactogen and progesterone in cultured syncytiotrophoblasts,[15] but there have been no published reports studying the correlation between PR in human chorionic villi and the outcome of medical abortion with mifepristone and misoprostol.

Progesterone, estrogen, and their receptors can be modulated by each other, and are responsible for physiological changes of the endometrium and also essential for the maintenance of pregnancy and development of embryo. As early as 1975, Hsueh et al[16] showed that progesterone can decrease the sensitivity of tissue to estrogen by acting on the cytoplasmic estrogen receptor (ER) to decrease the quantity of uterine ER. Decreased ER alpha, ER beta, and PR-B levels in the human endometrium may be related to prolonged uterine bleeding after medical abortion by mifepristone accompanied by misoprostol.[17] Therefore, some investigators proposed that downregulation of ER was also related to the outcome of medical abortion; such a proposition, however, completely focuses on the endometrium.

Many other factors such as insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF),[18,19] are thought to contribute to the development of human embryos and to be related to the outcome of medical abortion. Antiestrogen tamoxifen may inhibit the growth of leiomyoma by interrupting an IGF-1 autocrine loop in the leiomyoma cell lines.[20] Animal experiments have established that the VEGF mRNA and protein can be upregulated by ER and PR, contributing to vasculogenesis and embryo development.[18] Studies about IGF-1 and VEGF are mostly carried out on leiomyoma and endometriosis, and there are few reports evaluating the roles of IGF-1 and VEGF in chorionic villi in medical abortion with mifepristone and misoprostol. Hence, IGF-1 and VEGF, which were hypothesized to be related factors for prediction of completeness of medical abortion, were also investigated using immunohistochemistry and reverse transcriptase polymerase chain reaction (RT-PCR) in chorionic villi tissues from women undergoing abortion.

In the present study, the relationship between ER, PR, IGF-1, and VEGF expression in chorionic villi and the outcome of medical abortion with mifepristone and misoprostol were studied. In addition, whether PR, ER, IGF-1, and VEGF in chorionic villi were related to the outcome of medical abortion was also explored.

2. Methods

2.1. Patients

Between March 2009 and April 2011, 89 women with early pregnancy requesting medical abortion for termination of pregnancy at The Second Affiliated Hospital of Wenzhou Medical University were considered for recruitment in this prospective study. Of these 89 potential study participants, 68 provided consent for inclusion in this study (Fig. 1). All patients were initially assessed by their provided medical history, physical examination, urine pregnancy test, routine blood test, electrocardiogram, liver function test, and ultrasonography. The inclusion criteria were as follows: (1) age 18−30 years old; (2) healthy women requesting medical abortion; (3) gestational age 35−49 days (based on the onset of the last menstrual period, bimanual examination, and ultrasound) and a gravid 1 para 0 with a singleton intrauterine pregnancy, with the presence of fatal heart beat being confirmed by careful ultrasound examination; and (4) women being informed of the advantages and risks of medical abortion, and signing an agreement of consent. The exclusion criteria were as follows: (1) complication of pregnancy; (2) drug allergy to mifepristone or misoprostol; (3) current use of long-term systemic steroids; (4) a medical history of disease related to the cardiovascular system, respiratory system, liver, kidney, or adrenal gland; (5) uncontrolled hypertension, cardiovascular disease angina, or diabetes mellitus; (6) *in situ* intrauterine devices; (7) pelvic inflammatory disease; (8) hemoglobin <80 g/L; (9) breastfeeding; (10) addiction to alcohol or smoking; and (11) lost to follow-up. The study protocol was approved by the Research Ethical Committee of The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China (20090103) and met the standards of the Declaration of Helsinki. Written consent was obtained from patients before the collection of samples.

2.2. Administration and efficacy

The method and dose administration of medicine followed the recommendation of the study of Zhuang et al.[12] All applicants were treated with 50 mg mifepristone administered orally on their first visit, followed by 25 mg mifepristone administered orally every 12 hours (total 150 mg) at home. During a second visit 48 hours later, women received 600 mg oral misoprostol and remained in the hospital under observation for 4 hours. During this observation period, tissues discharged from the