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A Simple Procedure for Termination of Pregnancy in the Late First Trimester with Mifeprostone and Misoprostol

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Abstract

Purpose: To assess the efficacy of medical methods for termination of pregnancy at 9 - 12 weeks of gestation. Methods: Between December 2008 and December 2010, the 116 consecutive women received 200 mg oral mifepristone and after 24 - 36 hours they applied 800 µg vaginal misoprostol to medically terminate pregnancy. If the products of conception did not pass, three further doses of 400 µg misoprostol were given vaginally at three hours intervals to medically terminate pregnancy. Results: Of the 116 patients undergoing the procedure 104 (90%) aborted completely. Half of the patients aborted within 6 hours. After medical termination, five per cent of the women were treated because of infection, and five per cent needed a revisit to hospital because of excessive bleeding. Two women received a blood transfusion. Previous live births or previous inducted abortion is presented in the study results. Conclusions: Medical abortion at 9 - 12 weeks' gestation is a safe alternative to surgery.

Keywords

Medical Termination of Pregnancy, Late First Trimester, Safe Abortion, Mifepristone, Misoprostol

1. Introduction

Up to 46 million abortions are performed worldwide each year [1]. An estimated half of the abortions are performed under unsafe conditions. Forty per cent of the world's women are living in countries with restrictive abortion laws which prohibit abortion or only allow abortion to protect a woman's life or her physical or mental health. As a result of that, unsafe abortions are made approximately 19 - 20 million per year [2]. Various drugs have been used for the legal medical first trimester termination, but the most common combination is mifepris-

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tone-misoprostol [3]. As an antiprogesterone, mifepristone blocks the receptors for progesterones and glucocorticoids and increases the sensitivity of the uterus to prostaglandins. Misoprostol is a prostaglandin analogue registered for use in non-steroidal anti-inflammatory drug (NSAID) induced gastric ulcer prevention and treatment, but it has also a strong uterotonic effect. In the United Kingdom, mifeprostone and misoprostol are licensed for medical termination of pregnancy (TOP) in the first trimester up to 63 days for amenorrhea. Current practice is to use low-dose (200 mg) mifepristone orally and 800 μg misoprostol vaginally. This blockage results in the breakdown of maternal capillaries in the deciduas, the synthesis of prostaglandins by the epithelium of decidual glands and inhibition of prostaglandin dehydrogenase. The successful medical treatment of legal abortion up to 63 days of gestation is demonstrated in various studies [3]-[7]. According to Cochrane reviews [3], medical treatment achieves the complete abortion in about 95% of pregnancies up to 9 gestational weeks.

According to the current Royal College of Obstetricans and Gynecologists (RCOG) guideline, surgical or medical termination should be offered to those within 9 - 13 weeks of gestation [8], but curettage is still more common practice to terminate the pregnancy before 13 weeks' gestation in many countries like the United States [9]. Some evidence suggests that women consider medical TOP highly acceptable [10] and will prefer the medical method for TOP [11]. It has also been recommended that medical TOP at 10 - 13 weeks' gestation should be an option for women who wish to avoid surgery or anesthesia [12]-[14]. Further research is needed as there has been less clinical research into medical methods of abortion and its efficacy at 9 - 13 weeks' gestation than at earlier weeks.

The aim of this study was to assess the efficacy of medical methods of termination at 9 - 12 weeks of gestation. We assessed and evaluated the efficacy of medical abortion in a series of 116 women who underwent abortion.

2. Methods

The study population consisted of 116 women who had undergone late first trimester termination at the Department of Gynecology and Obstetrics of Oulu University Hospital between December 2008 and December 2010. This study was conducted as a retrospective, observational study and the information was gathered from Oulu University Hospital patient records. The study population is described in **Table 1**. The median age of the women

Table 1. Patient characteristics.

Patient characteristics		Number of patients n = 116 (%)	Median (Range)
Age (yrs)			21 (14 - 44)
	<19	37 (32)	
	20 - 29	53 (46)	
	30 - 39	21 (18)	
	>40	5 (4)	
Parity			0 (0 - 4)
	0	70 (60)	
	1 - 2	36 (31)	
	>3	10 (9)	
Previous terminations			0 (0 - 4)
	yes	40 (34)	
	no	76 (66)	
Gestation, days			70 (56 - 83)
	≤63	15 (13)	
	64 - 70	46 (40)	
	71 - 77	28 (24)	
	≥78	27 (23)	
Day case			
	yes	106 (91)	
	no	10 (9)	

was 21 years. Eight (7%) of the women were under 17 years of age and five (4%) were over 40 years. Most women (60%) had no previous deliveries. 40 (34%) women had undergone a previous induced abortion.

At the primary examination all women were counselled about the termination process. Exclusion criteria for receiving medical abortion included suspected ectopic pregnancy, chronic adrenal failure, long-term corticosteroid treatment, hemorrhagic disorders or treatment with anticoagulants, severe asthma and multiple (>5) pregnancies. Assessment of gestational age was based on transvaginal ultrasound measurement (crown rump length). All women were screened for *Clamydia trachomatis* and treated by antibiotics if the test was positive. No prophylactic antibiotics were given.

All patients were primarily offered the medical procedure [15] [16]. Medical abortion is standard procedure in our clinic and it is primarily offered of all patients including women less than 63 days of gestation. During the study period only three surgical abortions on these weeks were performed. One patient had severe asthma and two patients were immigrants, which used interpreter services. Without common language the medical procedure was not an option. Patients were informed for teratogenicy of the medication used. We emphasized that the procedure is permanent and after taking the first tablet pregnancy cannot be continued.

The patients were given 200 mg mifeprostone orally in the hospital under nursing supervision and allowed to go home. After 24 - 36 hours they returned to the outpatient clinic and applied 800 µg misoprostol vaginally. A Visual Analogue Scale (VAS) was used to evaluate subjective pain experienced by the women during the whole termination process. The patients were offered mild oral analgesia e.g. nonsteroidal anti-inflammatory drugs (NSAID) and opiate analgesia when needed. If needed, parecervical blocade was also administrated. The termination process was observed and recorded routinely at the ward by the nurses. If products of conception were not passed, up to three further doses of 400 µg misoprostol were given vaginally at three hours intervals. After bleeding, patients went home. Pregnancy test was scheduled at their local health center after four to five weeks after abortion. Ultrasound was used to confirm abortion from April 2010. All patients were given emergency contact numbers after discharge.

The main outcome measures were need of surgical evacuation after medical treatment, complications such as incidence of treated infections, completion of abortion and bleeding requiring blood transfusion, induction to abortion time that is the time interval in hours from administration of misoprostol to passing the products of conception and VAS.

The data analysis included Kruskall Wallis test and Mann-Whitney U-test, which were used to analyze the statistical significance of differences between the groups. A chi-square test was applied for comparing discrete variables. The relationship between cumulative abortion rate and time from induction to abortion was evaluated by nonlinear regression model (S-mode). Numbers were expressed as median (range), mean (SD) or number and percentage.

3. Results

During the trial period 116 patients with 56 - 83 days' amenorrhea requested medical TOP. The median gestation time was 70 days. The indication was social in all cases. Complete abortion was achieved in 104 (90%) cases, *i.e.*, no surgical measures were needed. A total of 106 (91%) women were managed as day cases. Most (96%) of the abortions occurred within eight hours after induction and all TOPs were completed within 12 hours (**Figure 1**). The nonlinear regression model (S mode) gives an estimate for abortion rate as percents over a given time (**Figure 1**). VAS was used to evaluate subjective pain experienced by the women (**Table 2**). It seemed that as the time from induction to abortion increased, there was parallel accretion of VAS but after VAS reached 6, this trend did not continue. Paracervical blockage was needed in five cases. The results show that parity or previous termination had no impact on induction to abortion time (**Table 3**). Late complications that occurred after discharge from hospital and required readmission included pelvic infection disease in 5% and excessive bleeding in 5% of the patients. Evacuation was performed in 7% of the cases because of uncompleted abortion e.g. conception material. Two women required blood transfusion.

There were three ongoing pregnancies that resulted in parturition. The three ongoing pregnancies were due to the fact that one patient had not taken the pregnancy test and two women decided to continue the pregnancy after a failed medical abortion. The patients contacted to our clinic on weeks 15, 17 and 26. For two patients and option for new termination procedure was offered but patients were willing to continue pregnancy and acknowledged the risks. None of the women whose pregnancy was ongoing had previous abortions. Two of them

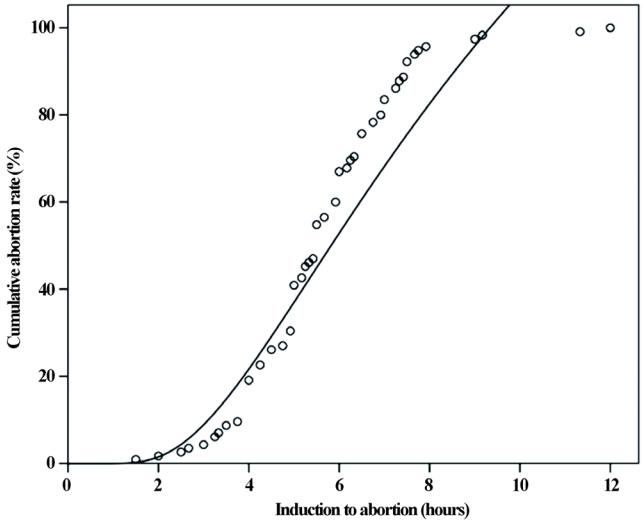

Figure 1. Abortion rate.

Table 2. Pain experienced by the patient.

VAS	Number of patient n (%)	Mean (SD)	Sig. (p-value)
0 Painless	14 (12.1%)	4.71 (1.5 - 6.5)	
1 - 3 Mild	26 (22.4%)	5.25 (2.67 - 9.17)	
4 - 6 Moderate	38 (32.7%)	6.5 (3 - 12)	
7 - 9 Severe	35 (30.2%)	5.5 (3.25 - 7.67)	
10 Unbearable	3 (2.6%)	5.5 (5 - 6.25)	
All	116 (100)	4.73 (2.854)	0.006

Table 3. Duration of the termination.

Induction to abortion, hours		n = 116 (%)	median (range)
Gestation, days			5.5 (1.5 - 12)
	63	15 (13)	
	64 - 70	46 (40)	
	71 - 77	28 (24)	
	≥78	27 (23)	
Parity	Nullipara	70 (60)	5.00 (1.5 - 9.17)
	≥1 LBs	46 (40)	5.00 (1.5 - 9.17)
Previous terminations	yes	40	5.085 (1.5 - 9)
	no	76	5.5 (2.5 - 12)

were nullipara and one had three previous live births. All the three infants were male. Two of them were considered as normal newborn infants and one was slightly premature. These infants developed normally as far as our data reached.

4. Discussion

Medical termination for pregnancy has become an increasingly more common practice. The method was used in 79% of all pregnancy terminations in Finland in 2011. During the first trimester (<12 weeks) the medical method

was applied in 86% of terminations. In 2010 indications for abortions in Finland were social in 92%, medical in 0.5% and fetal defect-related in 3% of the cases. Other indications comprised 5% of the cases, including indications such as mother's age (under 17 or over 40 years) [15].

Surgical evacuation-dilatation has for decades been the standard treatment of early pregnancy termination. Surgical management is an invasive procedure and it is associated with complications such as infection, hemorrhage, cervical injury, uterine perforation and Asherman's syndrome. Medical management with a high success rate is therefore a good alternative [4]. However, the limitation of this study is relatively small sample size.

Medical TOP in the late first trimester using the regimen described above has a good success rate. When judged by the efficacy of medical termination in the early part of the first trimester our results are comparable with previous publications [6] [17] [18]. When compared with previous studies of late first semester medical TOPs, the overall complete abortion rate was close to the success rates reported in previous studies [13] [14] [19].

There is some evidence that misoprostol is teratogenic causing an increased risk of Möbius syndrome and terminal transverse limb defects [20]; likewise fetal exposure to both mifepristone and misoprostol is also associated with Möbius syndrome [21]. Prevalence of Möbius syndrome in newborns is estimated somewhere between 1:50,000 and 1:500,000 [22]. It is characterized by the absence or underdevelopment of cranial nerves VI and VII, by which back and forth eye movement and facial expressions are controlled thus resulting e.g. in facial paresis. Möbius syndrome is also described as rhombencephalic maldevelopment [23].

Despite the exposure to mifepristone and misoprostol all the infants in our study were diagnosed as normal and there were no signs of abnormalities during the follow-up period until December 2011 when the researchers were able to follow their growth. Because of ongoing pregnancies we have changed our procedure and nowadays we perform an ultrasound for all patients before they leave our clinic. However, even though there were three ongoing pregnancies and these newborns appeared to be healthy, more information is needed on ongoing pregnancies after medical TOP. This would enable reliable evaluation of the impact of the drugs used in medical TOP on fetus that has been exposed.

Diagnosis of incomplete abortion was primarily based on clinical indications. We believe that we were able to avoid unnecessary curettage, which is often offered to women with any signs of debris in the uterus or moderate ongoing bleeding. Although an ongoing pregnancy after an attempted abortion clearly represents a treatment failure and needs to be addressed, it is extremely likely that ongoing pregnancies will be identified in time. The pregnancy test used in this study was 100% accurate if it was performed, and the women were encouraged to contact the outpatient clinic if they had problems. This suggests that ultrasound is not always necessary, especially if availability is poor as in developing countries [24]. The study findings indicate that women may be able to accurately and safely determine their need for a follow-up visit. However, if there is a possibility that a patient will fail to do the hCG test, ultrasound right after medical TOP seems to be the best option to ensure that the uterus is empty.

5. Conclusion

We conclude that medical termination of pregnancy should be offered routinely to women. It is a safe alternative to surgical method at 9 - 12 weeks' gestation.

Conflicts of Interests

None.

References

[1] WHO (2003) Safe Abortion. Technical and Policy Guidance for Health Systems. Geneva. http://whqlibdoc.who.int/publications/2003/9241590343.pdf

[2] Sedgh, G., Singh, S., Shah, I.H., Åhman, E., Henshaw S.K. and Bankole A. (2012) Induced Abortion: Incidence and Trends Worldwide from 1995 to 2008. *The Lancet*, **379**, 625-632. http://dx.doi.org/10.1016/S0140-6736(11)61786-8

[3] Kulier, R., Kapp, N., Gülmezoglu, A.M., Hofmeyr, G.J., Cheng, L. and Campana, A. (2011) Medical Methods for First Trimester Abortion. *Cochrane Database of Systematic Reviews*, **11**, Article ID: CD002855. http://dx.doi.org/10.1002/14651858.cd002855.pub4

[4] Colleselli, V., Schreiber, C. and Mangesius, S. (2014) Medical Management of Early Pregnancy Failure (EPF): A Re-

trospective Analysis of a Combined Protocol of Mifepristone and Misoprostol Used in Clinical Practice. *Archives of Gynecology and Obstetrics*, **289**, 1341-1345. http://dx.doi.org/10.1007/s00404-013-3105-4

[5] Tendler, R., Bornstein, J. and Kais, M. (2015) Early versus Late Misoprostol Administration after Mifepristone for Medical Abortion. *Archives of Gynecology and Obstetrics*. (In Press) http://dx.doi.org/10.1007/s00404-015-3722-1

[6] von Hertzen, H., Piaggio, G. and Wojdyla, D. (2009) WHO Research Group on Post-Ovulatory Methods of Fertility Regulation. Two Mifepristone Doses and Two Intervals of Misoprostol Administration for Termination of Early Pregnancy: A Randomised Factorial Controlled Equivalence Trial. *BJOG*, **116**, 381-389. http://dx.doi.org/10.1111/j.1471-0528.2008.02034.x

[7] Augustin, G., Majerovic, M. and Luetic, T. (2013) Uterine Perforation as a Complication of Surgical Abortion Causing Small Bowel Obstruction: A Review. *Archives of Gynecology and Obstetrics*, **288**, 311-323. http://dx.doi.org/10.1007/s00404-013-2749-4

[8] Royal College of Obstetricians and Gynaecologists (2001) The Care of Women Requesting Induced Abortion, Evidence-Based Clinical Guideline Number 7. RCOG Press, London. https://www.rcog.org.uk/globalassets/documents/guidelines/abortion-guideline_web_1.pdf

[9] Pazol, K., Zane, S.B., Parker, W.Y., Hall, L.R., Berg, C. and Cook, D.A. (2011) Medical Abortion at 63 to 90 Days of Gestation. *MMWR Surveillance Summaries*, **60**, 1-41.

[10] Løkeland, M., Iversen, O.E., Dahle, G.S., Nappen, M.H., Ertzeid, L. and Bjørge, L. (2010) Medical Abortion at 63 to 90 Days of Gestation. *Obstetrics & Gynecology*, **115**, 962-968. http://dx.doi.org/10.1097/AOG.0b013e3181da0c3e

[11] Woldetsadik, M.A., Sendekie, T.Y., White, M.T. and Zegeye, D.T. (2011) Client Preferences and Acceptability for Medical Abortion and MVA as Early Pregnancy Termination Method in Northwest Ethiopia. *Reproductive Health*, **8**, 19-21. http://dx.doi.org/10.1186/1742-4755-8-19

[12] Ashok, P.W., Hamoda, H., Flett, G.M., Kidd, A., Fitzmaurice, A. and Templeton, A. (2005) Patient Preference in a Randomized Study Comparing Medical and Surgical Abortion at 10-13 Weeks Gestation. *Contraception*, **71**, 143-148. http://dx.doi.org/10.1016/j.contraception.2004.08.013

[13] Hamoda, H., Ashok, P.W., Flett, G.M. and Templeton, A. (2005) A Randomised Controlled Trial of Mifepristone in Combination with Misoprostol Administered Sublingually or Vaginally for Medical Abortion up to 13 Weeks of Gestation. *BJOG*, **112**, 1102-1108. http://dx.doi.org/10.1111/j.1471-0528.2005.00638.x

[14] Hamoda, H., Ashok, P.W., Flett, G.M. and Templeton, A. (2005) Medical Abortion at 9 - 13 Weeks' Gestation: A Review of 1076 Consecutive Cases. *Contraception*, **71**, 327-332. http://dx.doi.org/10.1016/j.contraception.2004.10.015

[15] Patua, B., Dasgupta, M. and Kumar, S. (2013) An Approach to Evaluate the Efficacy of Vaginal Misoprostol Administrated for a Rapid Management of First Trimester Spontaneous Onset Incomplete Abortion, in Comparison to Surgical Curettage. *Archives of Gynecology and Obstetrics*, **288**, 1243-1248. http://dx.doi.org/10.1007/s00404-013-2894-9

[16] Official Statistics of Finland, Health (2011) Induced Abortions. THL—National Institute for Health and Welfare. Statistical Report 21/2012, 1.10.2012.

[17] Oppegaar, K.S., Qvigstad, E., Fiala, C., Heikinheimo, O., Benson, L. and Gemzell-Danielsson, K. (2015) Clinical Follow-Up Compared with Self-Assessment of Outcome after Medical Abortion: A Multicentre, Non-Inferiority, Randomised, Controlled Trial. *Lancet*, **385**, 698-704. http://dx.doi.org/10.1016/S0140-6736(14)61054-0

[18] Shaw, K.A., Topp, N.J., Shaw, J.G. and Blumenthal, P.D. (2013) Mifepristone-Misoprostol Dosing Interval and Effect of Induction Abortion Times: A Systematic Review. *Obstetrics & Gynecology*, **121**, 1335-1347. http://dx.doi.org/10.1097/AOG.0b013e3182932f37

[19] Bracken, H., Ngoc, N.T., Schaff, E., Coyaji, K., Ambardekar, S. and Westheimer, E. (2007) Mifepristone Followed in 24 Hours to 48 Hours by Misoprostol for Late First-Trimester Abortion. *Obstetrics & Gynecology*, **109**, 895-901. http://dx.doi.org/10.1097/01.AOG.0000259319.18958.76

[20] da Silva Dal Pizzol, T., Knop, F.P. and Mengue, S.S. (2006) Prenatal Exposure to Misoprostol and Congenital Anomalies: Systematic Review and Meta-Analysis. *Reproductive Toxicology*, **22**, 666-671. http://dx.doi.org/10.1016/j.reprotox.2006.03.015

[21] Bos-Thompson, M.A., Hillaire-Buys, D., Roux, C., Faillie, J.L. and Amram, D. (2008) Möbius Syndrome in a Neonate after Mifepristone and Misoprostol Elective Abortion Failure. *Annals of Pharmacotherapy*, **42**, 888-892. http://dx.doi.org/10.1345/aph.1K550

[22] Briegel, W. (2006) Neuropsychiatric Findings of Möbius Sequence. *Clinical Genetics*, **70**, 91-97. http://dx.doi.org/10.1111/j.1399-0004.2006.00649.x

[23] Verzijl, H.T., van der Zwaag, B., Cruysberg, J.R. and Padberg, G.W. (2003) Möbius Syndrome Redefined: A Syndrome of Rhombencephalic Maldevelopment. *Neurology*, **61**, 327-333. http://dx.doi.org/10.1212/01.WNL.0000076484.91275.CD

[24] Kaneshiro, B., Edelman, A., Sneeringer, R.K. and Ponce de Leon, R.G. (2011) Expanding Medical Abortion: Can Medical Abortion Be Effectively Provided without the Routine Use of Ultrasound? *Contraception*, **83**, 194-201. http://dx.doi.org/10.1016/j.contraception.2010.07.023