

The role of parity in medical abortion up to 49 days of amenorrhoea

Philippe Lefebvre, Martine Cotte, Nicole Monniez and Gerard Norel

Service d'Orthogénie, Centre Hospitalier de Roubaix, Roubaix, France

ABSTRACT

Objective To identify possible risk factors for failure of medical abortion.

Method Retrospective study of data collected between 1 January 2001 and 31 December 2005, concerning 1850 women who, for medical abortion up to 49 days of amenorrhoea, had received 600 mg oral mifepristone followed 48 h later by 400 µg oral misoprostol and, if necessary, a second oral dose of 400 µg.

Results The method was effective in 97.1% of cases. Fifty four failures (2.9%) were recorded, including seven continuing pregnancies (0.4%). The global efficacy rate of this mifepristone-misoprostol regimen is among the best using similar treatment protocols. The proportion of failures augmented with parity.

Conclusion This study suggests that parity is a major factor influencing the success of medical abortion. A greater parity of the patients was associated with a lower efficacy of treatment.

KEY WORDS Medical abortion, Mifepristone, Misoprostol, Risk factors, Failure, Parity, Human chorionic gonadotrophin (hCG)

INTRODUCTION

Mifepristone for termination of pregnancy (TOP), in association with a prostaglandin, was first licensed and introduced in France in 1988. Since then, it has been approved in 30 other countries. In 2006, the drug combination was included in the 'essential drugs list' of the World Health Organization¹.

Much research has been carried out to define the most effective and best tolerated drug regimens of medical abortion with mifepristone. In particular, the dose of mifepristone and the type, dose and route of administration of the prostaglandin have been studied.

The European Medicines Evaluation Agency (EMA) recently reviewed the conditions for use of mifepristone (Mifegyne®). A European ruling resulting from this review states that, when used in

association with 400 µg of oral misoprostol for TOP up to 49 days' gestation, 600 mg is the approved dosage for mifepristone². However, whatever the protocol applied, there are always failures that require the administration of additional drugs or the use of instrumental evacuation of the uterine cavity.

We intended to identify risk factors for failure of medical abortion by using observational data from routine hospital practice.

METHOD

For this retrospective cohort study, data from women who had an attempted medical abortion up to 49 days

Correspondence: Dr Philippe Lefebvre, Service d'Orthogénie, Centre Hospitalier de Roubaix, 85, rue de Nancy, F-59100 Roubaix, France. Tel: + 33 320 993 230. Fax: + 33 320 993 241. E-mail: philippe.lefebvre@ch-roubaix.fr

of amenorrhoea at the Hôpital de Roubaix between 1 January 2001 and 31 December 2005 were reviewed.

The duration of pregnancy was evaluated by ultrasonographic measurement of the gestational sac and the crown rump length (CRL), usually on the day mifepristone was to be taken. A CRL of 10 mm was used as upper limit for treatment.

The departmental protocol consists of the oral administration of 600 mg of mifepristone, followed 48 h later by the oral administration of 400 µg of misoprostol. In case the products of conception (POC) have not been expelled, a second oral dose of 400 µg misoprostol is administered 3 h later. Expulsion of the POC is verified by the department nurses. All patients are given a follow-up appointment, two weeks ± two days following administration of the misoprostol.

The serum level of human chorionic gonadotrophin (hCG) was determined on the day mifepristone was to be taken and again at the follow-up appointment. The difference between both values was used to assess outcome. The success of the method is defined as a drop in hCG serum levels of at least 90% between D1 and D15, or by the expulsion of POC confirmed macroscopically by the nurses. In case of absence of bleeding, decrease in hCG levels of less than 90% or persistent abundant metrorrhagia, a transvaginal ultrasound is carried out.

Treatment is considered to have failed in case of:

- continuing pregnancy,
- total or partial retention of POC requiring aspiration or, more rarely, repeat administration of misoprostol, and
- need for an emergency curettage.

The success of the method is defined as a complete abortion not requiring any additional treatment.

Six factors possibly influencing success were analysed: age and parity of the woman, duration of the pregnancy, hCG level on the day mifepristone was administered (D1), hCG level at the follow-up appointment (D15), and the dose of misoprostol administered.

The statistical analysis consisted of the comparison of mean values (quantitative variables) or frequencies (qualitative variables) between successful cases and failed cases. The quantitative variables studied were: the age of the patients, the duration of the pregnancy

and the hCG level. For each variable, the mean values were compared using either the *t*-test or the Mann-Whitney *U* test, depending on whether the conditions for use of parametric tests were met or not. The qualitative variables studied were parity and the dose of misoprostol administered. For each variable, frequencies were compared with the chi-squared (χ^2) test. Limit for significance was set at $p=0.05$. For statistical calculations use was made of StatEL software (www.adscience.eu).

RESULTS

During the study period, 2448 medical abortions were attempted. In 179 cases, the outcome could not be verified. In another 419, misoprostol was given 72 h after mifepristone and these were classified as protocol deviations. Both these groups were therefore excluded. In total the data of 1850 patients were suitable for analysis; there were 1796 (97.1%) successes and 54 (2.9%) failures. Among the 54 failures, 7 (0.4%) had an ongoing pregnancy and 42 (2.3%) had retained POC. Four women required emergency surgical treatment (three for haemorrhage and one for intense pain), and one patient was lost to follow-up: these five cases were considered failures since their hCG on D15 was higher than on D1.

For the 419 patients who were *not* treated according to the protocol, the outcome was significantly different: in 383 cases (91.4%) the treatment was successful, whereas in 36 cases (8.6%) it failed ($\chi^2 = 28.9$; $p < 0.000001$) (Table 1). This observation

Table 1 Medical abortion: overall results

	Number of cases	Success n (%)	Failure n (%)	χ^2
Misoprostol 48 h after mifepristone	1850	1796 (97.1%)	54 (2.9%)	
Misoprostol 72 h after mifepristone	419	383 (91.4%)	36 (8.6%)	28.9; $p <$ 0.000001
Excluded (lost to follow-up)	179			
Total number of patients	2448			

confirms how important it is to keep to a 48 h interval between the administration of mifepristone and that of misoprostol.

Influence of age

The age ranged from 14–47 years in the sample. The mean age of women whose TOP was successful (27.2 ± 7.2) differed significantly from that of women in whom it failed (30.8 ± 6.5 ; $p < 0.000078$) (Figure 1). However, age is strongly linked to parity. To determine whether parity or age, independently from each other, influenced the result, a multivariate analysis was carried out.

Women who failed to abort in accordance with the protocol were studied separately, taking their parity (0, 1, 2–3, and 4 or more) into account (Table 2). No significant difference was found between the mean age of patients successfully treated and the mean age of those who were not, when parity was taken into account.

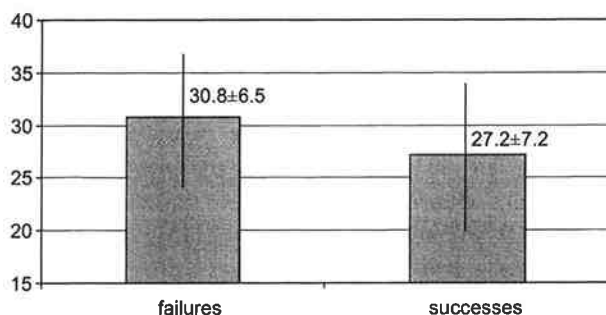


Figure 1 Mean age (\pm SD) of patients successfully treated vs. that of women in whom the attempted medical abortion failed ($p < 0.000078$).

Table 2 Mean age and parity of patients successfully treated vs. those of women in whom the attempted medical abortion failed

Parity	Successful treatment		Failed treatment		p
	Number of women	Mean age \pm SD	Number of women	Mean age \pm SD	
0	861	22.6 \pm 4.8	12	24.7 \pm 4.1	NS (M&W)
1 to 3	809	30.8 \pm 6.2	31	31.8 \pm 6.1	NS (t-test)
4 and more	126	35.9 \pm 5.0	11	34.7 \pm 5.6	NS (t-test)

SD, standard deviation; NS, not significant; M&W, Mann-Whitney *U* test.

Influence of parity

Initially, the χ^2 test was meant to be used, to compare frequencies of representation of the following parities among successful and failed cases: P0 (nulliparity), P1, P2, P3 and P4+ (four and more previous deliveries). However, the number of P4+ women relative to those of P0, P1, P2 and P3 was too small for the corresponding results to be meaningful. Consequently, results were compared differently (Table 3):

- P0 (nulliparous: 1.4% failures) versus P+ (parity ≥ 1 : 4.3% failures) ($p < 0.0002$),
- P0 (nulliparous: 1.4% failures) versus P1 (one delivery in the past: 3.6% failures) ($p < 0.012$)
- P0 (nulliparous: 1.4% failures) versus P1–2–3 (one, two or three previous deliveries: 3.7% failures) ($p < 0.0022$),
- P1–2–3 (1, 2 or 3 previous deliveries: 3.7% failures) versus P4+ (four and more previous deliveries: 8% failures) ($p < 0.02$).

It thus appears that the efficacy of the protocol starts to decrease in a significant manner for women who had at least one delivery. The failure rate increases with parity; in women with four children or more, it is six-fold that of those who never delivered. However, there were no significant differences in success rates and failure rates between women of P1, P2 and P3 (Figure 2).

Influence of gestational length

According to our protocol of medical abortion, mifepristone had to be taken not later than at 49 days of amenorrhoea. The mean pregnancy duration in successfully treated cases (42.5 ± 4.6 days) did not

significantly differ from that of failures (43.6 ± 4.7 days).

hCG level

Influence of the hCG serum level on D1

The concentration of hCG on D1 (at the time mifepristone was taken) ranged from 117 to 300 000 IU/L. The mean hCG concentration on D1 of women successfully treated ($37\,371 \pm 30\,134$ IU/L) did not differ from that of patients who failed to abort

($46\,054 \pm 39\,674$ IU/L) (Figure 3). However, the spread of the values is so wide that it could mask a possible difference between these two groups. To account for this wide variance in hCG concentrations, we looked at the logarithms of the hCG values: log(hCG) on D1 ranged from 1.43–5.48. The t-test showed that, for patients successfully treated according to the protocol, the mean log(hCG) on D1 (4.40 ± 0.45) did not significantly differ from that of women who failed to abort (4.45 ± 0.54).

Influence of the hCG serum level on D15

As the serum levels, which were logged for 1393 patients, varied widely, we carried out a logarithmic analysis. The mean log(hCG) on D15 of women successfully treated according to the protocol (1.70 ± 0.80) differed significantly from that of patients who failed to abort (3.63 ± 0.64) ($p < 0.00001$). This large range of values hinted that a threshold level for hCG at D15 may exist, beyond which failure would be confirmed in all cases. To prove this, we built a ROC (Receiver Operating Characteristics) curve³, using ‘hCG concentration at D15’ as a diagnostic variable (Figure 4). The area under this ROC curve (AUC) is 0.948 ± 0.028 and the black dot marks the threshold value at which the diagnostic test separates successes from failures best. As a test which discriminates perfectly has an AUC of 1, we can consider that this variable performs quite well in this regard. The threshold value corresponds to a hCG level on D15 of 1020 IU/L, with a sensitivity of 0.875 and a specificity of 0.947 (Table 4).

Table 3 Comparison of frequencies distribution between success and failure groups, according to parity (χ^2 test)

Parity	Frequencies		χ^2	p
	Successful treatment	Failed treatment		
P0	861	12	13.9	<0.0002
P+	935	42		
P0	861	12	6.27	<0.012
P1	318	12		
P0	861	12	9.4	<0.0022
P1-2-3	809	31		
P1	318	12	0.007	NS
P2	313	12		
P3	178	7		
P1-2-3	809	31	5.39	<0.02
P4+	126	11		

NS, not significant.

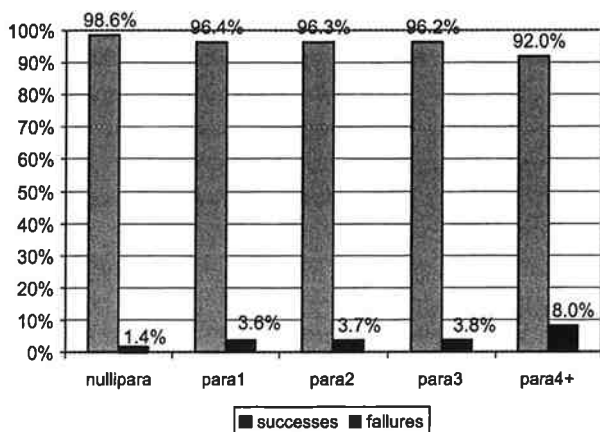


Figure 2 Influence of parity on the success rate of medical abortion.

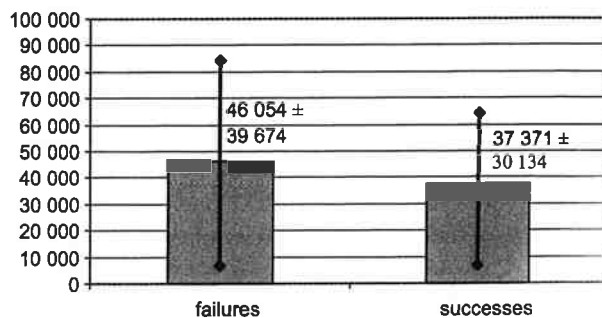


Figure 3 Comparison of the mean hCG serum level (IU/L \pm SD) on D1 in women successfully treated with that of women in whom medical abortion failed.

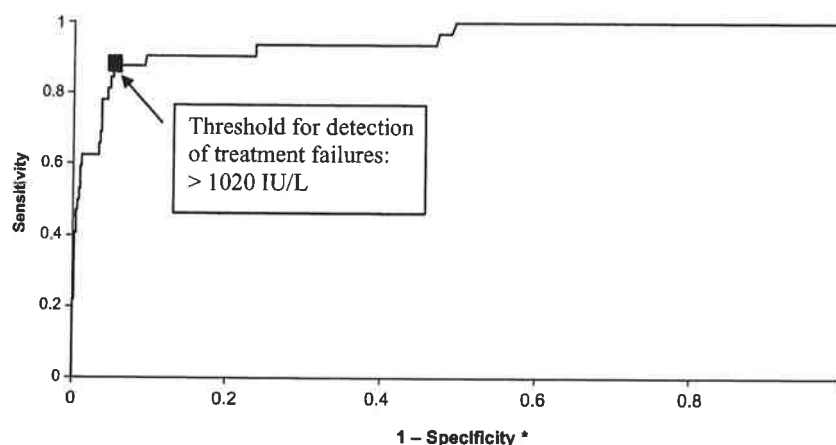


Figure 4 ROC curve for detection of failures by means of determination of the hCG serum level on D15 (area under the curve = 0.948 ± 0.028). *Note: the abscissa (x-axis) of a ROC curve indicates (1 - Specificity) in order to reach the upper-left corner of the graph when the diagnostic test combines high sensitivity and high specificity.

Table 4 Diagnostic indices for a threshold value of hCG concentration on D15 (1020 IU/l)

Number of studied subjects	1393
Test precision	0.945
Sensitivity of diagnostic test	0.875 (95% CI: 0.760–0.990)
Specificity of diagnostic test	0.947 (95% CI: 0.870–0.959)

Test precision: proportion of cases correctly diagnosed by the test.

Sensitivity: proportion of failures correctly identified by the diagnostic test.

Specificity: proportion of successes correctly identified by the diagnostic test.

CI, confidence interval.

Influence of hCG variation between D1 and D15

We then analysed the variation of hCG between D1 and D15. As we had done for the hCG level on D15, we built a ROC curve with 'percentage of hCG variation between D1 and D15' as a diagnostic variable (Figure 5). The area under this ROC curve is 0.951 ± 0.027 and the black dot mark the threshold value at which the diagnostic test discriminates best between successes and failures. It corresponds to a change in hCG between D1 and D15 of -93.5%, with a sensitivity of 0.813 and a specificity of 0.974 (Table 5).

Misoprostol dose

Twenty-eight patients (1.5%) did not receive misoprostol because abortion had already taken place

before admission to hospital. As a result, no additional treatment was required for any of these women; uterine vacuity was confirmed by ultrasound.

Six hundred and sixty-two women (35.7%) aborted after one dose of 400 μ g of misoprostol.

Thirty-five women (1.9%) were discharged from the hospital before the three hour assessment could be made; despite there being no evidence that abortion had taken place they did not receive a second dose of misoprostol.

A second dose of misoprostol was given to 1149 women (62.1%).

Of the 673 patients (36.4%) who received a single dose of misoprostol, 11 women (1.6%) required additional treatment to complete the abortion, including one emergency aspiration curettage for haemorrhage.

In the group that received two doses of misoprostol ($n=1149$), 43 (3.7%) were classified as failures for having required aspiration curettage, including two for heavy bleeding and one for severe pelvic pain following misoprostol administration.

In 28% of the cases, expulsion occurred outside the hospital.

DISCUSSION

In spite of its retrospective character, this study is useful in that it includes 1850 patients, who were treated by an experienced team according to a consistent and well defined protocol. The overall success rate of treatment in women from this cohort

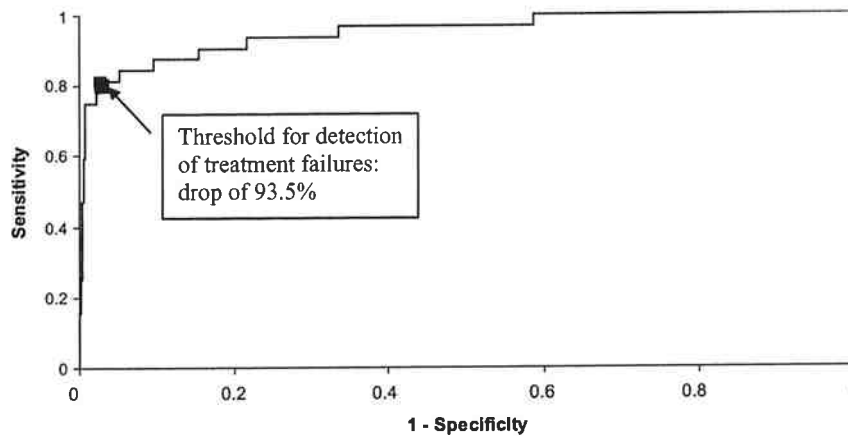


Figure 5 ROC curve for detection of failures by means of determination of the difference between hCG serum levels on D1 and D15 (area under the curve = 0.951 ± 0.027).

Table 5 Diagnostic indices for threshold value: decrease of 93.5% between the hCG serum levels on D1 and D15

Number of studied subjects	1393	
Test precision	0.9698	
Sensitivity of diagnostic test	0.8125	95% CI: 0.6773–0.9477
Specificity of diagnostic test	0.9735	95% CI: 0.9179–0.9821

was 97.1% which is at the upper end of the range of efficacy (90–99%) found in the literature for studies using similar treatment protocols (Table 6).

The study showed greater parity to be a risk factor for a lesser efficacy of the treatment. A similar correlation was reported in other studies in which 600 mg mifepristone followed by 400 µg oral misoprostol were given for medical abortion up to 49 days gestation. Both increasing gravidity¹² and parity¹⁰ have been shown to be linked to more frequent failures of treatment. The relationship has also been demonstrated in studies concerning 1st and 2nd trimester abortions induced by low doses of mifepristone in association with either gemeprost^{12,13} or misoprostol given vaginally¹⁴. Possibly the myometrium in young nulliparae is more receptive to prostaglandins and its contractility greater.

The serum level of hCG is correlated with the duration of the pregnancy. It doubles every two to three days between the 4th and 8th weeks of amenorrhoea. High hCG serum levels on the day of administration of mifepristone seem to be more

Table 6 Studies with similar protocol: mifepristone 600 mg followed by misoprostol orally

Study	Misoprostol dose µg	N	Complete abortion (%)	Ongoing pregnancy (%)
Peyron et al. 1993 ⁴	400	488	96.9	0.8
Aubeny et al. 1995 ⁵	400*	385	98.7	0.5
Winikoff et al. 1997 ⁶	400*	487	95.5	1.2
Spitz et al. 1998 ⁷	400	753	94.6	NA
Aubeny & Chatellier 2000 ⁸	400**	827	92.0	1
Aubeny 2001 ⁹	400**	119	99.0	0
Wiebe et al. 2002 ¹⁰	400**	1973	98.4	0.02
Faucher et al. 2005 ¹¹	400**	524	90.5	0
	400	339	93.8	0.6

*In these studies, a second dose of misoprostol 200 µg was administered in case the POC had not been expelled 3 h after the first dose.

**In these studies, a second dose of misoprostol 400 µg was administered in case the POC had not been expelled 3 h after the first dose.

frequently found in women in whom the method ultimately fails. However, gestational age was limited to less than 50 days of amenorrhoea in this study and, with regard to this index, no significant difference was

detected between women successfully treated and those whose medical abortion failed.

In our series, all patients received 600 mg of mifepristone, followed by an initial dose of 400 μ g of misoprostol. Giving a second dose of misoprostol after 3 h probably increases the likelihood that expulsion of POC occurs during the period of hospitalization; however, the retrospective, non-comparative nature of this study precludes any conclusion about the value of administration of this second dose in terms of overall efficacy. The literature on this subject is contradictory^{5,9}. One recent study demonstrated that administration of a second misoprostol dose may reduce the risk of continuing pregnancy, but the dose of mifepristone given before misoprostol was only 200 mg¹⁵.

A medical abortion is considered successful when not requiring surgical evacuation of retained POC before the following menstruation occurs. Ultrasound based diagnostic imaging and the monitoring of hCG levels are the two tools that enable complete abortion to be confirmed.

By means of a ROC curve we demonstrated the existence of a threshold value on D15 of about 1000 IU/l hCG, below which treatment can be considered to have been successful. Above this value, an ultrasound will be needed to rule out the retention of POC. Thus, a single hCG measurement on D15 may be used as a diagnostic test for success.

Another ROC curve shows that a 93.5% decrease of hCG between D1 and D15 is a threshold value differentiating successes from failures of medical abortion. Determination of the drop in hCG between D1 and D15 offers an alternative diagnostic tool for assessment of outcome, but it requires two hCG measurements.

The comparison of baseline and follow-up hCG serum levels is a simpler and more reliable indicator than ultrasound evaluation, which is operator dependent^{16,17}.

One should keep in mind that the failure of medical abortion is not defined in the same way in all studies. The means used to verify the efficacy of treatment have an influence on the results¹⁸. If ultrasound is used, some consider that only ongoing pregnancies or the presence of a persistent gestational sac should be seen as failures¹⁹.

Evaluation of the endometrial thickness and interpretation of non homogeneous contents of the uterine cavity are difficult, and should not dictate clinical intervention. The decision to treat should be based on the presence of a persistent gestational sac or compelling clinical signs and symptoms¹⁶.

CONCLUSION

This large retrospective cohort study has shown that parity, especially above three, reduces the efficacy of medical abortion up to 49 days gestation by the oral administration of 600 mg mifepristone followed 48 h later by 400 μ g misoprostol.

The risk of failure of medical abortion when parity exceeds three has implications for patients' counselling and may influence their choice of method, especially if a surgical method (vacuum aspiration) is more likely to be successful.

The decrease of serum hCG levels within two weeks after treatment to less than 10% of the initial value, is a reliable diagnostic feature of the completeness of the medical abortion.

A threshold value was identified which may support developing a lighter and more cost-effective follow-up protocol using a single hCG measurement.

To refine and confirm the indices likely to influence the outcome of medical abortion up to 49 days amenorrhoea, a *prospective* study of women undergoing this procedure is in progress in several centres of the Nord-Pas de Calais region in France.

ACKNOWLEDGEMENTS

Special thanks to Dr Marie Duriez for her contribution in the development and monitoring of this study, and to Mr Stephane Herault, AD-Science, who verified the statistical analysis.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

1. World Health Organization. *Model list of essential medicines*, 14th ed. Geneva: WHO. <http://mednet3.who.int/EMLib/>
2. European Medicines Evaluation Agency: <http://www.emea.eu.int/pdfs/human/press/pr/13270607en.pdf>

3. Hanley JA, McNeil BJ. Method for comparing the area under two ROC curves derived from the same cases. *Radiology* 1983;148:839-43.
4. Peyron R, Aubeny E, Targosz V, et al. Early pregnancy interruption with RU 486 (mifepristone) and the orally active prostaglandin misoprostol. *N Engl J Med* 1993; 328:1509-13.
5. Aubeny E, Peyron R, Turpin CL, et al. Termination of early pregnancy (up to 63 days of amenorrhea) with mifepristone and increasing doses of misoprostol. *Int J Fertil Menopausal Stud* 1995;40(Suppl. 2):85-91.
6. Winikoff B, Sivin I, Coyaji KJ, et al. Safety, efficacy, and acceptability of medical abortion in China, Cuba, and India: A comparative trial of mifepristone-misoprostol vs. surgical abortion. *Am J Obstet Gynecol* 1997;176: 431-7.
7. Spitz IM, Bardin CW, Benton L, Robbins A. Early termination of pregnancy with mifepristone (RU486) and the orally active prostaglandin misoprostol. *New Engl J Med* 1998;21:1509-13.
8. Aubeny E, Chatellier G. A randomized comparison of mifepristone and self-administered oral or vaginal misoprostol for early abortion. *Eur J Contracept Reprod Health Care* 2000;5:171-6.
9. Aubeny E. A two-stage increase in the dose of misoprostol improves the efficacy of medical abortion with mifepristone and prostaglandins. *Eur J Contracept Reprod Health Care* 2001;6:54-5.
10. Wiebe L, Dunn S, Guilbert E, et al. Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. *Obstet Gynecol* 2002;99:813-9.
11. Faucher P, Baunot N, Madelenat P. The efficacy and acceptability of mifepristone medical abortion with home administration misoprostol provided by private providers linked with the hospital: a prospective study of 433 patients. *Gynecol Obstet Fertil* 2005;33:220-7.
12. Bartley J, Tong S, Everington D, Baird DT. Parity is a major determinant of success rate in medical abortion: a retrospective analysis of 3161 consecutive cases of early medical abortion treated with reduced doses of mifepristone and vaginal gemeprost. *Contraception* 2000;62: 297-303.
13. Tang OS, Thong K-J, Baird DT. Second trimester medical abortion with mifepristone and gemeprost: A review of 956 cases. *Contraception* 2001;64:29-32.
14. Child TJ, Thomas J, Rees M, MacKenzie IZ. A comparative study of surgical and medical procedures: 932 pregnancy terminations up to 63 days gestation. *Human Reprod* 2001;16:67-71.
15. Coyaji K, Krishna U, Ambardekar S, et al. Are two doses of misoprostol after mifepristone for early abortion better than one? *BJOG* 2007;114:271-8.
16. Cowett AA, Cohen LS, Lichtenberg ES, Stika CS. Ultrasound evaluation of the endometrium after medical termination of pregnancy. *Obstet Gynecol* 2004;103: 871-5.
17. Harwood B, Meckstroth KR, Mishell DR Jr, Jain JK. Serum beta-human chorionic gonadotrophin levels and endometrial thickness after medical abortion. *Contraception* 2001;63:255-6.
18. Haimov-Kochman R, Arbel R, Sciaky Tamir Y, et al. Risk factors for unsuccessful medical abortion with mifepristone and misoprostol. *Acta Obstet Gynecol Scand* 2007;86:462-6.
19. Fiala C, Safar P, Bygdeman M, Gemzell-Danielsson K. Verifying the effectiveness of medical abortion: Ultrasound versus hCG testing. *Eur J Obstet Gynecol Reprod Biol* 2003;109:190-5.