

# **Guideline for the treatment of women undergoing termination of pregnancy**

Dutch Association of Abortion Specialists (NGvA)  
[www.ngva.net](http://www.ngva.net)

# **Guideline for the treatment of women undergoing termination of pregnancy**

## ***Initiative***

Dutch Association of Abortion Specialists (NgvA)

## ***Supported by***

Dutch Order of Medical Specialists (OMS)

## **Funding**

The development of this guideline was financially supported by a grant from the Dutch Ministry of Health, Welfare and Sport to the Dutch Association of Abortion Specialists, for the purpose of stimulating the quality of abortion care in The Netherlands.

## **Colophon**

'Guideline for the treatment of women undergoing termination of pregnancy'  
translated by Joop Hoekstra © 2011

Original title: 'Richtlijn behandeling van vrouwen die een zwangerschapsafbreking ondergaan' © 2011

Nederlands Genootschap van Abortusartsen (Dutch Association of Abortion Specialists)

Mercatorlaan 1200

NL-3528 BL Utrecht

The Netherlands

Tel. +31(0)30-2823823

Email: [secretariaat@ngva.knmg.nl](mailto:secretariaat@ngva.knmg.nl)

Website: <http://www.ngva.net/>

## **All rights reserved**

The text in this publication may not be multiplied, stored in a digital data base, or made public in any form or format, whether electronically, or mechanically (by photocopying or in any other manner), unless the prior permission of the editor was granted. Permission for the use of (part of) this text may be obtained from the editor by mail or email exclusively. For mail and email addresses: see above.

## Recommendations: an overview

Below is a summary list of all recommendations from the monodisciplinary guideline 'Treatment of women undergoing termination of pregnancy'.

What is the most efficient and effective method in first trimester termination of pregnancy?

Where a surgical method is preferred, the study group considers vacuum aspiration as the first choice, in view of the low percentage of complications.

Are there any differences in success rate, patient contentment or the number of complications between first trimester surgical termination of pregnancy and medical termination of pregnancy?

A woman with an amenorrhoea length under 63 days must be informed about the treatment options: surgical or medical.

A woman must be informed about the differences between both forms of treatment; it must be made clear to her that medical termination of pregnancy takes more time and has a higher risk of complications, such as continuing pregnancy, incomplete abortion and bleeding, compared to surgical termination of pregnancy.

What evidence can be inferred from the (inter)national literature for the application of priming by prostaglandins and their administration route in first trimester termination of pregnancy?

Routine priming of the cervix with prostaglandins (e.g. misoprostol) has no added value in first trimester surgical termination of pregnancy.

What is the most efficient and effective medical treatment in first trimester termination of pregnancy?

Women with amenorrhoea under 63 days must be informed about the treatment options open to them: surgical or medical.

Women must be informed about the differences between both treatment courses and be told that medical termination of pregnancy takes longer and has a higher risk of complications, such as continuing pregnancy, incomplete abortion, and haemorrhage, compared to surgical termination of pregnancy

The preferred medical intervention is by 200 mg mifepristone orally followed up by a minimum of 800 mcg misoprostol vaginally

An interval of eight to seventy-two hours between the administration of mifepristone and misoprostol should preferably be maintained.

For this indication, the recommended dosages of mifepristone and misoprostol, have not been registered; neither has the administration protocol. It is therefore a legal requirement to inform the woman about this, preferably in writing.

The importance of follow-up checks must be emphasized - also in writing - because even after severe haemorrhages it cannot be excluded that the pregnancy is still intact. Follow-up must take place after one to four weeks, depending on the stage of the pregnancy at the start of the intervention.

In the case of a continuing pregnancy or incomplete expulsion of the amniotic sac after medical treatment, suction curettage is offered as a rule. A second medical termination procedure may be considered at follow-up after one week.

What is the optimal method for termination of pregnancy in the second trimester of pregnancy?

For women in their second trimester of pregnancy, D&E is recommended for use in abortion clinics.

In hospitals, women should be offered a choice between medical termination of pregnancy and D&E; for the latter option, the woman should be referred to an abortion clinic.

The study group recommends the institution of a national working group to develop a registration system for late complications of second trimester termination of pregnancy.

What evidence can be derived from the (inter)national literature with respect to the application of priming with prostaglandins and their course of administration in first trimester termination of pregnancy?

Cervical priming by misoprostol in the first trimester is recommended.

Is it possible to use misoprostol combined with D&E after a sectio caesarea?

It is recommended to apply D&E, with misoprostol priming if necessary, for second trimester termination of pregnancy in the case of women with one low transversal C-section in their anamnesis.

Which genital bacterial infections are common in women undergoing termination of pregnancy and how should they be treated?

As Chlamydia trachomatis is most common among women between 15 and 25, it is recommended to treat them prophylactically for this condition after a surgical termination of pregnancy.

What antibiotic policy should be preferred in the case of surgical termination of pregnancy?

After surgical termination of pregnancy, it is recommended to administer 1.000 mg azithromycin as a prophylaxis to the patient on the same day.

When there is a suspicion of bacterial vaginosis four times 500 mg metronidazol is to be prescribed.

What antibiotic policy should be preferred in the case of medical termination of pregnancy?

The study group takes the position that antibiotic prophylaxis in medical termination of pregnancy is not necessary.

When should ultrasound scanning be applied in termination of pregnancy?

What is the function of ultrasound scanning in establishing the diagnosis of pregnancy?

In termination of pregnancy ultrasound must be employed to establish the diagnosis of pregnancy, multi-foetal pregnancy and abnormal pregnancy.

What is the role of ultrasound in determining pregnancy length?

Pregnancy length must always be determined by ultrasound and be documented. Ultrasound will also show if there is a vital intra-uterine pregnancy inside a normal uterus.

What is the role of ultrasound during surgical termination of pregnancy?

Pre-operative abdominal ultrasound scanning must be used in the case of complex interventions (like deviant positioning, congenital abnormalities, pathology) and in surgical abortion in the second trimester.

The use of ultrasound scanning during first and second trimester interventions is appropriate

Macroscopic inspection of the curettement must be carried out.

What is the role of ultrasound scanning after surgical termination of pregnancy?

There are good reasons to carry out ultrasonography at the conclusion of the

treatment, to exclude the presence of retained tissue.

It is advisable to conduct ultrasound scanning when new or lingering complaints are observed during the period of time after the termination of pregnancy, such as severe abdominal pain, loss of too much blood or continuing haemorrhage.

If a woman has no complaints after a termination of pregnancy, ultrasound scanning has little added value. Generally, no abnormalities are found.

If the pregnancy test is still positive after four weeks, it is necessary, however, to conduct ultrasonography.

What is the role of ultrasound after medical termination of pregnancy

It is advisable to carry out a sonography after a medical termination of pregnancy, in the case of continuing abdominal pains, excessive blood loss or prolonged bleeding, or continuing symptoms of pregnancy.

It is advisable to carry out sonography at one to four weeks after a medical termination of pregnancy, depending on the stage of the pregnancy.

When must rhesus factor determination take place and what is the treatment in the case of Rh-?

Up to 7/0 weeks (49 days) of amenorrhoea there is no need to administer anti-d immunoglobulin.

Starting at 7/0 weeks (49 days) of amenorrhoea Rh(D) negative women undergoing termination of pregnancy must be protected with an adequate dose of anti-d, of 250 IE in the first and 375 IE in the second trimester, with the exception of already isosensitized women.

## **Composition of the study group**

- P. Hanewald MD (chair), abortion specialist, NGvA
- Ms.M. Denteneer MD, abortion specialist, NGvA
- Ms.Talens MD, abortion specialist, NGvA
- J.R. Soedirman MD, (formerly) NGvA
- L. Querido MD, abortion specialist, NGvA (until July 2010)
- W. Shadmanfar MD, abortion specialist, NGvA
- Ms. M. van Kleffens MD, abortion specialist, NGvA
- Ms. E. Bonsen MD, abortion specialist, NGvA

Supported on the part of OMS by

- Ms. J.W. Hagemeyer MSc, senior consultant, OMS, Utrecht
- Ms. Wessels MSc, information specialist, OMS, Utrecht

# Table of contents

	Chapter 1 Introduction.....	10
	1.1 Background.....	10
	1.2 Objective of this guideline.....	10
	1.3 Target group.....	11
5	1.4 Procedure .....	11
	1.5 Conflict of interests / independence of study group members .....	14
	1.6 Legal implications of guidelines.....	14
	1.7 Review .....	15
	1.8 References.....	15
10	Chapter 2 First trimester termination of pregnancy .....	16
	Chapter 3 Second trimester termination of pregnancy.....	50
	Chapter 4 Antibiotic policy .....	80
	Level 3.....	98
	Level 3.....	100
15	Level 3.....	100
	Level 2.....	104
	Level 3.....	104
	Level 3.....	104
	Level 2.....	108
20	Level 3.....	108
	Level 3.....	112
	Level 3.....	112
	Level 3.....	113
	Chapter 6 Rhesus factor .....	117
25	Appendix 1 Search strategy.....	127
	Appendix 2 Terms and definitions.....	135
	Appendix 3 Statement of interests.....	137
	Appendix 4 Evidence tables.....	139



# Chapter 1 Introduction

## **1.1 Background**

Approximately 33,000 abortions take place in The Netherlands each year. In our country, termination of pregnancy is regulated by law. The Termination of Pregnancy Act (Waz (1984)) is the most important legal rule, specifying the framework in which the intervention may be carried out.

The Netherlands can be ranked among the countries with the lowest abortion figures worldwide (Netherlands Health Inspectorate, 2009).

The law was evaluated in 2005 (Visser et al., 2005). It was concluded that the Waz is generally well respected, a view shared by the inspectorate; this also applies to the heart of the legal rule, the various aspects of the decision making process. The overall balance between a woman's right to assistance and the protection of unborn life that the legislators had in mind is borne out in practice. The quality of the care delivered is good, but may be further improved; recommendations were made for improving the quality in referrals, counselling and decision making (Visser et al, 2005; p. 183-186). On the basis of this evaluation, the government saw no reason to adapt the law and endorsed most recommendations (Parliamentary Papers II 2005/06, 30 371, nr. 2).

The Dutch Association of Abortion Specialists (NGvA) received funding from the Ministry of Health, Wellness and Sport for a period of four years starting in 2008, to stimulate the quality of abortion care, by developing and realizing, i.e., an integrated quality policy. An important part of the project plan under funding is the development of a number of evidence-based guidelines. Second in this series is the current guideline "Treatment of women undergoing termination of pregnancy".

## **1.2 Objective of this guideline**

The object of the guideline is to improve the quality of abortion care by optimizing the treatment of women undergoing termination of pregnancy. Thus, the guideline is designed to function as a directive for a uniform care offer in the treatment of women undergoing a termination of pregnancy in The Netherlands.

### **1.3 Target group**

This guideline is primarily intended for abortion specialists involved in performing terminations of pregnancy. In addition, this guideline is also directed at all care providers involved in the treatment of women undergoing termination of pregnancy, in particular: general practitioners, gynaecologists, nurses, (medical) psychologists and social workers. As a secondary objective this guideline may also serve as information document for policy makers and funding agencies involved in this particular care offer.

### **1.4 Procedure**

#### *Composition and working method of the study group*

For the development of this guideline a monodisciplinary study group of abortion specialists was instituted by the NGvA Board in 2009. Members were mandated by the NGvA to take part. The study group participants share responsibility for this guideline. Gynaecologists were asked to supply their critical comments in the final stages of its drafting.

#### *Guiding questions*

1. What is the most efficient and effective treatment for termination of pregnancy in first trimester pregnancies, either surgical, medical or by mixed approach?
2. What is the most effective an efficient treatment for termination of pregnancy in second trimester pregnancies, either surgical, medical or by mixed approach?
3. What is the appropriate antibiotic policy for each method of treatment and in either phase of the pregnancy?
4. What circumstances make it necessary to apply ultrasound scanning before termination of pregnancy?
5. What circumstances make it necessary to determine a woman's Rhesus Factor and what is the treatment for RH-negative women?

This guideline does not discuss the technical aspects of the surgical method(s) for termination of pregnancy. Neither will the subjects of other guidelines, specifically counselling, pain management and aftercare, be treated here; the relevant guidelines have been - or will be - developed

separately. When the current guideline reached the final stage, it became clear that (too) little attention was paid to late(r) complications. It is suggested that this issue be addressed by a joint study group of gynaecologists and abortion experts in the near future.

#### *Method of guideline development*

This guideline was drafted following the “Appraisal of Guidelines for Research & Evaluation” (AGREE) ([www.agreecollaboration.org](http://www.agreecollaboration.org)). This instrument is a widely (and internationally) accepted instrument for judging the quality of guidelines.

The study group worked on the creation of the draft guideline for two years. Desktop searches were undertaken and group members assessed the content and quality of the literature. As a next step the study group members would write a section for the guideline, in which the relevant literature had been incorporated. If no relevant scientific literature was available the text was written on the basis of the group members’ own expertise. During meetings the texts were elucidated and discussed. Next, texts were edited by the editing committee and then finalized in a plenary session. The Department of Professional Quality Support of the Dutch Order of Medical Specialists supported and made recommendations to the study group.

#### *Strategy for literature search and assessment*

First, a quick scan was carried out of existing guidelines in Dutch or English and of the databases of the National Guideline Clearinghouse (<http://www.guideline.gov/>), NICE (<http://www.nice.org.uk/>), SIGN (<http://www.sign.ac.uk/>) and of the Medical Reference Organisation for quality of care CBO (<http://www.cbo.nl/thema/Richtlijnen/>). In addition, the SUM Search search engine (<http://sumsearch.uthscsa.edu/>) was used to trace guidelines in Dutch or English. Finally, systematic reviews in de Cochrane Library were identified. Next, for each of the initial questions the Medline electronic databases (OVID) (1967-2008) were browsed on the basis of specific browsing terms for scientific studies published in Dutch or English. Furthermore, an additional search “by hand” was undertaken for studies in Dutch or English taking the literature lists of the articles identified as a starting point. As a first step (systematic reviews or meta-analyses of) randomized controlled studies (RCTs) were focused on. If more than one systematic review was available, the most recent was chosen. Where RCTs were not available the search was widened to include prospective controlled studies, comparative studies, prospective non-comparative and retrospective studies.

The articles selected were then assessed by study group members on their applicability, the quality of the research, and finally graded for degree of evidence. For this purpose the division as shown in table 1 was used.

In studying and interpreting the results of scientific research the study group members were frequently confronted with problems. Sometimes hardly any, or only obsolete literature could be found on a particular topic. The quality of the literature varied, with some studies falling short of current quality standards; the populations under study were sometimes very small, rendering the validity of the results questionable. Besides, termination of pregnancy is an intervention which is valued differently in different cultures, causing the results of the studies to be hard or impossible to transfer to the Dutch situation.

**Table 1. Classification of the methodological quality of individual studies**

<b>Evidence level</b>	<b>Intervention study</b>	<b>Diagnostic accuracy study</b>	<b>Impairment or side-effects, aetiology, prognosis</b>
<b>A1</b>	Systematic review / meta-analysis of at least 2 studies independently carried out		
<b>A2</b>	Randomized double blind comparative clinical study of good quality and adequate size	Study in relation to a reference test ('golden standard') with cut off values defined beforehand and independent assessment of the results, with a sufficiently large series of consecutive patients who all underwent both index and reference test	Prospective cohort study of adequate size and follow-up, adequately checked for 'confounding' and with selective follow-up sufficiently excluded.
<b>B</b>	Comparative study but not with all the features mentioned under A2 (also case-control study, cohort study)	Study by reference test method, but lacking some of the features mentioned under A2	Prospective cohort study, but lacking some of the features mentioned under A2 or retrospective cohort study or case-control study
<b>C</b>	Non-comparative study		
<b>D</b>	Expert opinion		

**Table 2. Level of evidential value of the conclusions based on the evidence underlying the conclusion**

<b>Level</b>	<b>Conclusion based on</b>
<b>1</b>	Research at level A1, or at least 2 studies at level A2 carried out independently
<b>2</b>	1 study at level A2 ,or at least 2 studies at level B carried out independently
<b>3</b>	1 study at level B or C

*Drafting of recommendations*

The 'recommendations' were phrased in reply to each guiding question and were based both on data from scientific studies and on the study group's most important deliberations. In their deliberations the validity of the literature selected and its applicability to the Dutch situation were discussed. The patients' preference, availability of the facilities and organisational aspects also played a role.

*Implementation and evaluation*

In the various stages of guideline development the implementation of the guideline and the practicability of the recommendations were taken into account. Explicit attention was given to factors which may promote or impede the introduction of this guideline in practice.

This guideline is only available in digital format and was distributed among all relevant professional groups and all abortion clinics and hospitals. The document can also be downloaded from the website of the Dutch Association of Abortion Specialists ([www.ngva.nl](http://www.ngva.nl)). This guideline is intended to be used for the development or evaluation of local protocols. The guideline is not intended as a list of points for attention or checklist in decision making.

**1.5 Conflict of interests / independence of study group members**

Declarations by the members of the study group about potential (economic) conflicts of interest are open to inspection and can be viewed at the Department of Professional Quality Support of the Dutch Order of Medical Specialists; an overview has been added in appendix 3. No conflict of interest was reported.

**1.6 Legal implications of guidelines**

Guidelines contain recommendations based on a maximum of scientific evidence. Recommendations are part of the ambition to provide good or 'optimal' quality care. As these recommendations are based on 'general proof of optimal care' and the study group's relevant insights brought up by its members, professionals may deviate from this guideline in individual cases where appropriate. If the patient's situation demands, such a deviation may even be absolutely necessary. There must be good arguments for such a step, however; it must be well-documented, and discussed with the patient where relevant.

## **1.7 Review**

No later than 2017 the Board of NGvA will determine if this guideline is still up to date. If necessary a new study group will be installed to see to its revision. The validity of the guideline will terminate earlier if new developments make it prudent to have it revised.

As holder of this guideline the NGvA is the first responsible for its up-to-date status. The users of this guideline share the responsibility for it and shall inform the first responsible about relevant developments within their professional fields.

## **1.8 References**

Inspectie voor de Gezondheidszorg. (2009). Jaarrapportage 2008 van de Wet afbreking zwangerschap

Den Haag: Inspectie voor de Gezondheidszorg. (Netherlands Health Inspectorate, 2008 annual report.)

M. Visser et al (2005). Evaluatie Wet afbreking zwangerschap. (Waz Evaluation.)

## Chapter 2            First trimester termination of pregnancy

### Guiding question

What is the most efficient and effective treatment in first trimester pregnancies: surgical, medical or by mixed approach?

### 2.1 Introduction

The NGvA members drew a sharp demarcation line between first and second trimester, because they felt a need to define the necessary competence of abortion doctors – and so their training – according to clearly distinguishable areas. Ultrasound scans render foetal size an objectifiable parameter; in the NGvA general meeting of September 2009 the line between first and second trimester was drawn at a BPD (biparietal diameter) < 23 mm (12 weeks + 6 days amenorrhoea = first trimester) and ≥23 mm (13 weeks am. = second trimester). In the guideline ‘Counselling of women considering termination of pregnancy’ this criterion was subsequently redefined: pregnancies up to 91 days are now considered first trimester pregnancies. Abortion techniques in both pregnancy trimesters can be either surgical or medical in nature, but this distinction is clearly too simplistic in practice. Because studies do not strictly differentiate between purely surgical approaches and surgical approaches after initial medical priming, conclusions from a scientific perspective are hard to draw. The same is true with regard to the absence of the degree of dilatation. It is to be expected that mixed approaches will be developed more and more.

On 21 September 2005 the Cochrane, Medline, Embase en Popline literature D-bases were screened for literature allowing the answering of the guiding question above. By applying filters for systematic reviews and for randomized controlled trials, efforts were made to detect and collect literature for first trimester termination of pregnancy (‘first trimester’, ‘early abortion’). In particular, a search was made for literature on surgical methods (‘curettage’, ‘vacuum curettage’, ‘curettage and dilatation’, ‘vacuum extracti\*’, ‘surgical methods’) and medical interventions (‘abortive agent’, ‘mifepristone’, ‘misoprostol’, ‘prostaglandin’, ‘methotrexate’) under ‘induced abortion’ and ‘cervical ripening’. A language filter was applied, allowing only the selection of articles in English, Dutch, French and German. As the Cochrane Database of Systematic Reviews turned up three reviews discussing the literature up to 2000 (at least), it was decided to restrict further desk research to the period between 1999 and 2005. By this strategy 195 articles were uncovered in total. On 20 December

2009 a renewed literature search with respect to surgical termination of pregnancy was undertaken in the same D-bases, this time for the period from 2005 through 2009. This search did not yield new literature or perspectives regarding the surgical termination of pregnancy. However, several studies were published which attempt to compare surgical and medical termination of pregnancy.



## **2.2 Surgical interventions in first trimester pregnancies**

### **Guiding question**

What is the most efficient and effective method for surgical termination of pregnancy in first trimester pregnancies?

### **Summary of the literature**

In a Cochrane systematic review, carried out by Kulier et al. in 2001, different surgical methods for first trimester termination of pregnancy were compared. A search of mutual comparisons of manual vacuum aspiration, electric vacuum aspiration and dilatation and curettage was conducted, with a specific view to excessive blood loss, blood transfusion, perforation of the uterus, cervical impairment, reoperation, fever, rehospitalisation and mortality. No more than three (older) RCTs were included in this study.

In the trials no maternal mortality or perforations of the uterus were found. In those trials which compared vacuum aspiration with dilatation and curettage a reduced length of surgery was found of 1.09 minutes (95% BI: 0.65-1.53) for women undergoing vacuum aspiration. At a pregnancy length of less than 9 weeks this difference was even somewhat larger (1.84 minutes). Other comparisons showed no differences. Not much value should be attached to this systematic review, in the light of the small number of studies in the underlying comparisons and the obsolete nature of the material underlying the results.

2001 was also the year of a study by Hemlin et al., in which manual and electric vacuum aspiration were compared in a randomized trial. In it, 197 women with a pregnancy length of up to 57 days, who opted for surgical termination, were randomized across the two approaches under study. 179 interventions were carried out in the end, all of them successful in the sense that there was no trace of ongoing pregnancy afterwards. The percentage of necessary repeat curettages and incurred infections was equal in both groups, just like the average haemorrhage length and the percentage of women suffering haemorrhage for a longer period of time.

Dean et al., too, compared manual and electric vacuum aspiration in women presenting for a termination of pregnancy during the first trimester of their pregnancy. In their study, 84 women with a length of pregnancy up to 10 weeks were randomly assigned to one of two groups. In particular, acceptance of either method was reviewed; acceptance was primarily assessed on the parameter 'disturbance by the noise of the intervention'. Other subjective measures were also analyzed. There

appeared to be no significant differences in intervention length, blood loss, complications, pain relief and recovery time. Neither could a difference be established between the pain experienced by the patient and the doctor's estimation of that pain. Women who underwent electric vacuum aspiration more frequently reported their observation of the accompanying noise; 19% found this noise slightly disturbing. This finding was higher than for the group who underwent manual vacuum aspiration ( $p = 0.03$ ).

## Conclusions

<b>Level 2</b>	<p>Vacuum aspiration and dilatation and curettage do not apparently differ from each other in terms of complications and side-effects. Surgery length is a little shorter for vacuum aspiration.</p> <p><i>A2 Kulier 2001</i></p>
----------------	---

<b>Level 2</b>	<p>It seems plausible that manual and electric vacuum aspiration are both safe methods for termination of pregnancy. Randomized trials did not reveal differences in effectiveness, side-effects or complications.</p> <p><i>B Hemlin, Dean 2003</i></p>
----------------	--

## Discussion and evaluation

Suction curettage is a safe method for pregnancy termination in the first trimester; this method shows good results and few complications. Success and complication scores vary between 0 and 5% across studies. Scores will also depend on the abortion doctor's degree of experience.

In the - mostly non-Dutch - literature many surgical terminations of pregnancy were performed under general anaesthesia. This is different for the Dutch situation, although daily practice seems to show an increase in the patients' wish for sedation or general anaesthesia. The pain experienced may be reduced, but the costs are higher; these concern for instance the purchase of surveillance appliances, the training of professional staff and the involvement of an anaesthesiologist.

The option to receive sedation (or not) is at the patient's discretion and must be respected and facilitated.

## Recommendations

Where a surgical method is preferred, the study group considers vacuum aspiration as the first choice, in view of the low percentage of complications.

## References

- Dean G, Cardenas L, Darney P, Goldberg A. *Acceptability of manual versus electric aspiration for first trimester abortion: a randomized trial*. *Contraception* 2003; 67:201-06.
- Hemlin J, Moller B. *Manual vacuum aspiration, a safe and effective alternative in early pregnancy termination*. *Acta Obstet.Gynecol.Scand.* 2001; 80:563-67.
- Kulier R, Gulmezoglu AM, Hofmeyr GJ, Cheng LN, Campana A. *Medical methods for first trimester abortion*. *The Cochrane Database of Systematic Reviews* 2004, Issue 2.Art.No.: CD002855.pub3.DOI: 10.1002/14651858.CD002855.pub3. 2004.
- Kulier R, Fekih A, Hofmeyr GJ, Campana A. *Surgical methods for first trimester termination of pregnancy*. *The Cochrane Database of Systematic Reviews* 2001, Issue 4.Art. No.: CD002900.DOI: 10.1002/14651858.CD002900. 2001.

## **2.3 Surgical versus medical termination of pregnancy in the first trimester**

### **Guiding question**

Are there any differences in success rate, patient contentment or number of complications between surgical and medical termination of pregnancy in the first trimester?

### **Summary of the literature**

In 2010, a Cochrane review by Say et al. was published. This review covers seven studies comparing medical methods versus vacuum aspiration. Four different interventions, prostaglandins only, mifepristone only, mifegyne plus misoprostol, and methotrexate plus misoprostol are compared with vacuum aspiration. The most important outcomes concern effectiveness, side-effects and patient comfort. This review shows that women undergoing medical termination of pregnancy generally suffer more blood loss than women undergoing vacuum aspiration. As regards experienced pain comparisons are difficult to make, as women undergoing surgical termination of pregnancy very often received one or other form of - general - anaesthesia. In The Netherlands, local anaesthesia is still applied in many cases. The authors conclude - admittedly on the basis of limited evidence - that, in the first trimester, vacuum aspiration is more effective than medical termination with prostaglandins alone, and that vacuum aspiration proceeds faster, with less bleeding and less pain.

In 2004 an RCT by Rorby et al. was published. This study included 1.033 women with a pregnancy length under 63 days. Part of these women were randomly assigned to a surgical or medical approach, the other part were free to choose. Surgical termination entailed vacuum aspiration under general anaesthesia, the medical intervention entailed 600 mg. of mifepriston and 1 mg. of gemeprost. These regimes thus differ somewhat from the Dutch situation. At two and eight weeks after the intervention the women filled out questionnaires with respect to contentment, side-effects and expectations. In both questionnaires, after two and eight weeks, the same patterns were found; women who had opted for surgical termination were satisfied to highly satisfied at 92%, versus 94% in the randomized surgical group. Satisfaction was lower for the medical group; of the women who had opted for medical termination, 82% were satisfied to highly satisfied, while in the randomized group this was true for 68%. Satisfaction in the medical group was inversely related to gestation length, intensity of the pain experience and the prevalence of nausea

and vomiting. In the case of surgical termination these factors had no influence. The authors conclude that satisfaction is high in both groups, but higher after surgical termination of pregnancy. They also conclude that contentment figures are higher if women are allowed to choose which method they wish to undergo for the termination of their pregnancy.

The study 'Randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks gestation' by Robson et al appeared in Health Technology Assessment in 2009. (TOPS). The surgical intervention included women with a pregnancy length of 6 to 14 weeks. Two hours before the intervention each woman was administered 400 micrograms of misoprostol, the intervention was carried out by suction curettage under general anaesthesia. The medical intervention was carried out under 14 weeks of pregnancy. Each woman took 200 milligrams of mifeproston orally and presented at the clinic 36 to 48 hours later. Under 9 weeks of pregnancy the regime was 800 micrograms of misoprostol vaginally and sometimes 400 micrograms of misoprostol 4 hours later if there had been no onset of the termination. In pregnancies over 9 weeks 800 micrograms of misoprostol vaginally was again the starting dose, followed by 400 micrograms (vaginally) every 3 hours, up to a maximum of 4 doses. If no effect was observed, 200 micrograms of mifeproston were administered vaginally, followed by a mg. of gemeprost, every 3 hours, with a maximum of 5 doses. If no onset of the termination was observed, the surgical approach was applied. The outcome measure in this study was whether women would again choose to undergo the same method in a possible next termination of pregnancy. 1,877 women were included in total. The medical approach was more negatively appreciated than vacuum aspiration. More pain was reported. There was no difference across the two groups as regards anxiety or feelings of depression after three months. With the medical approach, there were more emergency requests: 4.2% versus 0.7% of the women presented at the emergency department. Despite the latter effect, the authors calculated that the surgical method is more expensive than the medical termination, also due to the general anaesthesia and hospitalisation involved.

In 2004 and 2005, the American Food and Drug Administration (FDA) reported on septic shock as a potential complication after using mifepristone and misoprostol. Five women died as a result of septic shock, caused by *Clostridium sordellii*. This happened within a week after medical termination of pregnancy.

The authors of the articles reviewed indicate that the pathophysiology is not fully clear; there was no clear-cut explanation for these deaths. Further research is required.

Besides, the authors point out the extremely small risk of incurring this complication. In Europe, around 1.5 million women have made a choice for medical termination over the past 15 years. The complication mentioned was described no more than once in Europe (Fischer et al.. 2005; Greene et al. 2005; Fiala et al. 2005). In Portugal one *Chlostridium sordellii* infection with fatal consequences was reported in 2009 (21<sup>st</sup> European Congress of Clinical Microbiology and Infectious Diseases, ECCMID, Milan, 07.10.2011).

### Conclusions

<b>Level 1</b>	Compared to surgical termination of pregnancy, medical termination in the first trimester causes higher blood loss, while the intervention also lasts longer.  <i>A1 Say et al. 2010</i>
----------------	--

<b>Level 3</b>	It seems plausible that, compared to vacuum aspiration, medical termination of pregnancy more frequently causes complications.  <i>B Robson et al. 2009</i>
----------------	---

<b>Level 4</b>	It is unlikely that there is a relation between medical termination of pregnancy and toxic shock syndrome.  <i>D Fischer et al.. 2005; Greene et al. 2005; Fiala et al. 2005</i>
----------------	--

### Discussion and evaluation

Various complications may occur in first trimester termination of pregnancy. When a surgical intervention is performed, particularly vacuum aspiration, these may comprise perforation, bleeding, infection or an incomplete abortion, or complications of anaesthesia.

During and after medical termination severe and long-term blood loss may occur, besides failed or incomplete abortion, or an infection. Complication figures for first trimester termination of pregnancy in The Netherlands have unfortunately not been sub-labeled for surgical or medical termination. Inquiries at the National Health Inspectorate and a study of the LAR data showed a complication score for The Netherlands of 4 in 1,000 first trimester terminations. This amounts to 0.4% of all

first trimester abortions carried out in this country. The literature does not further elucidate on these figures, but success rates can be derived. The 0.4 % reconstructed for The Netherlands is considerably lower than the figures for failed abortions found in the international literature. For instance, the Cochrane review speaks of success rates of between 71% (with a regime of prostaglandins only) and 97.5% (a regime of mifegyne with misoprostol) and a success rate of between 94% and 100% for surgical termination of pregnancy.

The differences in complication figures are relatively large and explanations cannot be readily provided. Does underreporting play a role? Are professionals in The Netherlands more experienced, since abortion treatment is a medical specialism here and the abortion doctor a recognized specialist? This is not clear and raises the question, to what extent the studies found can be used for the Dutch situation. Apart from the complication figures, the regimes under the medical approach are different as well, and also the maximum length of gestation for which medical termination of pregnancy is (still) carried out and the fact that very many surgical methods are applied under general anaesthesia. These shortcomings have made the drafting of (well-founded) conclusions and recommendations a slightly dubious affair.

### **Recommendations**

A woman with amenorrhoea under 63 days must be informed about the treatment options open to her: surgical or medical

A woman must be informed about the differences between both forms of treatment; it must be made clear to her that medical termination of pregnancy takes more time and has a higher risk of complications, such as ongoing pregnancy, incomplete abortion and bleeding, compared to surgical termination of pregnancy

### **References**

- Fiala e.a. *Review of medical abortion using mifepristone in combination with a prostaglandin analogue*. Contraception 74; 66-86 2005
- Fischer e.a. *Fatal toxic shock syndrome associated with Clostridium sordellii after medical abortion*. New England journal of medicine, Dec. 2005
- Greene, *Fatal infections associated with Mifepristone-induced abortion*. New England journal of medicine, Dec. 2005
- Niinimaki e.a. *'Immediate complications after medical abortion compared with surgical termination of pregnancy'*. 2009
- Rorby e.a. *'Medical versus surgical abortion; comparing satisfaction and potential confounded in a partly randomized study'*. 2004
- Robson e.a. *'Randomised preference trial of medical versus surgical termination of pregnancy less than 14 weeks'*

*gestation.'* (TOPS), 2009  
Say e.a. Cochrane review: *Medical versus surgical methods for first trimester termination of pregnancy.* 2010  
Loeber. *Motivation and satisfaction with early medical vs. surgical abortion in the Netherlands.* *Reproductive health matters*, 2010;18(35):145-153.



## **2.4 Cervix priming in the first trimester**

### **Guiding question**

What evidence may be inferred from the (inter)national literature with respect to the application of priming with prostaglandins and their administration route in first trimester termination of pregnancy?

### **Introduction**

Prostaglandins have been applied for a long time to prepare the uterus mouth (cervix uteri) for dilatation. Prostaglandins facilitate dilatation. Blood loss during and after the intervention is reduced. Cervical priming is regularly used in surgical termination of pregnancy. In abortion clinics, misoprostol is the prostaglandin almost exclusively applied to prime the cervix. Below, aspects of effectiveness, side-effects and safety will be discussed.

### **Summary of the literature**

In first trimester termination of pregnancy prostaglandins make dilatation of the cervix easier. Various prostaglandin analogues have been developed (Goldberg e.a., 2001; Goldberg e.a., 2003; Shannon e.a., 2004; Sivalal e.a., 2004). Misoprostol is a prostaglandin E1 analogue (PGE1), which came on the market in 1988. As regards first trimester terminations, ample research was conducted into misoprostol as a cervix primer.

Misoprostol (as a cervix primer) has no detectable effect on the complication rates for the first trimester (Goldberg e.a., 2003). The side-effects of misoprostol are less than those of earlier prostaglandins (Ngai e.a., 2003). Misoprostol has the advantage over gemeprost that it is cheap and stable at room temperature (Ngai e.a., 2003; Sivalal e.a., 2004).

Misoprostol can prompt a spontaneous abortion in the first trimester. The addition of mifepristone will accelerate this process (Goldberg e.a., 2001; Ngai e.a., 2003).

Mifepristone - a competitive progestogen antagonist - is more expensive as a cervix primer than misoprostol. According to the Royal College of Obstetricians and Gynaecologists (RCOG), mifepristone must be administered 36-48 hours before the intervention.

The optimal time lapse between cervix priming with the help of misoprostol and treatment is estimated at 2 to 4 hours; most articles mention a (minimum) time lapse of 3 hours (Goldberg e.a., 2001; Goldberg e.a., 2003). All of these articles are concerned with cervix priming in the first trimester.

The best route of administration for misoprostol appears to be the vaginal administration of 400 mcg, but buccal or sublingual administration is a good alternative (Goldberg e.a., 2001; Goldberg e.a., 2003). The further the gravidity has progressed, the higher the sensitivity to uterotonics. For this reason decreasing doses of misoprostol are required to achieve similar effects (Goldberg e.a., 2001). The scientific basis outlined above is mainly founded on five review articles of good quality. The most recent review article dates from 2004. In 2010, a renewed search turned up two articles, neither of which yielded any new insights. The RCOG guideline recommends priming in nulliparae, women under 18 and women with a pregnancy length of 10 weeks or more.

A claim found again and again holds that cervix priming in the first trimester will reduce the number of complications. This claim is based, partially, on two articles from 1983 and 1984, respectively, which are often cited. These and other older articles were left out here because, at the time, there was no use of misoprostol. Goldberg et al. (2003) conclude there is no difference in the number of complications with or without cervix priming in the first trimester. In either case, the number of complications is very low

The evidence tables in the RCOG guideline show a complication rate of about 1 per 1,000, which underlines Goldberg’s conclusion.

**Conclusion**

<b>Level 3</b>	<p>It seems safe to assume that misoprostol as a cervix primer in the first trimester does not show a clear reduction in the number of complications, partly because complications in the first trimester are rare.</p> <p><i>B Goldberg, 2003</i></p>
----------------	--

<b>Level 4</b>	<p>It is likely that misoprostol in the first trimester contributes to the ease of dilatation in nulliparae, women under 18 and in women with a pregnancy length of more than 10 weeks.</p> <p><i>D RCOG, 2004</i></p>
----------------	--

<b>Level 4</b>	<p>It is likely that 400 mcg of misoprostol taken as a cervix primer at two to four hours before first trimester vacuum aspiration may be administered by either vaginal, buccal or sublingual route.</p>
----------------	---

## Discussion and evaluation

In other countries, cervix priming often precedes first trimester surgical treatment. In The Netherlands, suction curettage (in the first trimester) is carried out with a relatively thinner suction tube, making cervix priming (mostly) unnecessary.

The time of stay in the clinic will be considerably longer when priming is applied; this requires additional investments on the part of both patient and clinic.

As mentioned above, priming does not influence the number of complications or their nature; however, side-effects and medication-related risks may occur.

## Recommendation

Routine priming of the cervix with prostaglandins (e.g. misoprostol) has no added value in first trimester surgical termination of pregnancy.

## References

- Ashok PW, Flett GM, Templeton A. *Mifepristone versus vaginally administered misoprostol for cervical priming before first-trimester termination of pregnancy: a randomized, controlled study*. *Am.J.Obstet.Gynecol* 2000; 183 (4): 998-1002.
- Goldberg AB, Greenberg MB, Darney PD. *Misoprostol and Pregnancy*. *NEJM* 2001 Jan 4; 344 (1): 38-47.
- Goldberg AB, Carusi DA, Meckstroth KR. *Misoprostol in Gynecology*. *Current Women's Health Reports* 2003; 3: 475-483.
- Ngai SW, Tang OS, Ho PC. *Prostaglandins for induction of second-trimester termination and intrauterine death*. *Best Practice & Research Clinical Obstetrics & Gynaecology* 2003; 17 (5): 765-775.
- Shannon CS, Winikoff B. *Misoprostol, an emerging technology for women's health, report of a seminar*. Population Council 2001, updated to 2004: 1-66.
- Sharma S, Refaey H el, Stafford M, Purkayastha S, Parry M, Axby M. *Oral versus vaginal misoprostol administered one hour before surgical termination of pregnancy: a randomised controlled trial*. *BJOG* 2005 April; 112: 456-460.
- Sivalal S, Sivasampu S. *Health technology assessment report, misoprostol in pregnancy*. Health technology assessment unit, medical development division, ministry of health Malaysia 2004: 3-29.
- Vimala N, Mittal S, Kumar S. *Sublingual misoprostol before first trimester abortion: a comparative study using two dose regimens*. *Indian J Med Sci* 2004; 58 (2): 54-61.
- Royal College of Obstetricians and Gynaecologists (RCOG) *Guideline: the Care of Women Requesting Induced Abortion*, Chapter 7, 2004



## 2.5 Medical termination of pregnancy

### Guiding question

What is the most efficient and effective medical treatment in first trimester medical termination of pregnancy?

### Introduction

Below, the guiding question with respect to the medical treatment for first trimester termination of pregnancy is discussed. There will be a focus on the use of mifepristone in combination with misoprostol.

There is a multitude of publications on the results of studies into medical termination of pregnancy. In view of the poor results, the various monotherapies may be left aside. Most successful are combinations of methotrexate with prostaglandin analogues and mifepristone with prostaglandin analogues.

In The Netherlands, methotrexate is not applied in medical termination of pregnancy, although it is in the treatment of extra-uterine pregnancies.

Since the registration of mifepristone in 1999, medical treatment has conquered a position for itself as a first trimester intervention, besides curettage. Advantages mentioned by Dutch gynaecologists (compared to surgical treatment): smaller risk of impairment of cervix and uterus, no anaesthesia, no intravenous incursion, fewer systemic complications like heart failure, ease of the intervention (Brouns, Burger, & van Wijngaarden, 2010). Since its registration, further studies have taken place, to optimize the combination treatment of mifepristone, particularly with misoprostol, in terms of their efficacy and unwanted side-effects. Besides, the legal product information (Summary of Product Characteristics) has changed since the introduction.

### Mifepristone

The suppression of progesterone during early pregnancy causes uterus contractions and expulsion of the embryo through a mechanism involving prostaglandin (Csapo, Pulkkinen, & Kaihola, 1973). Mifepristone has the following effects on uterus and cervix:

- Mifepristone provokes contractility in the uterus by restraining the effects of progesterone and increasing the sensitivity of the myometrium to prostaglandins (Garfield, Blennerhassett, & Miller, 1988) (Swahn & Bygdeman, 1988a);
- Mifepristone leads to necrosis of the deciduas by impacting the capillary endothelial cells, which causes rejection of the trophoblast, accompanied by bleeding, decrease in HCG levels and an increased release of prostaglandin

(Johannisson, Oberholzer, Swahn, & Bygdeman, 1989) (Schindler et al., 1985) (Herrmann et al., 1982);

- Mifepristone ripens the cervix, which stimulates expulsion.

Studies in human subjects gave the impression that the contractility of the uterus does not increase earlier than 24-36 hours after administration of mifepristone and is preceded by increased sensitivity of the myometrium to prostaglandins (Swahn & Bygdeman, 1988b). Uterus sensitivity to exogenously administered prostaglandin rose to five times its normal level. However, the effect of vaginally administered misoprostol becomes noticeable within 15 minutes, while the effects of the mechanisms induced by mifepristone listed above may possibly not be complete (Creinin et al., 2007).

When taken orally, mifepristone is easily resorbed and shows peak serum levels within two hours, depending on the dosage, both in pregnant and in non-pregnant women (Shi et al., 1993). At dosages between 100-800 mg of mifepristone the serum peak levels are comparable (2,0-2,5 µg/ml). These non-linear pharmacokinetic findings are probably associated with the saturation of a specific transport protein: alpha-1-acid glycoprotein, starting at 100 mg mifepristone. It would seem likely, therefore, that a dosage of 100 mg is already effective, while it is extremely unlikely that a dosage above 600 mg would show better effects (Lahteenmaki et al., 1987) (Heikinheimo et al., 1987) (Heikinheimo, 1989) (Heikinheimo, Tevilin, Shoupe, Croxatto, & Lahteenmaki, 1986).

### Misoprostol

Misoprostol is a synthetic prostaglandin E1 analogue, with both a mucosa protecting and a gastric acid reducing capacity. The mucosa protecting effect is based on the fact that misoprostol stimulates the production of mucus and hydrogen carbonate, next to other possible mechanisms such as the maintaining or strengthening of perfusion levels in the gastric mucosa. Resorption is quick and nearly complete. The active substance is misoprostolic acid, which is formed almost at once. Misoprostol is not registered as a support agent to combine with mifepristone in termination of pregnancy, but it is indicated to prevent the formation of ulcers of the stomach or bowel provoked by NSAIDs.

Gemeprostat(SmPC:<http://www.medicines.org.uk/emc/medicine/3968/SPC/Gemeprostat/#PRODUCTINFO>)

Gemeprostat, too, is a prostaglandin E1 analogue, which is administered in a dosage of 1 mg by means of a pessary inserted in the vagina, to effect:

- softening and dilatation of the cervix opening prior to surgical intervention in the first trimester;
- induction of an abortion in the second trimester.

### **Summary of the literature**

The first relatively large-scale study on the combination of mifepristone and misoprostol was performed on 873 women with an amenorrhoea length of up to 49 days (Peyron et al., 1993). Peyron et al. described two successive studies in which all women used 600 mg mifepristone orally, followed 48 hours later by a single oral dose of misoprostol (400 µg). In the second study the women were allowed an extra 200 µg of misoprostol orally if the expulsion of the foetus had not taken place within four hours. In the group as a whole, abortion occurred in 4% of the women through mifepristone alone. In the first group, complete termination of pregnancy occurred in 96.9% of the 488 women (95% CI: 94.1-97.7%); in the second group of 385 women in 98.7% (95% CI: 96.8-99.5%). Statistically, these differences are non-significant. The abortion percentages during the first four hours after misoprostol were 61% and 69%, respectively. Nausea, vomiting and diarrhoea were found in 40%, 15%, and 10% of the women, respectively.

In a multicenter trial by Aubény en Peyron (Aubeny et al., 1995) involving 1,108 women with an amenorrhoea length up to 63 days, the same mifepristone/misoprostol schedule was followed up with an oral dose of 200 µg misoprostol if abortion did not start within three hours after the first dose; the highest success percentages were found at a shorter amenorrhoea length: 97.6% up to 42 days am.; 94.8% at 42-49 days am.; 93.4% at 50-56 days of amenorrhoea and 86.8% at 57-63 am. Continuation of the pregnancy was found to be related to an increased amenorrhoea length: in 0.8%, 1.4%, 1.6% and 5.1%, respectively. On the whole, 61.6% of the women had no expulsion of the foetus within three hours after the first dose of misoprostol and were given a second dose of 200 µg.

A Cochrane systematic review on medical interventions (Kulier, Gulmezoglu, Hofmeyr, Cheng, & Campana, 2004) appeared in 2004. It included randomized clinical trials, in which different medical interventions were compared to each other or a placebo in women in the first trimester of their pregnancy. Although 39 randomized clinical trials were included in this well-delivered systematic review, it must be observed that most analyses were based on only a few studies, sometimes even no more than one. This entails that many results were based on a limited

number of patients, so that differences found between mono or combined use of medication often show wide reliability intervals. From one of the studies included in this meta-analysis it appeared that administration of 200 mg mifepristone, followed up by 800 µg misoprostol on day 1 gave a slightly raised risk of incomplete abortions compared to the administration of misoprostol on day 3 (RR: 1.94; 95% RI: 1.05-3.58) (Schaff et al., 2000a).

The review also showed that the combination of mifepristone and misoprostol (800 µg) mentioned above lead to higher success rates under vaginal administration than under oral administration of misoprostol (RR: 4.41; 95% RI: 2.32-8.38) (Schaff, Fielding, & Westhoff, 2001a). In the same analysis vaginal administration gave a slightly lower risk of nausea and diarrhoea, but a slightly higher risk of vomiting at the same time.

The other results from this systematic review are statistically non-significant.

Von Hertzen et al. (von Hertzen et al., 2003a) and Honkanen et al. (Honkanen et al., 2004) described various aspects of a WHO study, in which three misoprostol regimes were compared in 2,219 women with a pregnancy length of up to nine weeks, calculated from the last menstruation period. In this population, Von Hertzen et al. analysed first of all the effectiveness of the intervention, while Honkanen et al. focused on the side-effects and women's perceptions, for which three study arms were compared:

- O/O: oral mifepristone (200 mg) on day 1, oral misoprostol (0.8 mg) and a vaginal placebo on day 3, oral misoprostol (0.4 mg) twice daily on day 4 through 10;
- V/O: oral mifepristone (200 mg) on day 1, vaginal misoprostol (0.8 mg) and an oral placebo on day 3, oral misoprostol (0.4 mg) twice daily on days 4-10;
- V: oral mifepristone (200 mg) on day 1, vaginal misoprostol (0.8 mg) and an oral placebo on day 3, oral placebos twice daily on days 4-10.

For the women in the O/O group the percentage rate for a complete abortion was 92.3% (95% RI: 90.1-94.1); in the V/O group this was 93.5% (95% RI: 92.9-96.2) and in the V group 93.5% (95% RI: 91.5-95.2). The differences between these groups were statistically non-significant. After stratification for length of pregnancy there were no significant differences in abortion success rate. In the O/O group more women than in the other group indicated that they suffered from diarrhoea (6.8% vs. 1.8% and 1.1%,  $p < 0.0001$ ). Women in the O/O group reported low abdominal pain directly after the administration of misoprostol, while women in the V/O group and V group reported this after 3 hours ( $p$  varying from  $< 0.0001$  to 0.0027, directly after administration versus after 3 hours).



In a randomized study, Creinin et al. (Creinin et al., 2004a) compared administration of misoprostol 6 to 8 hours after administration of mifepristone with administration of misoprostol 24 hours after administration of mifepristone. In this prospective multicenter trial 1,080 women with a pregnancy up to 63 day after the last menstruation were included. In terms of effectiveness of the medication there was no significant difference between both groups (95.8% vs. 98.1%). In the interval between the administration of mifepristone and misoprostol more side-effects of the medication were observed in the 24 hour group of women than in the other group. Besides, women in this group suffered more from nausea and vomiting after administration of misoprostol than the group of women with a shorter interval between mifepristone and misoprostol.

In a double blind placebo controlled randomized clinical trial Liao et al. (Liao et al., 2004) compared mifepristone 75 mg caplets with mifepristone 150 mg tablets, followed up with misoprostol in both arms of the trial. Apart from the effectiveness of these different forms of administration, the side effects and the prevalence of bleeding were studied in 480 woman participants with a pregnancy length up to 49 days after the last menstruation period. Complete abortion was achieved in 95.4% in the group using the tablets and 96.3% in the group receiving mifepristone in capsule form. These percentages do not differ significantly from each other. The duration of the haemorrhages experienced by the women and their intensity were similar to their experience during normal menstruation; the side-effects were comparable for both groups under study.

In a multicenter randomized clinical trial, Schaff et al. (Schaff, Fielding, & Westhoff, 2001b) compared the effectiveness of oral versus vaginal administration of misoprostol after administration of mifepristone 200 mg. All women with a pregnancy length up to nine weeks were given mifepristone 200 mg, followed up after two days by one of three regimes: 400 µg misoprostol orally, 800 µg misoprostol orally or 800 µg misoprostol vaginally. The complete abortion percentage was highest in the group undergoing vaginal administration of misoprostol ( $p < 0.001$ ), even after additional vaginal administration of misoprostol in all groups ( $p < 0.001$ ). Oral misoprostol 400 µg showed the smallest effect; the success rate was lower in more advanced pregnancies. After vaginal administration more women suffered cramps compared to oral administration, but fewer had diarrhoea ( $p < 0.001$ ). In both groups with oral administration more women found the pain acceptable ( $p = 0.017$ ).

Tang et al. (Tang, Chan, Ng, Lee, & Ho, 2003a) studied the difference in effectiveness between sublingual and vaginal administration of misoprostol 800 µg, 48 hours after administration of mifepristone 200 mg. In this double blind placebo controlled randomized clinical trial 224 women with a pregnancy up to nine weeks were included. Complete abortion was achieved in 98.2% of the women in the sublingual group and in 93.8% in the vaginal group. This difference was non-significant, statistically. But the women in the sublingual group did report nausea, vomiting, diarrhoea, shivering and fever more often ( $p < 0.05$ ).

#### Mifepristone at lower doses

On the basis of the pharmacokinetic profile described above, it was supposed that mifepristone at lower doses could have a similar degree of effectiveness. In 1992, Thong en Baird (Thong & Baird, 1992) were the first to describe the results of mifepristone 200 mg followed up 48 hours later by 600 µg of misoprostol taken orally by 100 women with an amenorrhoea length of up to 56 days. The effectiveness found was at 92%, while in 79% of the women expulsion of the foetus occurred within 4 hours after taking misoprostol.

The success rate at an amenorrhoea length of up to 57 days is 93.8% after administration of mifepristone 200 mg and 94.3% at 600 mg (WHO 1993); these figures are 92.4% and 91.7% at an amenorrhoea length of 57-63 days (WHO 2001), in combination with gemeprost in both studies. Following this, most major studies investigated the use of 200 mg of mifepristone.

After their previous review of 2004, Kulier et al. recently updated their review (Kulier R., Kapp N., Gülmezoglu A.M., Hofmeyr G.J., Cheng L., & Campana A. The Cochrane Library, 2010, Issue 8). They cite Von Hertzen et al. (2009), who compared 200 and 100 mg of mifepristone followed up by 800 µg misoprostol administered vaginally, 24 or 48 hours later, in women with an amenorrhoea length of 63 days or less. Effectiveness and side-effects were similar in all four groups.

#### Alternative administration routes of misoprostol

In their meta-analysis, Kulier et al. (2010) had fewer women with a complete abortion after oral administration of 800 µg of misoprostol than after vaginal administration of misoprostol at the same dose (statistically significant; based on two trials among 1,407 women in total: RR 3.05; 95% RI 1.98-4.70). Nausea and diarrhoea less frequently occur after vaginal administration of misoprostol, compared to oral administration. In other comparisons (buccal versus vaginal, buccal versus oral, sublingual versus vaginal, sublingual versus oral) buccal and sublingual administration

proved equally effective as vaginal administration, but the first two cause more side-effects to occur and, more particularly, an unpleasant taste.

Table 1: Vaginally administered mifepristone in combination with misoprostol  
200 mg of mifepristone followed up by 800 µg of misoprostol vaginally

Authors	Dosage-interval	< 50 days			50-56 days			57-63 days		
		N	S	F	N	S	F	N	S	F
(Ashok, Penney, Flett, & Templeton, 1998)	36-48 hrs	928	98.5 %	0.2%	1072 a	96.7 %	0.8%			
(Schaff et al., 1999)	48 hrs	660	97.4 %	0.3%	273	96.3 %	1.1%			
(Schaff, Fielding, Eisinger, Stadius, & Fuller, 2000)	48 hrs	578	97.7 %	0.2%	251	96.8 %	0.4%	30 8	96.0 %	1.0%
(Bartley, Brown, Elton, & Baird, 2001)	48 hrs	232	99.6 %	0.0%	164	98.2 %	0.0%	55	96.5 %	1.8%
(Schaff, Fielding, & Westhoff, 2002)	36-48 hrs	349	98.2 %	0.6%	113	98.2 %	0.0%	60	93.3 %	0.0%
(Tang, Chan, Ng, Lee, & Ho, 2003b)	48 hrs	26	96.2 %	0.0%	86	93.1 %	2.7%			
(von et al., 2003b) von Herten	36-48 hrs	223	95.1 %	-	242	93.4 %	0.4% <sup>b</sup>	26 8	92,2 %	0.0%
(von et al., 2003b) von Herten	36-48 hrs [c]	240	94.6 %	-	246	93.1 %	0.2% <sup>b</sup>	25 4	96.5 %	0.0%
(Creinin et al., 2004b)	6-8 hrs	245	97.1 %	0.0%	154	94.2 %	0.0%	12 6	95.2 %	0.8%
(Creinin et al., 2004b)	23-25 hrs	258	98.4 %	0.0%	157	97.5 %	0.6%	11 6	98.3 %	0.0%
(Shannon et al., 2006)	24-48 hrs [d]	240	95.4 %	0.0%	59	90.8 %	0.0%			
(Creinin et al., 2007)	< 15 min	266	95.5 %	0.4%	159	94.3 %	1.3%	12 9	95.3 %	0.8%
(Creinin et al., 2007)	23-25 hrs	229	98.3 %	0.4%	172	95.3 %	0.0%	14 5	96.6 %	0.0%



Dosage-interval = interval between mifepristone and misoprostol

N = number of women

S = complete expulsion

F = continuing pregnancies

a = 50-63 days of amenorrhoea

b = continuing pregnancies, combined group up to 56 days of amenorrhoea

c = after vaginal misoprostol during 1 week: misoprostol 400 µg orally 2dd

d = after limited blood loss the option of self-administration of a second dose of misoprostol after 24 hrs

Administering misoprostol in the buccal pouch (between cheek and gum) appears to be equally effective as vaginal administration. Middleton et al. (2005) randomized 442 women with an amenorrhoea length of 56 days across groups receiving 200 mg of mifepristone followed up 1-2 days later by 800 µg of misoprostol in the buccal pouch (allowed to melt for 30 minutes, after which the residue could be swallowed down), and vaginally, respectively. Complete abortion was achieved in 95% and 93% of the women, respectively (non-significant, statistically). Side-effects were similar, with the exception of diarrhoea, which occurred significantly more frequently in the group who received misoprostol via the buccal pouch. A second study confirmed this degree of effectiveness at longer lengths of amenorrhoea, up to 63 days (Winikoff et al., 2008).

Misoprostol was also given sublingually in combination with mifepristone. In a randomized study among 340 women with an amenorrhoea length up to 13 weeks 200 mg of mifepristone was followed up either with 600 µg of misoprostol sublingually (n=171) or with 800 µg of misoprostol vaginally (n=169), 36-48u later, with an additional 400 µg of misoprostol via the same channel if needed. Most women (62%) had been pregnant longer than 63 days of amenorrhoea. The effectiveness was similar in both groups (97% versus 98%, respectively). However, after sublingual administration subjects reported diarrhoea, shivering and an unpleasant taste significantly more frequently (Hamoda, Ashok, Flett, & Templeton, 2005).

#### Shorter time interval between mifepristone and misoprostol

Creinin et al. (2001) compared the effectiveness of oral misoprostol in 86 randomized women if administered 24 or 48 hours after mifepristone, respectively. Complete abortion was achieved in 50% and 91% of the women, respectively (RR = 0.55, 95% CI: 0.42-0.73).

Greater effectiveness is reached if misoprostol is administered non-orally.

Misoprostol 800 µg was self-administered vaginally, at 24, 48 or 72 hours after 200 mg of mifepristone (Schaff et al., 2000b). At follow-up after one week the misoprostol dose was repeated if necessary, whenever expulsion could not be confirmed by ultrasound. In this multicenter trial a total group of 2,295 women with an amenorrhoea length up to 56 days were randomized. Complete abortion was observed in 98%, 98%, and 96% of the women (95% CI 97-99, 97-99, 95-97 respectively). Up to 63 days of amenorrhoea, the same clinicians also observed a high effectiveness using misoprostol 800 µg vaginally at 24 hours after mifepristone (Schaff, Fielding, & Westhoff, 2001c).

Creinin et al. (2004b) investigated the use of vaginal misoprostol inserted at 6-8 hours (n=540) or 23-25 hours (n=540) after mifepristone. In this multicenter study, 1,080 women with an amenorrhoea length of 63 days at most were randomized. The achieved complete abortion percentages were 96% and 98%, respectively. The percentages of continuing pregnancies were 0.4% and 0.1%, respectively. Conspicuous was that the number of side-effects was larger in the group with misoprostol after 23-25 hours.

Guest et al. (2007) undertook a similar randomized study in 450 women with an amenorrhoea length up to 63 days, in which misoprostol was given 6 hours (n=225) or 36-48 hours after mifepristone. Complete abortion was observed in 89% and 96% of the women, respectively (RR=0.92; 95% CI: 0.84-0.98). The results in this British trial differ from those of the American study above. Guest et al. saw more incomplete expulsions (4% vs. 2%); also, more women had to undergo suction curettage later due to a retained amniotic sac (4% vs. 0.6%). The difference may well be associated with the fact that British women were inpatients, which made it easier to move on to suction curettage.

The American clinical study group of Creinin et al. (2007) also looked at the vaginal administration of misoprostol within fifteen minutes after mifepristone (n=567), compared to vaginal misoprostol at 23-25 hours after mifepristone (n=561) in 1,128 women with an amenorrhoea length of up to 63 days. In this multicenter randomized trial the number of complete abortions was equal, at 95% and 97%, respectively. Continuing pregnancies were seen in 0.7% and 0.2% of the women, respectively. They also investigated the simultaneous administration of mifepristone and misoprostol in the buccal pouch, but this proved insufficiently effective as a procedure (Lohr, Reeves, Hayes, Harwood, & Creinin, 2007).

In the meta-analysis by Kulier et al. (2010) the number of trials is too small to pass judgement on misoprostol given in one dose compared to misoprostol in two doses with a short interval (some hours) in between, or about misoprostol administered as a single dose compared to misoprostol administered over a number of successive days.

### Home treatment

During their first visit, women indicated that they worried and felt uncertain about the effectiveness of the medical treatment (Fielding, Edmunds, & Schaff, 2002), their feelings of guilt and ambivalence, and the wish to avoid surgical intervention. During home treatment their uneasiness decreased, while the sense of control they experienced over the treatment was felt to be agreeable. A number of women kept

worrying about their health in the longer term. In 22 home-treated New York women, in-depth interviews were also held (Elul, Pearlman, Sorhaindo, Simonds, & Westhoff, 2000). Almost all women were satisfied about treatment at home. They described the intervention as “natural”, “taking place in private”, and “non-invasive”. Side-effects were tolerable, especially with a trusted person at hand. There is no need to confine home treatment to an amenorrhoea length of 49 days; it can also take place at an amenorrhoea length up to 63 days, at least in Sweden (Kopp, Fiala, Stephansson, & Gemzell-Danielsson, 2010). In the United Kingdom there was less preference for home treatment at an amenorrhoea length > 49 days (Lohr, Wade, Riley, Fitzgibbon, & Furedi, 2010).

On the preconditions for home treatment, such as access to a clinic, presence of a hospital nearby, command of the local language or a widely spoken foreign language, or the need for follow-up, no literature was found.

#### Pain relief

**Ibuprofen was clearly more effective as a pain relief agent than paracetamol and the effectiveness of the combination treatment with mifeprison/misoprostol was apparently not inhibited (Livshits et al., 2009), not even when NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) were administered as a prophylactic agent (Fiala et al., 2005). No publications were found about the use of diclofenac combined with misoprostol (trade name: Arthrotec).**





## Conclusions

<b>Level 1</b>	<p>It was shown that the combination of mifepristone with misoprostol presents a favourable profile compared to monotherapy with one of these components, in terms of effectiveness and safety. The percentage of complete expulsions of the foetus to be expected after misoprostol can be put at between 92.5 and 98.7%.</p> <p>A1 <i>Kulier e.a., 2010</i> A2 <i>Anonymous, 2000</i></p>
<b>Level 1</b>	<p>It was demonstrated that mifepristone remains equally effective when the dose is lowered from 600 mg (registered dose) to 200 mg, on condition that the dose of misoprostol (orally taken) is at least 400 µg.</p> <p>A1 <i>Kulier e.a., 2010</i></p>
<b>Level 1</b>	<p>It was demonstrated that vaginally administered misoprostol is more effective than oral misoprostol and has fewer side-effects (nausea, diarrhoea). Emesis of oral misoprostol logically contributes to a lower degree of effectiveness.</p> <p>A1 <i>Kulier e.a., 2010</i></p>
<b>Level 2</b>	<p>It is likely that the dosage of mifepristone may be lowered further to 100 mg at doses of (vaginally administered) misoprostol of 800 µg.</p> <p>A2 <i>Von Hertzen, 2009</i></p>

## Discussion and evaluation

In 2007, the French authorities asked the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) to compare the effectiveness and safety of the use of mifepristone at an approved dosage of 600 mg for the indication of “medical termination of a developing intra-uterine pregnancy, in combination with a prostaglandin-analogue” with mifepristone at a dosage of 200 mg ([http://ec.europa.eu/health/documents/community-register/2007/2007061427908/anx\\_27908\\_en.pdf](http://ec.europa.eu/health/documents/community-register/2007/2007061427908/anx_27908_en.pdf)).

It is important to be aware of the ruling SmPC-texts for mifepristone and misoprostol, because deviations in dosage strength and administration pattern has legal consequences.

If the prescribing physician wishes to prescribe an agent in an “unlicensed” or “off label” format, (s)he must accept the responsibility for this choice. This responsibility can be defined as the explicit obligation to provide information and obtain the patient’s consent (so-called *informed consent*). When (serious) side-effects occur when medication is prescribed beyond the registered SmPC, the primary responsibility rests with the prescribing physician.

Among Dutch gynaecologists there is a wide variety in the use of mifepristone and misoprostol (Brouns et al., 2010): mifepristone as a monotherapy in two dosages (200 or 600 mg); misoprostol as a monotherapy (200, 400, 600, 800 µg); as a combination therapy misoprostol is given on one, two or three consecutive days, or 2-5 times on the same day.

Misoprostol in therapeutic dosages does not cause hypotension. In the author’s experience fainting (in the absence of pain) is primarily seen when a hot shower is taken (vasodilatation). A first case of vasospasm in a coronary artery after (vaginally administered) misoprostol to a 32-year old smoking and overweight woman was recently described in Barcelona (Illa et al., 2010). There are no indications of misoprostol causing disturbances in the metabolism of carbohydrates.

Only when sufficient communication is possible with the woman (both in terms of language and comprehension) may medical treatment be carried out.

After taking misoprostol, the woman may not be allowed to stay on her own. In home treatment with misoprostol the woman must be able to call for medical assistance.

The woman (and possibly her partner or other person sharing her household) must be given clear instructions, to whom they should turn if the woman suffers too much pain or blood loss (or shows any other medical problem).

There is a single publication according to which previous pregnancies, in particular when carried to term, negatively influence the effectiveness of medical termination of pregnancy (Odeh et al., 2010). This is not an experience shared by the study group members, rather to the contrary. Side-effects, too, appear to be less frequent or severe in the case of earlier deliveries.

The most frequent side-effects of the combination mifepristone/misoprostol are:

- highly frequent: bowel cramps (the first hours after administration of misoprostol); nausea, vomiting, diarrhoea (attributed to misoprostol), shivering and fever.
- frequent: bowel cramps, slight or modest; infection after abortion (suspected or confirmed infections were reported by < 5% of the women); severe haemorrhage (necessitating curettage in 1.4% of the cases).

There is discussion with respect to the time interval needed between the administration of mifepristone and misoprostol. This may vary from eight to seventy-two hours.

In practice variable time intervals are observed between treatment and follow-up, of between one and four weeks, depending on pregnancy length established at the start of the treatment. E.g., a patient receiving medical termination of pregnancy at nine weeks (63 days) must be checked-up sooner, to prevent a continuing pregnancy to transgress the first trimester demarcation line. In very early pregnancies this is less urgent.

### **Recommendations**

Women with amenorrhoea under 63 days must be informed about the treatment options open to them: surgical or medical.

Women must be informed about the differences between both treatment courses and be told that medical termination of pregnancy takes longer and has a higher risk of complications, such as continuing pregnancy, incomplete abortion, and haemorrhage, compared to surgical termination of pregnancy

The preferred medical intervention is by 200 mg mifepristone orally followed up by a minimum of 800 mcg misoprostol vaginally.

An interval of eight to seventy-two hours between the administration of mifepristone and misoprostol should preferably be maintained.

For this indication, the recommended dosages of mifepristone and misoprostol, have not been registered; neither has the administration protocol. It is therefore a legal requirement to inform the woman about this, preferably in writing.

The importance of follow-up checks must be emphasized - also in writing - because even after severe haemorrhages it cannot be excluded that the pregnancy is still intact. Follow-up must take place after one to four weeks, depending on the stage of the pregnancy at the start of the intervention.

In the case of a continuing pregnancy or incomplete expulsion of the amniotic sac after medical treatment, suction curettage is offered as a rule. A second medical termination procedure may be considered at follow-up after one week.

### **References**

Ashok, P. W., Penney, G. C., Flett, G. M., & Templeton, A. (1998). *An effective regimen for early medical*

*abortion: a report of 2000 consecutive cases.* Hum.Reprod., 13, 2962-2965.

Aubeny, E., Peyron, R., Turpin, C. L., Renault, M., Targosz, V., Silvestre, L. et al. (1995). *Termination of early pregnancy (up to 63 days of amenorrhea) with mifepristone and increasing doses of misoprostol [corrected].* Int J Fertil.Menopausal Stud., 40 Suppl 2, 85-91.

Bartley, J., Brown, A., Elton, R., & Baird, D. T. (2001). *Double-blind randomized trial of mifepristone in combination with vaginal gemeprost or misoprostol for induction of abortion up to 63 days gestation.* Hum.Reprod., 16, 2098-2102.

Brouns, J. F., Burger, M. P., & van Wijngaarden, W. J. (2010). *Evaluation of the introduction of a new treatment for the termination of pregnancy in The Netherlands.* Acta Obstet.Gynecol.Scand., 89, 1210-1213.

Creinin, M. D., Fox, M. C., Teal, S., Chen, A., Schaff, E. A., & Meyn, L. A. (2004a). *A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion.* Obstet.Gynecol., 103, 851-859.

Creinin, M. D., Fox, M. C., Teal, S., Chen, A., Schaff, E. A., & Meyn, L. A. (2004b). *A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion.* Obstet.Gynecol., 103, 851-859.

Creinin, M. D., Schreiber, C. A., Bednarek, P., Lintu, H., Wagner, M. S., & Meyn, L. A. (2007). *Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: a randomized controlled trial.* Obstet.Gynecol., 109, 885-894.

Creinin, M. D., Schwartz, J. L., Pymar, H. C., & Fink, W. (2001). *Efficacy of mifepristone followed on the same day by misoprostol for early termination of pregnancy: report of a randomised trial.* BJOG., 108, 469-473.

Csapo, A. I., Pulkkinen, M. O., & Kaihola, H. L. (1973). *The effect of luteectomy-induced progesterone-withdrawal on the oxytocin and prostaglandin response of the first trimester pregnant human uterus.* Prostaglandins, 4, 421-429.

Elul, B., Pearlman, E., Sorhaindo, A., Simonds, W., & Westhoff, C. (2000). *In-depth interviews with medical abortion clients: thoughts on the method and home administration of misoprostol.* J Am.Med Womens Assoc., 55, 169-172.

Fiala, C., Swahn, M. L., Stephansson, O., & Gemzell-Danielsson, K. (2005). *The effect of non-steroidal anti-inflammatory drugs on medical abortion with mifepristone and misoprostol at 13-22 weeks gestation.* Hum.Reprod., 20, 3072-3077.

Fielding, S. L., Edmunds, E., & Schaff, E. A. (2002). *Having an abortion using mifepristone and home misoprostol: a qualitative analysis of women's experiences.* Perspect.Sex Reprod.Health, 34, 34-40.

Garfield, R. E., Blennerhassett, M. G., & Miller, S. M. (1988). *Control of myometrial contractility: role and*

*regulation of gap junctions.* Oxf Rev.Reprod.Biol., 10, 436-490.

Guest, J., Chien, P. F., Thomson, M. A., & Kosseim, M. L. (2007). *Randomised controlled trial comparing the efficacy of same-day administration of mifepristone and misoprostol for termination of pregnancy with the standard 36 to 48 hour protocol.* BJOG., 114, 207-215.

Hamoda, H., Ashok, P. W., Flett, G. M., & 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.

Heikinheimo, O. (1989). *Pharmacokinetics of the antiprogestosterone RU 486 in women during multiple dose administration.* J Steroid Biochem., 32, 21-25.

Heikinheimo, O., Lahteenmaki, P. L., Koivunen, E., Shoupe, D., Croxatto, H., Luukkainen, T. et al. (1987). *Metabolism and serum binding of RU 486 in women after various single doses.* Hum.Reprod., 2, 379-385.

Heikinheimo, O., Tevilin, M., Shoupe, D., Croxatto, H., & Lahteenmaki, P. (1986). *Quantitation of RU 486 in human plasma by HPLC and RIA after column chromatography.* Contraception, 34, 613-624.

Herrmann, W., Wyss, R., Riondel, A., Philibert, D., Teutsch, G., Sakiz, E. et al. (1982). *[The effects of an antiprogestosterone steroid in women: interruption of the menstrual cycle and of early pregnancy].* C.R.Seances Acad.Sci.III, 294, 933-938.

Honkanen, H., Piaggio, G., Herten, H., Bartfai, G., Erdenetungalag, R., Gemzell-Danielsson, K. et al. (2004). *WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion.* BJOG., 111, 715-725.

Illa, M., Bennasar, M., Eixarch, E., Berge, R., Font, C., & Palacio, M. (2010). *Acute coronary artery vasospasm associated with misoprostol for termination of pregnancy.* Fetal Diagn.Ther., 27, 174-177.

Johannisson, E., Oberholzer, M., Swahn, M. L., & Bygdeman, M. (1989). *Vascular changes in the human endometrium following the administration of the progesterone antagonist RU 486.* Contraception, 39, 103-117.

Kopp, K. H., Fiala, C., Stephansson, O., & Gemzell-Danielsson, K. (2010). *Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days.* Hum.Reprod., 25, 1153-1157.

Kulier, R., Gulmezoglu, A. M., Hofmeyr, G. J., Cheng, L. N., & Campana, A. (2004). *Medical methods for first trimester abortion.* Cochrane.Database.Syst.Rev., CD002855.

Kulier R., Kapp N., Gülmezoglu A.M., Hofmeyr G.J., Cheng L., & Campana A. The Cochrane Library, 2010, Issue 8

Lahteenmaki, P., Heikinheimo, O., Croxatto, H., Spitz, I., Shoupe, D., Birgerson, L. et al. (1987). *Pharmacokinetics and metabolism of RU 486.* J Steroid Biochem., 27, 859-863.

Liao, A. H., Han, X. J., Wu, S. Y., Xiao, D. Z., Xiong, C. L., & Wu, X. R. (2004). *Randomized, double-*

*blind, controlled trial of mifepristone in capsule versus tablet form followed by misoprostol for early medical abortion.* Eur J Obstet.Gynecol.Reprod.Biol., 116, 211-216.

Livshits, A., Machtinger, R., David, L. B., Spira, M., Moshe-Zahav, A., & Seidman, D. S. (2009). *Ibuprofen and paracetamol for pain relief during medical abortion: a double-blind randomized controlled study.* Fertil.Steril., 91, 1877-1880.

Lohr, P. A., Reeves, M. F., Hayes, J. L., Harwood, B., & Creinin, M. D. (2007). *Oral mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study.* Contraception, 76, 215-220.

Lohr, P. A., Wade, J., Riley, L., Fitzgibbon, A., & Furedi, A. (2010). *Women's opinions on the home management of early medical abortion in the UK.* J Fam.Plann.Reprod.Health Care, 36, 21-25.

Middleton, T., Schaff, E., Fielding, S. L., Scahill, M., Shannon, C., Westheimer, E. et al. (2005). *Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period.* Contraception, 72, 328-332.

Odeh, M., Tendler, R., Sosnovsky, V., Kais, M., Ophir, E., & Bornstein, J. (2010). *The effect of parity and gravidity on the outcome of medical termination of pregnancy.* Isr.Med Assoc.J, 12, 606-608.

Peyron, R., Aubeny, E., Targosz, V., Silvestre, L., Renault, M., Elkik, F. et al. (1993). *Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol.* N.Engl.J Med, 328, 1509-1513.

Schaff, E. A., Eisinger, S. H., Stadalius, L. S., Franks, P., Gore, B. Z., & Poppema, S. (1999). *Low-dose mifepristone 200 mg and vaginal misoprostol for abortion.* Contraception, 59, 1-6.

Schaff, E. A., Fielding, S. L., Eisinger, S. H., Stadalius, L. S., & Fuller, L. (2000). *Low-dose mifepristone followed by vaginal misoprostol at 48 hours for abortion up to 63 days.* Contraception, 61, 41-46.

Schaff, E. A., Fielding, S. L., & Westhoff, C. (2001a). *Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion.* Contraception, 64, 81-85.

Schaff, E. A., Fielding, S. L., & Westhoff, C. (2001b). *Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion.* Contraception, 64, 81-85.

Schaff, E. A., Fielding, S. L., & Westhoff, C. (2001c). *Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion.* Contraception, 64, 81-85.

Schaff, E. A., Fielding, S. L., & Westhoff, C. (2002). *Randomized trial of oral versus vaginal misoprostol 2 days after mifepristone 200 mg for abortion up to 63 days of pregnancy.* Contraception, 66, 247-250.

Schaff, E. A., Fielding, S. L., Westhoff, C., Ellertson, C., Eisinger, S. H., Stadalius, L. S. et al. (2000a).

*Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: A randomized trial.* JAMA, 284, 1948-1953.

Schaff, E. A., Fielding, S. L., Westhoff, C., Ellertson, C., Eisinger, S. H., Stadalius, L. S. et al. (2000b). *Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: A randomized trial.* JAMA, 284, 1948-1953.

Schindler, A. M., Zanon, P., Obradovic, D., Wyss, R., Graff, P., & Herrmann, W. L. (1985). *Early ultrastructural changes in RU-486-exposed decidua.* Gynecol.Obstet.Invest, 20, 62-67.

Shannon, C., Wiebe, E., Jacot, F., Guilbert, E., Dunn, S., Sheldon, W. R. et al. (2006). *Regimens of misoprostol with mifepristone for early medical abortion: a randomised trial.* BJOG., 113, 621-628.

Shi, Y. E., Ye, Z. H., He, C. H., Zhang, G. Q., Xu, J. Q., Van Look, P. F. et al. (1993). *Pharmacokinetic study of RU 486 and its metabolites after oral administration of single doses to pregnant and non-pregnant women.* Contraception, 48, 133-149.

Spitz, I. M., Bardin, C. W., Benton, L., & Robbins, A. (1998). *Early pregnancy termination with mifepristone and misoprostol in the United States.* N.Engl.J Med, 338, 1241-1247.

Swahn, M. L. & Bygdeman, M. (1988a). *The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin.* Br.J Obstet.Gynaecol., 95, 126-134.

Swahn, M. L. & Bygdeman, M. (1988b). *The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin.* Br.J Obstet.Gynaecol., 95, 126-134.

Tang, O. S., Chan, C. C., Ng, E. H., Lee, S. W., & Ho, P. C. (2003a). *A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation.* Hum.Reprod., 18, 2315-2318.

Tang, O. S., Chan, C. C., Ng, E. H., Lee, S. W., & Ho, P. C. (2003b). *A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation.* Hum.Reprod., 18, 2315-2318.

Thong, K. J. & Baird, D. T. (1992). *Induction of abortion with mifepristone and misoprostol in early pregnancy.* Br.J Obstet.Gynaecol., 99, 1004-1007.

von, H. H., Honkanen, H., Piaggio, G., Bartfai, G., Erdenetungalag, R., Gemzell-Danielsson, K. et al. (2003a). *WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy.* BJOG., 110, 808-818.

von, H. H., Honkanen, H., Piaggio, G., Bartfai, G., Erdenetungalag, R., Gemzell-Danielsson, K. et al. (2003b). *WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy.* BJOG., 110, 808-818.

von, H. H., Piaggio, G., Wojdyla, D., Marions, L., My Huong, N. T., Tang, O. S. et al. (2009). *Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a*

*randomised factorial controlled equivalence trial. BJOG., 116, 381-389.*  
World Health Organisation. *Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial.* World Health Organisation Task Force on Post-ovulatory Methods of Fertility Regulation(2000). BJOG., 107, 524-530.  
Winikoff, B., Dzuba, I. G., Creinin, M. D., Crowden, W. A., Goldberg, A. B., Gonzales, J. et al.  
(2008). *Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial.* Obstet.Gynecol., 112, 1303-1310



# Chapter 3            Second trimester termination of pregnancy

## Guiding question

What is the most efficient and effective treatment in second trimester pregnancies: surgical, medical or by mixed approach?

### 3.1 General introduction

What is the optimal approach to termination of pregnancy in the second trimester? What are advantages and disadvantages of surgical interventions (dilatation and evacuation), with or without priming, and medical interventions (including mixed approaches)? What can be said with respect to effectiveness, efficiency, safety and complications?

The demarcation line between first and second trimester was defined at the NGvA's members' meeting of September 2009. The second trimester starts at an amenorrhoea length of 13 (weeks) + 0 (days), corresponding to a biparietal diameter (BPD) of >22.9 mm. In the guideline 'Counselling of women considering termination of pregnancy' the first trimester was defined as ending at 91 days' amenorrhoea. The upper boundary was established by law at the viability line, which is currently at 24 weeks' amenorrhoea. This figure depends on what views are held with respect to viability, which are, in part, related to medico-technical developments in the field of neonatology. Within this context, each clinic determines its own restrictions, depending on the competencies of the abortion specialists in the particular clinic and the clinic's license conditions.

In Dutch abortion care second trimester interventions generally employ dilatation and evacuation (D&E). In the literature consulted the following aspects were studied: length of treatment, time invested by client and professional, safety and complications of the method(s) used. A complementary search was undertaken in September 2011 with a focus on specific terms (Asherman's syndrome, DIC, low birth weight and prematurity). The search did not yield specific results on Asherman or DIC (Diffuse Intravascular Coagulation). In the eyes of the study group, it would appear useful to set up a registration system to collect data about late complications of D&E in the second trimester.

## **3.2 Surgical termination of pregnancy**

### **Guiding question**

What is the most efficient and effective surgical treatment (or mixed approach) in second trimester termination of pregnancy?

### **Introduction**

Surgical - or instrumental - termination of pregnancy is defined as any approach to termination of pregnancy using instruments, either dilators, (suction) curettes or evacuation forceps (tongs). Up to about 17 weeks this is generally done by means of mechanical dilatation, followed by evacuation, without cervix priming.

In more advanced pregnancies, different regimes are followed in the abortion clinics which carry out this intervention, viz. no cervical priming, priming with misoprostol 400 microgram, orally or vaginally, or the two-step method in pregnancies above 17 weeks in nulliparae and above 19 weeks in multiparae (in the first step, the membranes are ruptured and the umbilical cord is severed; in the second step evacuation takes place).

### **Summary of the literature**

No relevant literature was found before 2005. In 2010, six articles were found on early and late complications of D&E. One was of such limited quality that it was not included (Pauli), the other five are described below.

Lohr (2008) wrote a review in which she discusses current interventions in the second trimester, including their safety, pros and cons, acceptability and associated complications. Her article also reviews methods which make surgical termination of pregnancy in the second trimester safer and more efficient, like cervical priming and treatment under ultrasound scanning. Although the question remains whether surgical or medical termination in the second trimester should be preferred, she claims that the basis for deciding which method is to be used is multifactorial. Specialized training and the experience of performing sufficient numbers of interventions are necessary to carry out a D&E safely. Choice of procedure is also affected by the presence or absence of necessary equipment; the availability of an operating theatre; the policy with respect to facilities; acceptance by staff and preference of patients. When D&E is offered, women do not always wish to be randomized for a medical intervention (Grimes, 2004).

Advantages for both caretaker and patient are the precise planning allowed by the procedure, the short treatment time and the avoidance of hospitalization.

Second trimester surgical termination is in the developing stage. Variation in methods for cervical priming, instrumentation and complementary interventions like foeticide are carried out to achieve optimal safety and efficiency in uterus evacuation.

Cervical priming may take place through mechanical dilatation, slowly expanding osmotic dilators, or medically, with misoprostol or mifepristone. Laminaria and Dilapan are preferred in pregnancies of longer duration, to reduce the risk of cervix impairment or perforation compared to mechanical dilatation alone. The use of Dilapan or laminaria primarily depends on the professional's preference; osmotic dilators are not available in all circumstances; besides, they require admission and an overnight stay.

Misoprostol has been studied as an alternative; it is cheap, almost always available, and suitable for self-administration via a variety of routes: oral, vaginal, buccal and sublingual. However, the ideal dose, route and limitation in terms of gestation stage have not been established yet. Buccal misoprostol in doses of 400-800 mcg would seem to serve as adequate cervical priming up to 18 weeks of gestation. Women also appear to prefer one day treatments. Further study is needed to establish the possible benefits of combination regimes, especially in the case of later stage pregnancies.

Excessive blood loss is the most common complication in second trimester surgical termination of pregnancy; its risk increases with pregnancy length. Excessive haemorrhage may be caused by impairment of the cervix or uterus, an incomplete procedure or failure of the uterus to contract. Moreover, the risk of DIC (Diffuse Intravascular Coagulation) increases during the second trimester.

Uterus perforation is a potentially dangerous complication in second trimester surgical termination of pregnancy, with an incidence of 0.2-0.4%. Routine use of ultrasound during the intervention proved to reduce the risk of perforation (Darney, 1989); cf. chapter 5 for a further discussion of the role of ultrasound (or sonography) during treatment.

Recent studies with respect to D&E and complications in future pregnancies did not reveal any relationship. Premature partus appears less likely when laminaria were used, compared to mechanical dilatation, possibly as a consequence of the smaller impact on the cervix. According to Lohr there are no data about the effects of misoprostol, which is generally followed up with mechanical dilatation, and the outcome of succeeding pregnancies. Currently, however, data are available, cf. Winner and Nucatola on this point (below).

Lohr concludes that D&E is a safe, cost-effective method for termination of

pregnancy for women who are in a position to choose for this method in the second trimester of their pregnancy.

In a 2006 study, Jackson tried to establish if the anamnesis of women undergoing mid-trimester D&E (at 12-24 weeks of gestation) shows an increased risk of complications during a successive pregnancy, compared with a control group who had not undergone this intervention. This concerns a retrospective cohort study into women with D&E during the second trimester, which included dilatation by laminaria japonica. Of the 317 women who underwent D&E, 85 had a vital successive pregnancy. These women delivered a little earlier than the 170 control group women (at 38.9 versus 39.5 weeks,  $p=0.001$ ), but there was no significant difference between the two groups with respect to birth weight, spontaneous premature partus, abnormal placentation and total number of complications.

This study is limited in a number of respects. To be able to indicate a difference in premature partus < 37 weeks the groups under study would have to number 169 and 338 women, respectively. Absence of a difference with respect to less frequent pregnancy complications may be based on a type II error.

Neither can this study pronounce itself on the influence of D&E on other reproductive outcomes such as future fertility, ectopic pregnancy, neonatal findings or a succeeding spontaneous first or second trimester abortion.

As it stands, this study predicts an acute complication risk of 0.3%, which is within the limits otherwise known from the literature (0.23%- 0.69%) (Grimes, 1977, Cates, 1982).

In a retrospective cohort study, Turok compared outcome and cost of second trimester termination of pregnancy using D&E between specialized abortion clinics, hospitals in which the procedure was carried out by an assistant medical practitioner, or induced abortion in hospitals otherwise. This study concerned women in hospitals with a pregnancy length of 13-24 weeks and in clinics with a pregnancy length of 13-21 weeks.

Major complications occurred in 11% of the women undergoing D&E in the hospital; in 10% in the case of hospital induction and 1% of the women undergoing D&E in a specialized clinic. The cost level, too, was very different; \$1,105 for treatment in the specialized clinic, \$4,425 for a D&E in the hospital and \$5,029 for a hospital induction.

The conclusion is that second trimester termination of pregnancy by means of D&E in selected patients in a specialized clinic may be safer and cheaper than D&E or induction in the hospital; especially the skill and expertise of the professional conducting the termination of pregnancy play a major role.

The objective of the study by Nucatola was to determine a number of serious complications during second trimester abortions by means of D&E after cervical priming with misoprostol, at a gestation of 12-16 weeks, in 6,620 interventions, using retrospective data analysis. The author claims that cervix priming reduces the length of the intervention, causes less pain and blood loss and therefore belongs to the standard procedures for second trimester termination of pregnancy. In this study a perforation risk of 0.45/1000 is shown, compared to figures in the literature of 0.8-7/1000 for abortions with D&E. Misoprostol as a cervix primer was not shown to lead to an increased risk of perforation.

Winer’s study (9) is a case control study, to ascertain the effect of misoprostol on the risk of late spontaneous abortions and premature partus in successive pregnancies. 245 women with a partus at 16-36 weeks and 490 controls who delivered at 37 weeks or beyond were included in this study. The anamnesis of forty cases (16.3%) and 56 controls (11.5%) showed cervix priming with misoprostol alone, or in combination with mifegyne, had taken place in the context of vacuum curettage, evacuation or medical termination of pregnancy.

With an OR of 1.33 (CI 0.81-2.17) it may be concluded that the results confirm that induced abortion by means of misoprostol is safe for later pregnancies.

**Conclusion**

<b>Level 3</b>	<p>D&amp;E is a safe and cheap method for termination of pregnancy in the second trimester.</p> <p>C     <i>Lohr 2008; Turok 2008</i></p>
----------------	---

### **3.3 Cervix priming in surgical termination of pregnancy**

#### **Guiding question**

What evidence can be derived from the (inter)national literature for the application of prostaglandins and the course of administration in second trimester termination of pregnancy?

#### **Introduction**

Prostaglandins have been used for a long time to prepare the mouth of the uterus (cervix uteri) for dilatation. Prostaglandins make dilatation easier. Blood loss during and after the intervention is restricted. Priming is often applied in surgical interventions. In the abortion clinics misoprostol is the prostaglandin almost exclusively used to prime the cervix. Effectiveness, side-effects and safety are elements discussed further below.

#### **Summary of the literature**

Various prostaglandin analogues have been developed. Misoprostol is a prostaglandin E1 analogue (PGE1), which came on the market in 1988. Before 2005, few studies were found: Todd's study (Todd et al., 2002) is non-randomized and only covers 110 women. After 2005, four articles are found which investigate priming with misoprostol in D&E.

In a double blind randomized study involving 83 women Goldberg et al. (2005) compare the effect of laminaria one day prior to surgery and misoprostol 400 microgram vaginally at 3-4 hours pre-op. They measured spontaneous dilatation with either method, of 14 mm with laminaria and 11 mm with misoprostol before suction curettage, optionally followed up by an instrument, at a pregnancy length of 13-16 weeks. With nulliparae the intervention proceeds more quickly and smoothly with laminaria, in multiparae there is no difference. Women preferred misoprostol, as it requires only one visit to the clinic.

Carbonell et al. (2007) studied the effect of mifepristone administered two days prior to D&E. They randomized 900 women with a pregnancy length between 12 and 20 weeks across four groups in a prospective non-blinded trial. 450 women were given mifepristone 200 mg 2 days before D&E, the others were not. On the day of treatment, half the women in both groups received 600 microgram misoprostol vaginally and the other 225 received 600 microgram misoprostol sublingually. In the case of a rigid cervix Dilapan was added in all groups. One of the aspects studied was the degree of dilatation achieved without effort and the duration of the intervention.

In the mifepristone group 12.5 mm of dilatation was found; this was 8.5 mm without mifepristone. No relationship was found with respect to the misoprostol route. The time needed before the intervention was shorter in the mifepristone group: 1.7 versus 2.1 hours, respectively ( $p < 0.001$ ). The duration of the intervention itself was shorter in the mifepristone group in combination with sublingual misoprostol: 11.9 vs. 13 minutes ( $p = 0.007$ ); in the vaginal misoprostol group the difference was also observed, but was non-significant: 12.3 vs. 13 minutes,  $p = 0.031$ . In the mifepristone group cervix rigidity decreased from 65% to 15%, with less frequent application of Dilapan as a result.

Carbonell et al. arrive at the following conclusions. There are some problems attached to the use of mifepristone two days before the intervention, like increased costs (200 mg mifepristone comes at about €25,-); the fact that the woman needs to visit the clinic twice; the possibility of expulsion of the foetus before the actual intervention and the possibility of teratogenicity in women who do not return for a D&E. No indications of the latter problem arising have been found as yet, however. In contrast, they also observe advantages in the use of mifepristone two days before a D&E. One is the shorter waiting time after administration of misoprostol on the day of the intervention; further, the clear reduction in the use of Dilapan, which in itself saves on costs (one dose of Dilapan costs €20,-) and less risk of cervical lacerations. The biggest shortcoming in this study is the use of Dilapan, which was not applied at random, in contrast with other studies.

Edelman et al. (2006) gave 400 microgram misoprostol or a placebo 60 to 90 minutes before a D&E after laminaria one day earlier in women with a pregnancy length of 13 up to 15+6 weeks and from 16 to 20+6 weeks and observed the maximum dilatation achieved and the effort needed for dilatation. They found no significant differences. But if they only considered pregnancies from 19+0 onward, they did find a significant difference. However, the study had not been properly set up to fully warrant this latter finding.

Patel et al. (2006) undertook a descriptive retrospective study into the safety and effectiveness of buccal misoprostol in various dosages, sometimes combined with laminaria, in 19 different member centres of the Planned Parenthood Federation of America. These centres use the buccal misoprostol protocols in a number of variations, combined with laminaria or not, at one, two or three days prior to treatment. Of 2,218 women with an amenorrhoea between 12 and 23+6 weeks they looked at the (serious) adverse events registered, the ease of dilatation and side-effects. They found 19.39/1000 adverse events, of which 4.51/1000 were classified as serious, defined as: death; life-threatening medication problems; hospitalization or prolonged hospital stay; lasting or important disability or a disease. In 75.3% the

ease of dilatation was found to be adequate; they remarked that misoprostol at lower dosages is more adequate, both with and without laminaria. Side-effects increase with the dosage strength of the misoprostol. The authors conclude that there is no reason for worries with respect to the use of buccal misoprostol in D&E in the second trimester of the pregnancy.

The literature found does not suggest any adaptation of the usual dose of 400 mcg misoprostol as priming in the second trimester; there are no grounds for preferring a specific route, be it vaginal, sublingual, buccal or oral.

The further the pregnancy has progressed, the greater the sensitivity to uterotonics. As a result, gradually decreasing levels of misoprostol are needed to achieve the same effect (Goldberg e.a., 2001). For the induction of a termination of pregnancy 800 µg (every 12 hours) is needed in the first trimester (Darney&Sweet, 1989). In the third trimester this is only 50 µg (every 12 hours). The dosage for induction in the second trimester probably lies between 50 µg and 800 µg, showing decreasing necessary dosages for misoprostol as the number of weeks increases (Darney&Sweet, 1989).

In principle, Misoprostol shows the same dosage dependent side-effects (Goldberg e.a., 2001; Shannon e.a., 2004; Sivalal e.a., 2004) as other prostaglandins do, with gastro-intestinal side-effects, pain and fever (more than 38° Celsius rectally) as the most common (Goldberg e.a., 2001; Shannon e.a., 2004; Sivalal e.a., 2004; Goldberg e.a., 2003; Ngai e.a., 2003; Vimala e.a., 2004).

Prostaglandins have been associated with coronary failures (Goldberg e.a., 2001; Ngai e.a., 2003) and bronchospasms (Goldberg e.a., 2001), but these have never been reported for misoprostol. (Cf. also first trimester medical termination of pregnancy in the previous chapter).

Misoprostol may cause preoperative blood loss, but this is mostly modest (Sivalal e.a., 2004); however, serious blood loss may occur (Shannon e.a., 2004; Sharma e.a., 2005). The higher the dosage (Goldberg e.a., 2001; Goldberg e.a., 2003) and the longer the priming interval (Vimala e.a., 2004), the greater the risks.

### Conclusion

<b>Level 3</b>	It is likely that misoprostol 400 µg vaginally, three to four hours prior to the intervention, enables sufficient dilatation of the cervix D&E.	
	A2	<i>Goldberg et al., 2005, Edelman et al. 2006</i>
	C	<i>Todd et al., 2002</i>
	D	<i>RCOG guideline, 2004; SFP guidelines, 2007 en 2008</i>



### **3.4 The use of misoprostol after sectio caesarea**

#### **Guiding question**

Can misoprostol be used for a D&E after a sectio caesarea (C-section)?

#### **Introduction**

In practice it is suspected that the use of misoprostol in connection with a D&E after an earlier C-section increases the risk of a uterus rupture. This prompted a specific search for data on this subject.

#### **Summary of the literature**

Two systematic reviews appeared in 2009 with respect to the use of the prostaglandin misoprostol in the case of a second trimester termination of pregnancy after an earlier C-section, one by V. Berghella e.a. and one by V. Goyal. From the Berghella review (2009) of case studies and cohort studies in women with a pregnancy length of 16-28 weeks, in whom misoprostol was used as initial priming agent, the chances of a uterus rupture were established in the case of one earlier low transversal C-section 0.43% (95% CI 0.08-1.67%). When cases from case reports are added, this figure rises to 1.1%. Out of the five cases of uterus rupture found, three took place at 26 weeks; two of these were given oxytocin in addition to misoprostol. The other two cases, which took place under 26 weeks, received an overall dose of misoprostol equal to or greater than 1000 microgram. No uterus rupture was found in 46 cases with two earlier low transversal C-sections. From case reports two cases were uncovered. In either case there were additional risk factors involved, like chorioamnionitis in one of them; the other occurred during curettage. Of the seven cases of three prior C-sections none had a uterus rupture. Of the two cases of earlier classic C-sections one woman suffered a rupture (a fact from a personal retrospective data analysis by Berghella). The data are thus too limited to warrant judgment on the safety of misoprostol in second trimester termination of pregnancy in women with one or more low transversal C-section or after prior classic C-section. The conclusion is that misoprostol appears to be a safe abortion-inducing agent in women with one earlier low transversal C-section in their anamnesis, in the context of a second trimester termination of pregnancy; additional use of oxytocin, however, must be kept at a minimum.

In his systematic review, Goyal (2009) calculates risk levels of 0.28% (95% CI 0.08-1.00%) for uterus rupture in women with a prior C-section versus 0.04% (95% CI 0.01-0.20%) in women without prior C-section in their anamnesis. The study is concerned with the use of misoprostol in termination of pregnancy in the second

trimester. Goyal reviewed studies in which misoprostol alone was applied in women with one low transversal C-section and found a risk of 0 (95% CI 0-1.48%) among 256 women. When combined with another induction method use of misoprostol showed a risk of 0.43% (95% CI 0.12-1.55%) in women with a C-section in their anamnesis and 0.06% (95% CI 0.01-0.31%) in women with no C-section. In the two cases in which uterus rupture occurred, there had been induction by means of mifepristone, while misoprostol had been added to other agents. The review concluded that women with one prior low transversal C-section undergoing induction in the context of a second trimester termination of pregnancy with misoprostol only run no additional risk of a uterus rupture; when mifepristone is used, the risk amounts to 1.15% (95% CI 0.45-2.92%). In view of the small numbers the risk of a uterus rupture cannot be determined with sufficient statistical accuracy from these findings with respect to the use of mifepristone.

Besides these systematic reviews and the articles reviewed in them, two recent publications were uncovered, one about misoprostol, administered vaginally in a second trimester termination of pregnancy, and one about the safety of D&E in the case of a scarred uterus.

A study by Naguib (2010) concerns a prospective observation in women with a C-section in their anamnesis. They received induction with vaginally administered misoprostol 4x200 microgram every 4 hours in the context of a second trimester termination of pregnancy, at a gestation stage of 16 to 20 weeks. There were no cases of uterus rupture. As the study included no more than 50 women with a C-section in their anamnesis the authors conclude that inducing abortion in the second trimester by means of misoprostol at low dosages appears safe, but that larger-scale studies are needed to validate the results.

In a study by Ben Ami (2009) the safety of a D&E is determined in cases of scarred uterus in second trimester termination of pregnancy at 17-24 weeks of gestation, with prior use of laminaria japonica. They come to the conclusion that there are probably no raised levels of peri-operative risk, but that larger studies involving more subjects are needed to confirm these results.

**Conclusions**

<b>Level 3</b>	<p>It may be assumed that misoprostol is a safe abortion-inducing agent in the second trimester in women with a history of one low transversal C-section.</p> <p style="text-align: right;"><i>C Berghella 2009; Goyal 2009</i></p>
----------------	---

<b>Level 3</b>	<p>It is possible that mifepristone in women with one low transversal C-section in their anamnesis forms an additional risk in medical second trimester termination of pregnancy, as opposed to D&amp;E.</p> <p>C <i>Berghella 2009</i></p>
----------------	---

<b>Level 3</b>	<p>There are indications that additional oxytocin besides misoprostol, used for the induction of a D&amp;E in the context of a second trimester termination of pregnancy in women with one low transversal C-section in their anamnesis raises the risk of a rupture.</p> <p>C <i>Berghella 2009</i></p>
----------------	--

### 3.5 Mixed approaches

#### Guiding question

Is the two step method useful for termination of pregnancy in the second trimester of pregnancy?

#### Introduction

The term mixed approach refers to the two step method already described (cf. the Introduction under Surgical Termination of Pregnancy). In a specific search in March 2010 two references from Sweden were found, which are not accessible to us. RCOG mentions the two step method in its description of options for the second trimester. The search also lead to an article in which a study was described into foeticide prior to treatment with KCl (Elimian 1999).

#### Summary of the literature

In a retrospective status study, Elimian (1999) investigated 68 cases, to determine the effect of a cardiac puncture with KCl on the course of treatment with PGE2, in terms of the time lapse before expulsion and the necessary dose of PGE2. Twenty-two women received this priming treatment. The average time before expulsion is reported to be shorter when spontaneous intra-uterine foetal death (IUFD) occurs compared to intact pregnancies. Although there was a slight statistical deviation in the group with cardiac puncture with respect to gestation stage (21.7+/- 1.7 weeks versus 20.3 +/- 1.4 weeks) the average dose of PGE2 needed and the time interval from the start of the treatment with PGE2 until expulsion proved significantly shorter in the group with cardiac puncture.

#### Conclusion

<b>Level 3</b>	<p>It may be assumed that foeticide requires lower levels of prostaglandin and reduces the time interval before spontaneous expulsion.</p> <p><i>B      Elimian 1999</i></p>
----------------	--

### 3.6 Medical termination of pregnancy

#### Guiding question

What is the most efficient and effective medical course of treatment (including mixed approaches) for termination of pregnancy in the second trimester of the pregnancy?

#### Introduction

Medical termination of pregnancy in the second trimester consists of administering mifepristone on day one followed up by misoprostol according to a variety of regimes at admission two days later. In The Netherlands, this course of treatment is only practised in hospitals.

For the standard procedure in Dutch hospitals we refer to NVOG's<sup>1</sup> guideline "Termination of pregnancy up to 24 weeks" (2005).

#### Summary of the literature

In a double blind randomized controlled trial, Dickinson et al. (2002) studied the effectiveness and side-effects of three different dosages of vaginally applied misoprostol to effect termination of pregnancy between 14 and 30 weeks (Shannon e.a., 2004). In this trial, 150 women were randomly assigned to one of three groups, each with a different dosage. It is unclear from this study if part of the abortions were carried out on social indication. This may have been the case in 22 women at most: for these women, the indication for a termination of pregnancy was stated as 'maternal reasons', the others were cases of foetal death or foetal abnormality. This makes it difficult to interpret the results of this study for their adoption in the present guideline. In the group with the lowest dosage the time interval before abortion was longer than in the other groups (18.2 hours vs. 15.1 and 13.2 hours,  $p = 0.035$ ); besides, the percentage reaching abortion within 24 hours was smaller ( $p = 0.013$ ) and the percentage after 48 hours was larger ( $p = 0.021$ ). There was no difference as regards side-effects between the three groups.

In a study by Wong et al. two different regimes of vaginally administered misoprostol were compared in women with a pregnancy length of 14 to 20 weeks. In the high dosage group (400  $\mu\text{g}$  every three hours, with a maximum of five times in 24 hours) the time interval before abortion as calculated from the first dose was shorter than in the low dosage group (400  $\mu\text{g}$  every six hours, with a maximum of three times per 24 hours): the time intervals were 24.4 versus 43.4 hours on average ( $p < 0.01$ ). The success rate for termination of pregnancy within 48 hours was also higher in this

---

1

group (90.5% versus 75.7%,  $p < 0.02$ ). The side-effects noted in either group were more or less similar, with the exception of a higher incidence of fever in the high dosage group.

In a single blind randomized trial, Ngai et al. (2000) compared the differences in effects and side-effects of orally administered misoprostol 400 µg with vaginally administered misoprostol 200 µg. The administration of misoprostol was placebo-controlled and occurred after all 142 women in this study, who had been pregnant between 14 and 20 weeks, had received mifepristone. The women received a little over four doses of misoprostol on average, irrespective of the course of administration: oral or vaginal. However, in view of the differences in dosage between both courses, it may be concluded that a double dose of misoprostol is required when administered orally compared to the vaginal route of administration. Side-effects like nausea, dizziness, vomiting and fatigue were similar across both groups. The women who had been administered misoprostol orally suffered more from diarrhoea than women who had been given the vaginal application of this agent. Women who did not have an abortion within 24 hours did not have a preference for one of either method. Women who did succeed in reaching an abortion within 24 hours largely preferred oral administration, because they found it more suitable or less painful, or for reasons of privacy.

In the literature search carried out in 2010 various articles were found about second trimester medical termination of pregnancy, a number of which will be summarized below.

In a prospective randomized study among 54 women with a pregnancy length between 14 and 26 weeks, Nor Azlin et al. (2006) compared misoprostol 200 mcg vaginally every twelve hours (four doses max.) with Gemeprost 3 mg vaginally every three hours (five doses max.). They looked at time intervals before abortion, side-effects, experienced pain and costs. There was no significant difference between the number of women in both groups delivering within 48 hours. The women in the misoprostol group did have an earlier delivery (19.15 hours+14.70 versus 28.26 hours+48.52), but this difference was not significant either. Side effects and pain experience were equal in both groups, except that the Gemeprost group showed significantly more fever. In both groups subsequent curettage was required: 29.6% in the misoprostol group and 37% in the Gemeprost group. Treatment with misoprostol is much cheaper than with Gemeprost: \$ 0.60-2.30 versus \$ 48-122.

In a study by Bhattcharyya et al. (2006) 138 women (at 14 to 20 weeks) were randomly assigned to different regimes of misoprostol: group A received 400 mcg

misoprostol vaginally every three hours and group B a starting dose of 600 mcg, followed up by 200 mcg every three hours; in both groups a twelve hour administration pause was respected after twelve hours. The time interval between induction and abortion was similar for either group (about twelve hours), but women in group B with three or more previous children delivered more quickly. This group also needed significantly less misoprostol and showed significantly less fever. Only few women did not deliver within 48 hours in this study; it was not recorded whether an intervention was started when the placenta had not been born two hours after the foetus.

Copying first trimester trials Chai et al. (2009) set up a randomized prospective trial in 2009, to look at the option of administering mifepristone and misoprostol simultaneously, compared with the standard administration of misoprostol after 36-38 hours. 141 women were randomized: the time interval before abortion was shorter for the standard treatment: 4.9 hours vs. 10 hours ( $p < 0.0001$ ). After 24 hours, 100% of the subjects in the standard group had delivered and 91.5% in the intervention group;  $p = 0.028$ . Cold shivers and fever occurred significantly less frequently for the standard treatment; this is probably due to the much lower dosage of misoprostol.

The benefit of simultaneously starting mifepristone and misoprostol is a reduction of the woman's visits to the clinic by one. However, from research it had become clear that this advantage does not outweigh the disadvantages, namely that the woman delivers at home and needs to use more misoprostol before successful abortion; besides, after simultaneous administration the time interval before abortion is much longer, while 9.5% of the women had not delivered after 24 hours.

In a double blind randomized trial, Oi Shan Tang et al. (2005) compared oral and sublingual administration of 400 microgram misoprostol every three hours at a pregnancy length of 12-20 weeks. The sample size of 120 was based on the hypothesis that, in the sublingual group, 20% more women would deliver within 24 hours. However, this was not demonstrated: 91.5% vs. 85% is not significant. As the time interval until abortion does prove to be significantly shorter, they conclude that sublingual is superior to oral. In view of the set-up it is questionable if this conclusion is valid.

In two trials, Yilmaz et al. (2005, 2007) tried to ascertain if the wide variation in absorption of vaginal misoprostol could be improved by moistening the tablets with a physical salt solution or acetic acid, respectively. They compared dry tablets with

tablets moistened with a physiological salt solution in 2007 and did not find any differences. In 2005 they compared physiological salt with acetic acid and found that acetic acid would speed up the effect of misoprostol. However, Yilmaz does mention that contradictory findings were obtained in earlier trials. The acetic acid study was small and its sample size based on a small pilot.

In a randomized non-blinded trial, Bhattacharjee et al. (2008) compared the administration of sublingual versus vaginal misoprostol in nearly 300 women. They found no differences with respect to complete abortions after 24 and 48 hours, nor in the time interval until the delivery of the foetus, nor in side-effects. However, in both groups women preferred sublingual administration.

Karsidag et al. (2009) found the same outcome in a group of 49 women.

The only reference found for The Netherlands is Jansen et al. (2008). They compared mifepristone and misoprostol with Dilapan and Sulproston in 16 women. They concluded that there is no difference in effectiveness, as their hypothesis that they would achieve a time reduction of 50% - of 36 to 18 hours - until delivery was not proven to hold true and the Sulproston group already delivered after 20 hours. However, the Sulproston group had already been hospitalized for 24 hours at the start of the treatment with Sulproston. They decided to alter their protocol to mifepristone and misoprostol.

Von Hertzen et al. (2009) conducted a double blind randomized multicenter trial in seven countries and compared vaginal versus sublingual administration of misoprostol. They concluded that vaginal administration in nulliparae is more effective (lower failure rate after 24 hrs.). Apart from that they only found more fever after vaginal administration.

Hamoda et al. (2005) compared the sublingual and vaginal routes, but the trial's strength is too small for valid conclusions about effectiveness; their calculation of the sample size was inadequate. Women found their own route acceptable. Women in the sublingual group suffered more from an unpleasantly tasting mouth, in the vaginal group there was more flushing and lethargy. The sublingual group received more pain medication.

In a randomized trial among 162 women, Caliskan et al. (2009) found that 100 mcg sublingually in twelve doses every two hours is equally effective as 200 mcg sublingually with the same administration schedule.

Because the median treatment time after admission varies from 12 to 18 hours, (Dickinson et al., 2002; Tang et al., 2005; Yilmaz et al., 2007; Bhattacharjee et al.,



2008; Karsidag et al., 2009; Caliskan et al., 2009) and the practical consequences of this fact, this type of treatment is not possible in the setting of Dutch abortion clinics. It is a drawback of medical treatment that a surgical intervention turns out to be necessary after all in 10-30% of the cases, due to placenta retention and haemorrhages (Dickinson et al., 2002; Nor Azlin et al., 2006; Yilmaz et al., 2005; 2007).

It is noticeable that part of the studies discussed were done in the case of intra-uterine foetal death or foetal abnormalities (Yilmaz et al., 2005; 2007; Karsidag et al., 2009; Jansen et al., 2008).

## Conclusions

<b>Level 2</b>	<p>It may be assumed that a high loading dose (600 mcg) of misoprostol alone, followed up by more frequent administration of further doses improves the effectiveness of medical termination of pregnancy in the second trimester.</p> <p><i>A2 Dickinson, 2002</i> <i>B Wong, 2000; Bhattacharyya, 2006</i></p>
----------------	--

<b>Level 2</b>	<p>It may be assumed that simultaneous administration of mifepristone and misoprostol is less effective than administration of mifepristone at 36-48 hours before misoprostol</p> <p><i>B Chai, 2009</i></p>
----------------	--

<b>Level 3</b>	<p>In nulliparae, vaginal administration of misoprostol is more effective than sublingual administration, but this is not true for other women.</p> <p><i>B von Hertzen, 2009</i></p>
----------------	---

<b>Level 3</b>	<p>There are indications that women prefer sublingual administration of misoprostol.</p> <p><i>B Bhattacharjee, 2008</i></p>
----------------	--

### **3.7 Surgical versus medical termination of pregnancy**

#### **Guiding question**

What is the optimal method for termination of pregnancy in second trimester pregnancies?

#### **Introduction**

To be able to answer the question above a search was made for studies comparing surgical, medical and mixed courses of treatment. Little literature appeared to exist.

#### **Summary of the literature**

An attempt to compare medical (mifepristone followed up by misoprostol) and surgical termination of pregnancy (after insertion of laminaria instead of cervix priming with misoprostol) in the second trimester was undertaken by Grimes et al. (2004). The outcome appeared to favour surgical termination of pregnancy. Women who were treated with the combined medication suffered significantly more pain than women who underwent dilatation and evacuation ( $p = 0.03$ ; assessment of pain on a five point scale). As regards other outcome measures, no differences were found. The number of women willing to participate was small ( $n=18$ ), as women preferred surgical treatment and did not wish to be randomized. The trial was therefore prematurely stopped.

In 2010, two attempts were made to compose systematic reviews of the literature on this subject. Grossmann et al. searched Pubmed for English language RCTs<sup>2</sup> and cohort studies, using the following search terms: second trimester abortion, mid-trimester abortion, dilatation and evacuation, mifepristone and misoprostol. Because they found little, they extended their search to include cohort studies and successive case studies with more than 400 patient subjects. They particularly looked at complications like uterus perforation or rupture; haemorrhage necessitating transfusion; incomplete abortion necessitating surgical evacuation; cervical lesions; infection and other complications reported. They only found one RCT, viz. the one by Grimes et al. (2004) mentioned above, a retrospective cohort study from which an OR of 0.1 (CI 0.0-0.3) for adverse events was calculated for D&E vs. medical treatment.

In five articles, over 400 cases of D&E were studied. In addition, they found a case series with mifepristone-misoprostol.

---

<sup>2</sup> RCT: Randomized controlled trial

**Table 2. Summary of complications reported in six single-method studies: five D&E studies and one mifepristone–misoprostol study**

Country/year	D&E					Mifepristone– misoprostol
	United States <sup>9</sup> 1972– 1981	United States <sup>11</sup> 1979– 1980	Viet Nam <sup>13</sup> 1999– 2002	Canada <sup>10</sup> 1986– 1990	United States <sup>12</sup> 2002– 2003	Scotland <sup>4</sup> 1994– 2001
Weeks of pregnancy	13–26	13–16.5	13–18	15–20	12–23.9	13–21
Number of cases	11,747	1,392	439	547	2,218	1,002
Uterine perforation	0.4%	0	0.5%	0.2%	0.2%	0
Uterine rupture	0	0	0	0	0	0.1%
Haemorrhage requiring transfusion	0.2%	0.6%	0.2% <sup>a</sup>	0.2%	0.09%	0.7%
Incomplete abortion	0.3%	1%	0	0.4%	0.05%	8%
Cervical laceration with repair	1% <sup>b</sup>	0	0.2%	0	0.1%	0
Mild infection	0.8%	4.1% <sup>c</sup>	0	2%	0.09%	2.6% <sup>d</sup>
Severe infection	0.06%		0	0.4%	0.05%	0

*a* There were no cases requiring transfusion. The one case of haemorrhage required a hysterectomy.

*b* This series included cases in which laminaria or other forms of cervical preparation were not used, and a higher proportion of cases at 18 weeks or higher gestation that did not receive laminaria experienced cervical lacerations.

*c* Among the 507 women with follow-up data. Prophylactic antibiotics were not used. Severity of infection was not clearly defined.

*d* Among the 354 women with follow-up data.

They concluded that the evidence found suggests as regards complications that D&E, when in trained hands, should be preferred to medical termination of pregnancy. This claim is premature, as the medical intervention described in the literature generally concerns later terminations of pregnancy. They propose to have a larger randomized trial carried out.

Lohr (2008) undertook a systematic Cochrane review, looking for studies comparing D&E and medical abortion in the second trimester and also just found the study by Grimes et al. (2004) mentioned above and an earlier Grimes study dating from 1984.

The issue of Reproduction Health Matters mentioned earlier contains an essay by Grimes (2008) – who performed much research into surgical termination of pregnancy – in which he advocates surgical termination of pregnancy on bio-ethical and biological grounds. A surgical procedure avoids the situation that a woman has

to deliver an unwanted foetus, accompanied by assisting staff, and puts the burden of the termination of pregnancy primarily on the doctor's shoulders.

**Conclusions**

<b>Level 3</b>	Women in the second trimester of their pregnancy appear to suffer less pain during termination of pregnancy via D&E than during an abortion with mifepristone and misoprostol.  <i>B Grimes, 2004</i>
----------------	---

<b>Level 3</b>	D&E is increasingly safe thanks to cervix priming with misoprostol and the growing use of ultrasound.  <i>A2 Grossman, 2008</i> <i>D Lohr, 2008</i>
----------------	--

<b>Level 1</b>	The number of complications in both surgical and medical termination of pregnancy is low; in D&E the number is lower.  <i>A1 Grossman, 2008</i>
----------------	---

<b>Level 4</b>	Grimes claims that D&E is the preferred method for termination of pregnancy on social indication, as this procedure puts the burden of the termination of pregnancy on the physician's shoulders, too, and not just on the woman with the unwanted pregnancy and paramedic staff.  <i>D Grimes, 2008</i>
----------------	--

### **3.8 Discussion and evaluation**

In Dutch abortion clinics second trimester termination of pregnancy is carried out by D&E, involving cervix priming in a variable number of cases. In Dutch hospitals, in the majority of cases, second trimester termination of pregnancy is carried out on social indication in the event of foetal abnormalities. Medical termination is especially applied in pregnancies beyond the 18<sup>th</sup> week. If the woman prefers termination via D&E she is referred to one of the abortion clinics.

In The Netherlands, but also in the United States, Canada, England and Wales, the majority of elective second trimester terminations of pregnancy is performed with D&E. This is unlike the Northern European countries, where many medical interventions take place.

In abortion clinics medical termination of pregnancy is not offered because all interventions are polyclinic and must be carried out within 24 hours at the most. On the basis of the literature found it cannot be concluded whether medical termination or D&E is the best course of treatment in the second trimester. However, the study group finds that D&E is safer, more efficient and effective, providing the abortion specialist has ample skills.

Women usually prefer D&E, because it is commonly an outpatient intervention. It is recommended that hospitals and abortion clinics in each region come to an understanding about reciprocal referrals.

The safety of termination of pregnancy is partly determined by the method used, but also, and especially so, by pregnancy length. The table shows that postponing termination of pregnancy renders the intervention less safe (cf. table 2). In the case of second trimester D&E it is therefore necessary that the intervention is carried out by trained medical professionals in specialized second trimester clinics (Turok, 2008).

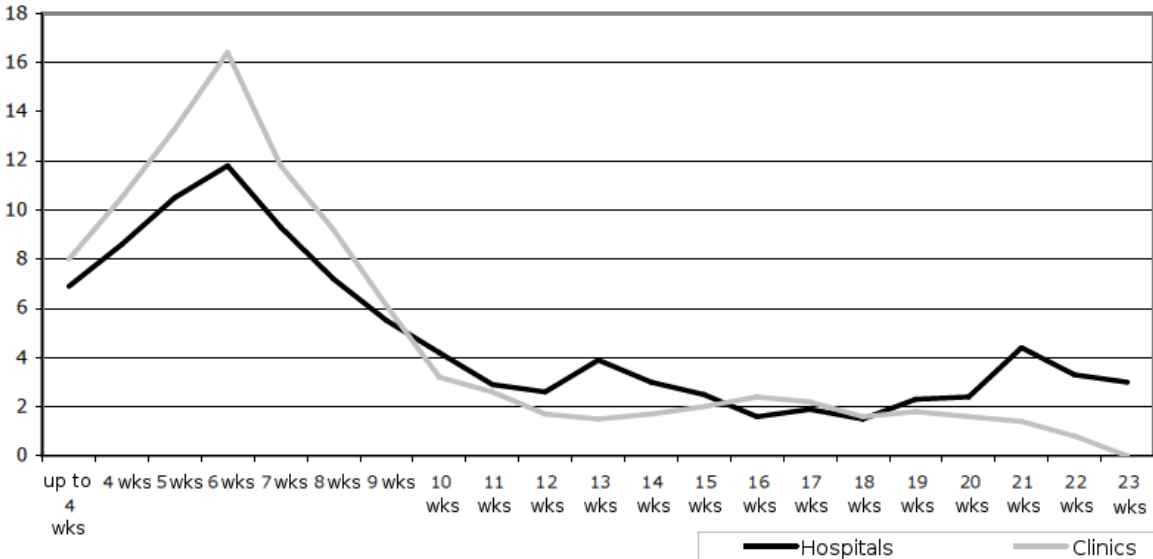
Two deaths after termination of pregnancy were reported to the committee investigating maternal death in The Netherlands between 1993 and 2005 (personal communication dr. J.J.M.van Roosmalen, committee chairperson). Roughly speaking this implies an incidence of 0.5 per 100,000 terminations of pregnancy. In neither case was the cause of death a direct consequence of the termination of pregnancy.

Table 2. Case-Fatality Rates for Legal Abortion, by Procedure and Gestational Age, United States, 1972 to 1987\*

Procedure	Gestational Age						Total
	≤8 wk	9–10 wk	11–12 wk	13–15 wk	16–20 wk	≥21 wk	
Curettage	0.3	0.7	1.1				0.5
Dilation and evacuation†				2.0	6.5	11.9	3.7
Labor induction				3.8	7.9	10.3	7.1
Total‡	0.4	0.7	1.1	2.2	6.9	10.4	1.0

\* Deaths per 100 000 abortions. Data obtained from Lawson et al. (33).  
 † Dilation and evacuation is instrumental abortion through the cervix at 13 or more weeks of gestation.  
 ‡ Includes deaths from other rare procedures, such as hysterotomy or hysterectomy.

**Relative distribution of termination of pregnancy by pregnancy length in 2009; terminations carried out in hospitals and clinics, respectively, as a percentage of the total number of terminations in hospitals and clinics (Igz, 2010; p.20).**



Of the total number of abortions the proportion of second trimester terminations (terminations of pregnancy beyond 13 weeks) was 16.2% (5,257). Most second trimester terminations of pregnancy, 4,688 out of 5,257 (89.2%) were performed by the 9 abortion clinics with a second trimester license. The remaining 530 second trimester terminations (10.8%) took place in 46 hospitals, mostly in academic medical centres (Igz, 2010; p.23).

The share of hospitals in second trimester abortions has tripled since 2000, from 3.4% to 10.8% (Igz, 2010; p. 42). Especially in 2007-2008 there was a relative increase in second trimester terminations in hospitals, particularly at a duration of 20 to 24 weeks. In 2006 7.4 percent of all abortions in hospitals were terminations between 20 and 24 weeks (140); in 2007 this was 11.5% (227) and in 2008 13.4% (276) (Igz, 2010; p. 37). In 2009 288 terminations between 20 and 24 weeks were carried out in hospitals: a small increase compared to 2008 (4%). The proportion of this group compared to the total of terminations in hospitals decreased slightly, to 13.2% (Igz, 2010; p. 23-24).

Total number of terminations of pregnancy per Dutch province in 2009, in hospitals or clinics, with specifications for the number of second trimester terminations of pregnancy and, separately, the number of early medical

	Total		Hospitals		Clinics		
	Total	2nd trimester	Total	2nd trimester	Total	Early abortions	2nd trimester
Groningen	1,359	1	72	1	1,287	617	0
Friesland	117	12	117	12	--	--	--
Drenthe	73	3	73	3	--	--	--
Overijssel	1,703	68	86	68	1,617	481	0
Gelderland	2,015	83	99	66	1,910	684	17
Flevoland	362	0	362	0	--	--	--
Utrecht	2,468	727	119	85	2,349	0	642
Noord-Holland	9,626	2,416	751	110	8,875	2,682	2,306
Zuid-Holland	10,538	1,390	386	129	10,152	2,198	1,261
Zeeland	423	0	9	0	414	161	0
Noord Brabant	2,078	61	80	61	1,998	515	0
Limburg	1,665	495	45	34	1,620	314	462
<b>Total</b>	<b>32,427</b>	<b>5,257</b>	<b>2,199</b>	<b>569</b>	<b>30,228</b>	<b>7,652</b>	<b>4,688</b>

abortions (IGZ, 2010; p. 42).

There has been little research comparing D&E and other (medical) courses of treatment, but at the Fiapac conference of October 2010 Marijke Alblas (2010) presented the results of a study comparing D&E and medical induction with misoprostol in pregnancies of 13-20 weeks. 220 women underwent D&E after cervical priming with misoprostol; 84 underwent medical induction. D&E was more effective, showed shorter admission times and fewer serious complications.



In The Netherlands, too, it should be possible to undertake such a study, comparing hospitals and abortion clinics.

## **Recommendations**

For women in their second trimester of pregnancy, D&E is recommended for use in abortion clinics.

In hospitals, women should be offered a choice between medical termination of pregnancy and D&E; for the latter option, the woman should be referred to an abortion clinic.

The study group recommends the institution of a national working group to develop a registration system for late complications of second trimester termination of pregnancy.

The use of misoprostol as cervical priming in the second trimester is recommended.

It is recommended to apply D&E, with misoprostol priming if necessary, for second trimester termination of pregnancy in the case of women with one low transversal C-section in their anamnesis.

### 3.9 References

- Igz (2010). *Jaarrapportage 2009 van de Wet afbreking zwangerschap* Den Haag: Inspectie voor de Gezondheidszorg [www.igz.nl](http://www.igz.nl).
- Lohr PA, *Surgical Abortion in the Second Trimester, Reproductive Health Matters*, Volume 16, Number 31, supplement 2008,151-61
- Grimes DA, Smith MS, Wtham AD. *Mifepristone and Misoprostol versus dilatation and evacuation for midtrimester abortion: a pilot randomised controleed trial*, BJOG, 2004; 111:148-53
- Darney P, Sweet RL, *Routine ultrasonography for second trimester abortion reduces incidence of uterine perforation*, J Ultrasound Med 1989, 8:71-5
- JacksonJE, Grobman WA, Haney E, Casele H. *Mid-trimester dilation and evacuation with laminaria does not increase the risk for severe subsequent pregnancy complications*. International Journal of Gynaecology an Obstetrics, 2007, 96(1):12-5
- Grimes DA, SchulzKF, Cates W, Jr., Tyler CW, Jr. *Mid-trimester abortion by dilatation an evacuation: a safe and practical alternative*. N.Engl.J.Med. 1977;296:1141-45
- Cates W. Fr., Schulz KF, Grimes DA, Horowitz AJ, Lyon FA, Kravitz FH et al. *Dilatation and evacuation procedures and second-trimester abortions. The role of physician skill and hospital setting*. JAMA 1982;248:559-63
- Turok DK, Gurtcheff SE, Esplin MS, Shah M, Simonsen SE, Trauscht-Van HJ, et al. *Second trimester termination of pregnancy: a review by site and procedure type*. Contraception 2008;77(3):155-61
- Nucatola D, Roth N, Saulsberry V, Gatter M. *Serious adverse events associated with the use of Misoprostol alone for cervical preparation prior to early second trimester surgical abortion (12-16 weeks)*. Contraception 2008;78(3):245-8
- Winer N, Resche-Rigon M, Morin C, Ville Y, RozenbergP. *Is induced abortion with misoprostol a risk factor for late abortion or preterm delivery in subsequent pregnancies?* European Journal of Obstetrics, Gynecology & Reproductive Biology 2009;145(1):53-6
- Todd CS, Soler M, Castleman L, Rogers MK, Blumenthal PD. *Buccal Misoprostol as cervical preparation for second trimester pregnancy termination*. Contraception. 2002;65:415-8
- Goldberg AB, Drey EA, Withaker AK, Mi-Suk Kang, Meckstroth KR and Darney PD. *Misoprostol compared with laminaria before early second-trimester surgical abortion: a randomized trial*. Obestetrics and Gynecology, 2005;106(2):234-41
- Carbonell JL, Garcia Gallego F, Perez Llorente M, Bermudez SB, Sanchez Sala, E, Varela Gonzale L, Sanches Texido C. *Vaginal vs. sublingual Misoprostol with mifepristone for cervical primin in second-trimester abortion by dilation and evacuation: a randomized clinical trial*. Contraception. 2007;75:230-7
- Edelman AB, Buckmaster JG, Goetsch MF, Nichols MD, Jensen JT. *Cervical preparation using laminaria with adjunctive buccal misoprostol before second trimester dilation and evacuation procedure: A randomized clinical trial*. American Journal of Obstetrics and Gynecology. 2006;194:425-30
- Patel A, Talmont E, Morfesis J, Pelta M, Gatter M, Momtaz MR, Piotrowski H, Cullins V, *the Planned Parenthood Federation of America Buccal*

- Misoprostol Waiver Group. Adequacy and safety of buccal Misoprostol for cervical preparation prior to termination of second-trimester pregnancy. Contraception;2006;73:420-30*
- Goldberg AB, Greenberg MB, Darney PD. *Misoprostol and Pregnancy. NEJM. 2001;344(1):38-47*
- Shannon CS, Winikoff B. *Misoprostol an emerging technology for women's health, report of a seminar, Population Council 2001, updated 2004:1-66*
- Sivalal S, Sivasampu S. *Health technology assessment report, Misoprostol in pregnancy. Health technology assessment unit, medical development division, ministry of health Malaysia 2004: 4-29*
- Goldberg AB, Carusi DA, Meckstroth KR. *Misoprostol in pregnancy. Current Women's Health Reports 2003;3:475-83*
- Ngai SW, Tang OS, Ho PC. *Prostaglandins for induction of second trimester termination and intrauterine death. Best Practice & Research Clinical Obstetrics and Gynaecology. 2003;17(5):765-75*
- Vimala N, Mittal S, Kumar, S. *Sublingual Misoprostol before first trimester abortion: a comparative study using two dose regimens. Indian J Med Sci. 2004;58(2)54-61*
- Sharma S, Refaey H el, Stafford M, Purkayastha S, Parry M, Axby M. *Oral versus vaginal misoprostol administration administered one hour before surgical termination of pregnancy: a randomised controlled trial. BJOG. 2005;112:456-60*
- Berghella V, Airoidi J, O'Neill AM, Einhorn K, Hoffman M. *Misoprostol for second trimester pregnancy termination in women with prior cesarean: a systematic review. BJOG.2009; online 1151-57*
- Goyal V. *Uterine Rupture in Second-Trimester Misoprostol-Induced Abortion After Cesarean Delivery, a systematic review. Obstetrics and Gynecology. 2009;113(5)1117-23*
- Naguib AH, Morsi Hm, Borg TF, Fayed ST, Hemeda HM. *Vaginal Misoprostol for second-trimester pregnancy termination after one previous caesarean delivery. International Journal of Gynaecology and Obstetrics. 2010;108(1)48-51*
- Ben-Ami I, Schneider D, Svirsky R, Smorgick N, Pansky M, Halperin R. *Safety of late second-trimester pregnancy termination by laminaria dilatation and evacuation in patients with previous multiple caesarean sections. AJOG. 2009;201:154.e1-5*
- Elimia A, Verma U, Tejani N. *Effect of causing fetal cardiac asystole on second-trimester abortion. Obstetrics and gynecology. 1999;94(1)139-41*
- Dickinson JE, Evans SF. *The optimization of intravaginal Misoprostol dosing schedules in second-trimester pregnancy termination. American Journal of Obstetrics and Gynecology. 2002;186:470-4*
- Wong Ks, Ngai CSW, Yeo ELK, Tang LCH, Ho Pc. *A comparison of two regimens of intravaginal Misoprostol for termination of second trimester pregnancy: A randomized comparative trial. Human Reproduction. 2000;15:709-12*
- Ngai SW, Tang OS, Ho PC. *Randomized comparison of vaginal (220 microgr every 3 h) and oral (400 microgr every 3h) Misoprostol when combined with mifepristone in termination of second trimester pregnancy. Human Reproduction. 2000;15:2205-8*

- Nor Azlin MI, Abdullah HSNA, Zainul Rashid MR, Jamil MA. *Misoprostol (Alone) in second trimester terminations of pregnancy: As effective as Gemeprost?* Journal of Obstetrics and Gynaecology. 2006;26(6):546-9
- Bhattacharyya SK, Mukheri J, Kamilya GS, Ray S, Hazra A. *Two regimens of vaginal misoprostol in second trimester termination of pregnancy - a prospective randomised trial.* Acta Obstetrica et Gynecologica. 2006;85:1458-62
- Chai J, Tang OS, Hong QQ, Chen QF, Cheng LN, NG E, Ho PC. *A randomized trial to compare dosing intervals of Misoprostol following mifepristone administration in second trimester medical abortion.* Human Reproduction. 2009;24(2):320-4
- Tang OS, Chan CCW, Kan ASY, Ho PC. *A prospective randomized comparison of sublingual and oral Misoprostol when combined with mifepristone for medical abortion at 12-20 weeks gestation.* Human Reproduction. 2005;20(11):3062-6
- Yilmaz B, Kelekci S, Ertas IE, Kahyaoglu S, Ozel M, Sut N, Danisman N. *Misoprostol moistened with acetic acid or saline for second trimester pregnancy termination: a randomized prospective double blind trial.* Human Reproduction. 2005;20(11):3067-71
- Yilmaz B, Kelekci S, Ertas IE, Ozel M, Sut N, Mollamahmutoglu L, Danisman N. *Randomized comparison of second trimester pregnancy termination utilizing saline moistened or dry Misoprostol.* Arch Gynecol Obstet. 2007;276:511-6
- Bhattacharjee N, Sha SP, Ghoshroy SC, Bhowmik S, Barui G. *A randomised comparative study on sublingual versus vaginal administration of Misoprostol for termination of pregnancy between 13 to 20 weeks.* Australian and New Zealand Journal of Obstetrics and Gynaecology. 2008;48:165-71
- Karsidag AYK, Buyukbayrak EE, Kars B, Dansuk R. *Vaginal versus sublingual Misoprostol for second-trimester pregnancy termination and effect on Doppler measurements.* International Journal of Gynecology and Obstetrics. 2009;106:250-3
- Jansen NE, Pasker-deJong P, Zondervan HA. *Mifepristone and Misoprostol versus Dilapan and sulprostone for second trimester termination of pregnancy.* The Journal of Maternal-Fetal and Neonatal Medicine. 2008;21(11):847-51
- von Hertzen H, Piaggio G, Wojdyla D, Nguyen TMH, Marions L, Okoiev G, Khomassuridze A, Kereszturi A, Mittal A, Nair R, Daver R, Pretnar-Darovec A, Dickson K, Nguyen DH, Nguyen HB, Hoang TDT, Pereogoudov A and for the WHO Research Group on Post-ovulatory Methods of Fertility regulation. *Comparison of vaginal and sublingual Misoprostol for second trimester abortion: randomised controlled equivalence trial.* Human Reproduction. 2009;24(1):106-12
- Hamoda H, Ashok PW, Flett GMM, Templeton A. *A randomized trial of mifepristone in combination with Misoprostol administered sublingually or vaginally for medical abortion at 13-20 weeks gestation.* Human Reproduction. 2005;20(8):2348-54
- Caliskan E, Doger, E, Cakiroglu Y, Corakei A, Yucesoy I. *Sublingual Misoprostol 100 microgram versus 200 microgram for second trimester abortion a randomised trial.* The European Journal of Contraception and Reproductive Health Care. 2009;14(1):55-60

- Grossman D, Blanchard K, Blumenthal P. *Complications after Second Trimester Surgical and Medical Abortion*. Reproductive Health Matters. 2008; 16(31 supplement)173-82
- Lohr PA Hayes JL, Gemzell-Danielsson K. *Surgical versus medical methods for second trimester induced abortion*. Cochrane Database of Systematic Reviews. 2008(1)
- Grimes DA. *The choice of second trimester abortion method: evolution, evidence and ethics*. Reproductive Health Matter. 2008;16(31 supplement)183-88
- RCOG. *The care of women requesting induced abortion (hoofdstuk 7)* 2004
- SFP. *Cervical preparation for second-trimester surgical abortion prior to 20 weeks of gestation*. Contraception. 2007;76:486-495
- SFP. *Cervical preparation for surgical abortion from 20-24 weeks gestation*. Contraception. 2008;77:308-14
- Alblas M, Blanchard K, Constant D, Grossman D, Harries JJ, Lince N,. *The efficacy, safety and acceptability of medical and surgical second trimester of pregnancy in Cape Town, South Africa*. Fiapac Congress 2010

## Chapter 4 Antibiotic policy

### Guiding question

What antibiotic policy should be preferred in surgical or medical termination of pregnancy?

### 4.1 Introduction

Before there were specialized abortion clinics and well-trained abortion specialists, infections after a termination of pregnancy occurred fairly frequently. Possible consequences were infertility, chronic abdominal complaints, extra-uterine gravidity, and neonatal problems. The following guiding question will be answered: what antibiotic policy should be preferred after surgical or medical termination of pregnancy?

Although no data at the national level about infections after a termination of pregnancy are available for The Netherlands, the incidence of the number of infections does not raise suspicions (Inspectorate's Report, 2009). A possible explanation could be that most clinics in The Netherlands prescribe prophylactic antibiotics.

A literature search was undertaken in Medline (up to 2010), with primarily studies from the US as a result. Unfortunately, little literature was found on complications due to infections in The Netherlands. The guidelines of the following authorities were consulted: The Dutch Society of Obstetrics and Gynaecology (NVOG), the Dutch Society of Dermatology and Venereology (NVDV), the National Society of Cardiology (Hart Stichting) with a view to endocarditic prophylaxis, the standards of the Dutch Association of General Practitioners (NHG), the Dutch Working Party on Antibiotic Policy (SWAB), and Soaids Netherlands.

Antibiotic prophylaxis is defined as follows: the administration of antibiotics for a short period of time in the context of surgical intervention, for the prevention of post-operative infections in the area of invasion (Van Kasteren, 2000).

Prophylaxis policy after termination of pregnancy can be based on Mayhall's surgical wound classification. Termination of pregnancy in the second or first trimester after pelvic inflammatory disease (= PID) is classified as a 'clean-contaminated' wound. Consequently, the advantages of prophylaxis outweigh the possible disadvantages (Mayhall, 1993). Van Kasteren (2000) defines the following criteria for the prescription of antibiotics: they must be directed at the expected causative microorganisms; they must be administered at the correct time and administration should not last longer than necessary; the spectrum must be as narrow as possible; they must be as safe and inexpensive as possible; it must be possible to administer them via the desired route.



## 4.2 Prevalence of genital bacterial infections

### Guiding question

Which genital bacterial infections are common in women undergoing termination of pregnancy and how should they be treated?

### Summary of the literature

Recently a screening for genital bacterial infections was carried out among youngsters between 16 and 29 years of age, in Amsterdam, Rotterdam and Southern Limburg. Over 630,000 invitations were sent out in the course of 15 months. In three rounds this target group was tested; 3,735 infections were traced. In the first round, 4.2% of the participants tested positive for *Chlamydia trachomatis* (CT); in the second round this figure was 4.0%, in the third round 3.5%. According to regions the figures are: Rotterdam 5.1%-4.9%-4.5% (round 1, 2, 3), Amsterdam: 3.6%-3.4%-2.9% and Limburg: 5.1%-4.7%-3.8% (van Bergen et al., 2010).

The prevalence in abortion patients of *Chlamydia trachomatis*, serotypes D through K, rates probably around 10% (data from abortion clinics in The Hague, Arnhem and Amsterdam). In The Hague, in 1998 and 1999, 1,009 and 972 women were screened, respectively; in Amsterdam there was a screening in 1992, in Arnhem probably before 1995.

In selective screening in Arnhem GP practices a prevalence for CT of 10% was been found for many years, but the total number of applications has been rising (unpublished data). The prevalence for CT among the Dutch population as a whole appears to be following a continuously ascending line, partly to be explained by increased willingness to test for sexually transmitted infections (STI)<sup>3</sup> (Mayhall, 1993; Epidemiologisch Bulletin, 2003; RIVM, 2009)<sup>4</sup>.

---

<sup>3</sup> In Dutch: SOA

<sup>4</sup> Epidemiological Bulletin; for RIVM, cf. next footnote

	Number of new diagnoses via GGD sti outpatient clinics		
	2009	2008	2007
Chlamydia	9,771	9,433	7,801
LGV	84	100	69
Gonorrhoea	2,422	1,964	1,827
Syphilis	512	604	559
Hepatitis B (acute infection)	198	212	220
Hepatitis C (acute infection)	48	30	46
Genital warts	2,729	2,465	2,061
Primary herpes genitalis	651	722	671

*Table: STI annual data from the RIVM 2009 annual report<sup>5</sup>*

In a cohort study of 93,331 STI consultations in The Netherlands the following results with respect to bacterial infections were found: 10.5% CT (2008: 10,8%); 52 % were under 25; 17.3% of those infected with CT were 15-19 years old; 12% were 20-24 years old; of the women infected with CT 4.2% also had gonorrhoea. Among specific ethnic groups, e.g. from Surinam, the Netherlands Antilles and Aruba, the percentage of infections with gonorrhoea and CT is higher: 14.9% and 15.8%, respectively. From the table above it appears that the number of lymphogranuloma venerum (LGV) infections has decreased. In 2009 there were 84 cases, against 100 in 2008. The number of syphilis infections is also going down each year: 4.3% in 2007; 3.9% in 2008; 2.8% in 2009 (Vriend et al., 2009). It appears that CT is the most common bacterial cause of a sexually transmitted infection, with an incidence of 60,000 of the 110,000 STIs reported in The Netherlands (Karimi et al., 2010).

10-30% of the women with cervicitis also suffer from an upwardly migrating infection in the small pelvis: Pelvic inflammatory disease (PID), with ultimate tubal infertility in about 15% and ectopic pregnancy in about 9% of the women after symptomatic PID.

<sup>5</sup> RIVM: Rijksinstituut voor Volksgezondheid en Milieu – National Institute for Public Health and the Environment

Neonatal pneumonia may also occur (NVDV, Richtlijn SOA diagnostiek en therapie, 1997<sup>6</sup>; NHG Standard for Pelvic inflammatory disease, 2006).

In about 25-50% of the cases of PID micro-organisms cohabiting in the lower tractus genitalis are supposed to play a role. These are endogenous bacteria, facultatively or obligatorily anaerobic, also observed in bacterial vaginosis, such as Bacteroides-species and peptostreptococcus, or aerobic bacteria, such as Escherichia coli, Streptococcus and Mycoplasma. Frequently, several microorganisms are found in a culture, while in 20% of the cases of PID the results from the culture / PCR remain negative. There are indications that a subclinical PID (silent PID), too, may lead to infertility (Trendmatige ontwikkelingen op de SOA-poliklinieken, 2003)<sup>7</sup>.

In around 60% of the women with PID it is possible to demonstrate an association with an exogenous infection with CT or Neisseria gonorrhoea. CT may well migrate to the endometrium and tuba in over 40% of the women, often without clinical or even laparoscopic symptoms of PID. In part of those women no CT can be demonstrated in the cervix (Laar, 2005).

## Conclusions

<b>Level 2</b>	Chlamydia trachomatis is probably the most common genital bacterial infection.  <i>C Vriend et al., 2009</i>
----------------	--

<b>Level 2</b>	Chlamydia trachomatis is probably most frequently found in the age groups of 15 to 25.  <i>C Vriend et al., 2009</i>
----------------	--

## Discussion and evaluation

Since the patient population in abortion clinics consists, to a large extent, of the age group of 15 to 25 year olds, a considerable number of women may be infected with CT. This concerns 39.1% of the total number of abortions (Inspectie Rapportage 2009)<sup>8</sup>.

## Recommendation

<sup>6</sup> NVDV Guideline for STI diagnostics and therapy.

<sup>7</sup> Development trends in STI outpatient clinics

<sup>8</sup> National Health Inspectorate, 2009 Annual Report

As Chlamydia trachomatis is most common among women between 15 and 25, it is recommended to treat them prophylactically for this condition after a surgical termination of pregnancy.

### **4.3 Antibiotic policy in the case of surgical termination of pregnancy**

#### **Guiding question**

What antibiotic policy should be preferred in the case of surgical termination of pregnancy?

#### **Summary of the literature**

Sawaya (1996) writes that, in American retrospective studies, the risk of infection is estimated at 0.5%. From prospective trials an incidence of infection was shown of between 5 and 20%. To prevent infection many care professionals routinely administer an antibiotic. Others only do so in the case of women with a raised risk profile (earlier STI/PID, multiple partner contacts). Sawaya reviews twelve randomized trials. The risk of infection in the group of women with antibiotic prophylaxis was 1- 11%. In the placebo group the risk was 5-23%. The NVOG<sup>9</sup> guideline on surgical termination of pregnancy (2005) underlines the necessity of antibiotic prophylaxis in every surgical termination of pregnancy. This would diminish the risk of postoperative infection by about 50%. Sawaya's meta-analysis demonstrates a 50% reduction of the chances of postoperative infection when prophylactic antibiotics are used in surgical termination of pregnancy.

Stray-Pedersen (1991) tested 1,193 women <35 years (53% < 25 years) for CT and other infections, before first trimester termination of pregnancy. 139 women (11.7%) proved to be CT infected and 0.8% suffered from *Neisseria gonorrhoea*; a group B streptococcal infection was found in 2.9% of these women. CT and gonorrhoea were mostly found in teenagers. 26 women (2.2%) developed PID; 13 women (0.9%) developed endometritis. Of the CT-positive women 95 had received pre-operative or peri-operative treatment; two of them developed PID (2.1%). Of the 44 women who had not been treated ten ended up with PID (22.7%). Of the group of 108 women who tested positive on *Mycoplasma hominis* and were not treated, (22.1%) eight (8.1%) developed PID. Of the group of ten women who had received treatment, not one developed PID.

---

<sup>9</sup> NVOG: Royal Society of Obstetricians and Gynaecologists of The Netherlands

A group of 1,672 women presenting for an abortion were tested by Penney (2001) on genital infections. Of 1,613 women the outcome was known at the start of the intervention. Three women tested positive on gonorrhoea (0.2%); 91 had CT (5.6%) and bacterial vaginosis was diagnosed in 282 women (17.5%). Of the 1,672 women, 826 were assigned to a prophylaxis group (Group P); the doctors treating them knew the test results. The medication given was: metronidazol 1 gram rectally immediately before the termination of pregnancy and doxycycline 100 mg orally 2 x dd for 7 days. 35 women developed an infection (4.6%). A group of 846 women in a “screen and treat” group (group S) with CT received doxycycline 100 mg 2 x dd for 7 days; those with gonorrhoea ciprofloxacin 250 mg and those with a bacterial vaginosis metronidazol 400 mg 2 x dd for 7 days. In this group 54 women developed an infection (6.8%).

Miller (2001) studied bacterial vaginosis in a group of women before surgical termination of pregnancy. Ultimately, data were obtained about the follow-up of 253 women. Of these, 154 (61%) had a bacterial vaginosis. A group of 131 women was given pre-operative metronidazol, another group of 122 women received a placebo. All women were given doxycycline as a CT prophylaxis. There was no difference between both groups as regards complications after the abortion.

Crowley (1998) studied women with a bacterial vaginosis before a termination of pregnancy. They were all screened for CT and treated where necessary. One group of 131 women were given a placebo and a comparable group of 142 women preoperative metronidazol 2 gram rectally. In the placebo group 21 women were infected (16%), in the metronidazol group this figure was 12 (8.5%).

Blackwell (1999) calculated that the costs of hospital admission for a post-abortion infection to be twice as high compared to screening for CT combined with a prophylaxis against CT and bacterial vaginosis.

From a randomized controlled trial it appeared that doxycycline for 3 days is equally effective as a 7 day dose (Lichtenberg, 2003). Azithromycin is

perhaps more expensive, but since two 500 mg tablets in one dose suffice, it is easier to use and favours therapy compliance (Pitsouni, 2007).

Bacterial vaginosis is the most common vaginal complaint among women in the child bearing age in The Netherlands. Bacterial vaginosis is not an STI or a vaginal infection (Dekker 2011 ). Of the women consulting their GP with vaginal complaints 20% has a bacterial vaginosis (Dekker 2005). The aetiology of bacterial vaginosis is unknown. Symptoms are a fishy vaginal smell, a grey-white, homogenous, thin, vaginal discharge, and itches at times. Half of the women with bacterial vaginosis show no symptoms.

Diagnosis for bacterial vaginosis is established if three of the four Amsel criteria are met: homogenous discharge, pH>4.5, a positive amine test (fishy odour) and clue cells in a physiological salt solution of the discharge (Amsel 1983).

Treatment of bacterial vaginosis is symptomatic; this means that medical treatment is not obligatory. A bacterial vaginosis may be treated with metronidazol or clindamycin. The effects of the different agents and administration courses have not been shown to vary (Oduyeba 2009). The NHG standard recommends to start treatment using 2 gram metronidazol or clindamycin cream once daily for a week. There is no need to treat the partner as well.

The Cardiac Society's guideline indicates that no prophylaxis for endocarditis is needed in the case of termination of pregnancy or placement of a spiral coil.

## Conclusions

<b>Level 2</b>	It may be assumed that antibiotic prophylaxis reduces the risk of an upwardly migrating infection.	
	A2	<i>Sawaya, 1996</i>
	B	<i>Penney, 2001</i>
	C	<i>Stray-Pedersen, 1991</i>
	D	<i>NVOG richtlijn, 2005</i>

<b>Level 3</b>	<p>There are indications that the percentage of PID decreases as a result of screening and treating for CT.</p> <p><i>B Penney, 2001</i></p> <p><i>C Stray-Pedersen, 1991</i></p>
<b>Level 3</b>	<p>It is likely that treatment with metronidazol diminishes the risk of genital infection.</p> <p><i>B Crowley 1998, Miller, 2001</i></p>
<b>Level 3</b>	<p>There are indications that prophylactic treatment of all women with antibiotics rather than screening and treatment is the most cost-effective manner of preventing infectious complications after induced termination of pregnancy.</p> <p><i>B Penney 2001; Mary 2010</i></p>
<b>Level 4</b>	<p>The Cardiac Society advises against prophylaxis for the prevention of endocarditis in either abortion curettage or placement of a coil.</p> <p><i>D Van der Meer, 2008</i></p>

### Discussion and evaluation

It is a striking fact that the number of complications after termination of pregnancy in The Netherlands is considerably lower than the international literature would lead one to expect. The number of complications in both full-scale and early abortions in The Netherlands is small. In its 2009 report on the matter the National Health Inspectorate speaks of 264 complications in 33,000 terminations of pregnancy; it is unclear, however, how many infections were registered, because these are generally grouped with different types of complications.



Infection as a complication after treatment is unusual in The Netherlands, in the context of both first and second trimester interventions. Of course, this is partly due to the antibiotic prophylaxis given. There is insufficient evidence for administering additional prophylaxis in the second trimester.

Second trimester specialists hold the view that there is a higher risk of contamination in second trimester treatment. For this reason they feel endocarditis prophylaxis to be indicated in the second trimester. The Cardiac Society has only pronounced itself on suction curettage; when consulted, it appeared to be unaware of the differences between various methods for abortion treatment, particularly about D&E as a second trimester intervention.

Medical therapy for bacterial vaginosis is only indicated when complaints cause discomfort, because the condition may disappear spontaneously. Although the international literature exclusively mentions doxycycline as medication against CT, azithromycin should be preferred. It is not unlikely that the price of doxycycline prompts its widespread use. Azithromycin may be a little more expensive, but as azithromycin can be taken in a single dose this strongly favours compliance.

When a woman undergoing surgical termination of pregnancy is also breastfeeding, azithromycin may still be prescribed, providing the child is not premature (under 3000 grams). Metronidazol is passed on to the mother's milk, rendering it unpleasantly metallic in taste. Toxicological studies are absent, but the available data do not indicate a raised incidence of foetal damage. As long as therapeutic dosages are used it is unlikely that any effect will be observed in the baby.

For existing PID the treatment is ofloxacin 400 mg 2 dd for fourteen days; metronidazol 500 mg 2 dd for a period of fourteen days. Or perhaps: ceftriaxon 250 mg i.m. (intra-muscularly), doxycycline 100mg 2 dd for fourteen days, metronidazol 500 mg 2 dd for a period of fourteen days (RCOG, 2008; Martens et al., 1993; Walker et al., 1993; Soper et al., 1992; Peipert et al., 1999).

The current therapy for gonorrhoea, unless specific resistance is found, is ceftriaxon 250 mg i.m. (Farmacotherapeutisch Kompas, 2010).

In cases of allergy to azithromycin, doxycycline can be an alternative: 100 mg 2 dd for a period of seven days. In the case of allergy to both azithromycin and doxycycline, amoxicillin 500 mg three times daily for seven days is prescribed. All cures must be fully complied with without interruption (Farmacotherapeutisch Kompas, 2010). The use of Azithromycin, in combination with vaso-constrictive agents such as methergine and syntocinon, may lead to arterial spasms and ischemic reactions.

### **Recommendations**

After surgical termination of pregnancy, it is recommended to administer 1.000 mg azithromycin as a prophylaxis to the patient on the same day.

When there is a suspicion of bacterial vaginosis four times 500 mg metronidazol is prescribed.

#### 4.4 Antibiotic policy in medical termination of pregnancy

##### Guiding question

What antibiotic policy should be preferred in medical termination of pregnancy?

##### Summary of the literature

In 2005, four US women died, and one Canadian woman in 2001, following a medical termination of pregnancy with mifepristone and misoprostol vaginally due to a septic shock caused by *Clostridium sordellii*. A similar case occurred in Portugal in 2009 (21<sup>st</sup> European Congress of Clinical Microbiology and Infectious Diseases, 2011). The infection was accompanied by leucocytosis, no fever and low blood pressure. Another woman died of a ruptured ectopic pregnancy. Mortality figures after abortion range from 0.1 per 100,000 up to 8 week of pregnancy, tot 8.9 per 100,000 at 21 weeks of gestation or more (Greene 2005).

Planned Parenthood analysed 72,195 women who had undergone medical termination of pregnancy with mifepristone and misoprostol vaginally. 67 serious infections were reported (0.09%). There was one case of death due to *Clostridium perfringens*. 78,794 women took misoprostol buccally; 20 women developed an infection (0.025%). In 35,837 women who took misoprostol buccally and received prophylactic doxycycline two infections occurred (0.005%). The pregnancy length in this group was 56 days. In a group under the same regime and a pregnancy length of 63 days the percentage of infections was also 0.005% (Planned Parenthood, 2005). A retrospective study showed that the number of serious infections after medical termination of pregnancy decreased by 93% after vaginal administration of misoprostol was replaced by buccal administration, in combination with routine use of antibiotics. In view of the small number of complications, vaginal administration of misoprostol is also admissible (Fjerstad, 2009). In The Netherlands antibiotic prophylaxis after medical termination of pregnancy is not common.

##### Conclusions

<b>Level 3</b>	In the USA, in pregnancies under 8 weeks, the mortality rate after medical termination of pregnancy equals that of surgical termination of pregnancy.  <i>C</i> <i>Greene, 2005</i>
<b>Level 3</b>	It may be assumed that antibiotic prophylaxis is not necessary in medical termination of pregnancy.

### **Discussion and evaluation**

Some critical remarks are in order with respect to the Planned Parenthood study. A randomized comparative trial between vaginal and buccal misoprostol would have been better. The number of infections is extremely small. To prevent an infection developing 1,000 women are unnecessarily given an antibiotic. Screening and treatment of CT in combination with medical termination of pregnancy may lead to a reduction of vaginal infection in young women. CT screening is usually impossible because of the time investment needed, the test is 99.5% certain. In the target group undergoing termination of pregnancy a higher percentage of CT infections may be expected.

### **Recommendation**

The study group takes the position that antibiotic prophylaxis in medical termination of pregnancy is not necessary.

## 4.5 References

- Van Kasteren, et al. Optimaliseren van het antibiotica beleid in Nederland, V. SWAB-richtlijnen voor perioperatieve antibiotische prophylaxis; Ned. Tijdschrift voor Geneeskunde Oktober 2000; 144(43)
- Mayhall C.G. Surgical infections including burns. Wenzel RP, editor, prevention and control of nosocomial infections. Baltimore 1993
- van Bergen et al. Chlamydia Screening 2008-2010: resultaten, conclusies en Recommendations. JEAM December 2010
- Trendmatige ontwikkelingen op de SOA-poliklinieken. Epidemiologisch Bulletin, Tijdschrift voor Volksgezondheid en Onderzoek in Den Haag 2003; 38 (1): 2-7.
- H.J. Vriend F.D.H. Koedijk, I.V.F van den Broek, M.G. van Veen, E.L.M. op de Coul, A.I. van Sighem, R.A. Verheij, M.A.B. van der Sande RIVM (Rijksinstituut voor Volksgezondheid en milieu) Jaarrapportage 2009.
- Soa jaarcijfers GGD-soa poliklinieken 2008
- Richtlijn SOA Diagnostiek en therapie. Nederlandse Vereniging voor Dermatologie en Venereologie 1997 van de. Uitgegeven mede onder auspiciën van de Nederlandse Vereniging voor Obstetrie en Gynaecologie en Nederlandse Vereniging voor Medische Microbiologen samenwerking met de Stichting SOA-bestrijding Tweede editie
- Karimi, A. et al. Chlamydia trachomatis-infecties, Epidemiology, diagnostics and treatment of urogenital Chlamydia trachomatis infections. Tijdschrift voor Infectieziekten; v o l . 5 n r . 6 - 2010
- NHG-Standaard 'Pelvic inflammatory disease' (Gebu 2006 (mrt); 40: 38-39.
- Laar M. Soa nemen opnieuw toe, voorlopige cijfers 2004. Soa Aids Magazine (Online) 2005, 2 blz. 28
- Jaarrapportage 2009 wet afbreking zwangerschap; inspectie gezondheidszorg; 11-02-2010; p21, 48
- Sawaya. USA Sawaya obstet Gynaecol 1996 87:884-90
- Stray-Pedersen Larsson PG, Platz-Christensen JJ, Dalaker K, Eriksson K, Fåhraeus L, Irminger K, Jerve F, Stray-Pedersen B, Wölner-Hanssen P. 1991
- Penney GC, Grimshaw JM, Ramsay CR, Walker AE, MacLennan G, Stearns SC, McKenzie L, Glasier A. BJOG. 2004 Jul;111(7):726-33. PMID: 15198764
- Miller BJOG 2004.111.982-8
- Crowley oktober 1996- december 1998 Crowley T, Low N, Turner A, Harvey I, Bidgood K, Horner P.
- Blackwell AL, Emery SJ, Thomas PD, Wareham K. Int J STD AIDS. 1999 Aug;10(8):508-13. PMID: 10471099
- Miller L, Thomas K, Hughes PH, et al. Randomised treatment trial of bacterial vaginosis to prevent post-abortion complication. BJOG 2004; 111: 982-8. 37)
- Mary N, Mahmood TA. Best Pract Res Clin Obstet Gynaecol. 2010 Aug;24(4):539-49. Epub 2010 Jun 12. Review.
- van Bergen et al, Chlamydia Screening 2008-2010: resultaten, conclusies en Recommendations ; JEAM. December 2010
- Lichtenberg ES, Shott S. A randomized clinical trial of prophylaxis for vacuum abortion: 3 versus 7 days of doxycycline. Obstet Gynecol 2003; 101: 726-31. 36
- Pitsouni E, Iavazzo C, Athanasiou S, Falagas ME. Single-dose azithromycin versus erythromycin or amoxicillin for Chlamydia trachomatis infection during pregnancy: a meta-analysis of randomised controlled trials. Int J Antimicrob Agents. 2007;30:213-21)
- RCOG richtlijnen Management of acute pelvic inflammatory disease. Green-top Guideline No. 32; November 2008
- Martens MG, Gordon S, Yarborough DR, Faro S, Binder D, Berkeley A. Multicenter randomized trial of ofloxacin versus cefoxitin and doxycycline in outpatient treatment of pelvic inflammatory disease. Ambulatory PID Research Group. Southern Med J 1993;86:604-10.

- Walker CK, Kahn JG, Washington AE, Peterson HB, Sweet RL. Pelvic inflammatory disease: metaanalysis of antimicrobial regimen efficacy. *J Infect Dis* 1993;168:969-78.
- Soper DE, Brockwell NJ, Dalton HP. Microbial etiology of urban emergency department acute salpingitis: treatment with ofloxacin. *Am J Obstet Gynecol* 1992;167:653-60.
- Peipert JF, Sweet RL, Walker CK, Kahn J, Rielly-Gauvin K. Evaluation of ofloxacin in the treatment of laparoscopically documented acute pelvic inflammatory disease (salpingitis). *Infect Dis Obstet Gynecol* 1999;7:138-44.
- Richtlijnen farmcotheapeutisch kompas; Tractus genitalis femininus / Middelen bij vaginale aandoeningen ) jaartal 2010; 6; 767.
- Grimes DA, Schulz KF. Prophylactic antibiotics for intrauterine device insertion: a metaanalysis of the randomized controlled trials. *Contraception* 1999;60:57-63.
- prophylactic antibiotics for intrauterine device insertion (Review) 15 Copyright © 2010 De Cochrane Collaboration. Geplaatst door John Wiley & Sons, Ltd ;BIJDRAGEN VAN AUTEURS Grimes D en K Schulz ;L Lopez herzien van de zoekresultaten in 2007 en 2009
- Richtlijnen endocarditis prophylaxis; van der Meer Hartstichting
- Michael F. Greene, M.D. 12-2005 new england journal of medicine 353;22hristin-Maitre S, Bouchard P, Spitz IM. Medical termination of pregnancy. *N Engl J Med* 2000;342:946-56.
- Clostridium sordellii* toxic shock syndrome after medical abortion with mifepristone and intravaginal misoprostol — United States and Canada, 2001-2005. *MMWR Morb Mortal; Wkly Rep* 2005;54:724.
- Mary Fjerstad;2009/Fjerstad *N ebg J Med*;2009 361(2).145-51
- Planned Parenthood 2005. [http://www.lifeissues.org/pp/report\\_05-06.pdf](http://www.lifeissues.org/pp/report_05-06.pdf).
- Dekker JH. Afdeling huisartsgeneeskunde UMCG. Vaginale aandoeningen: candidiasis, bacteriele vaginose en trichomoniasis; juli 2011 Seksoa.
- Dekker JH, Boeke AJP, Gercama AJ, Kardolus GJ, Boukes FS. NHG-standaard Fluor vaginalis. *Huisarts en Wetenschap*. 2005;48:459-466
- Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbiological and epidemiologic associations. *Am J Med*. 1983; 74:14-22
- Oduyebo OO, Anorlu RI, Ogunsola FT. The effects of antimicrobial therapy on bacterial vaginosis in non-pregnant women. *Cochrane Database Syst. Rev.* 2009 ;3 : CD006055

# Chapter 5                    Use of ultrasound

## **Guiding question**

When should ultrasound scanning be applied in termination of pregnancy?

### **5.1 Introduction**

Until the introduction of ultrasonographic techniques a diagnosis of pregnancy and the establishment of its duration were simply based on anamnesis and a bimanual internal examination, with the possible addition of a pregnancy test.

In the eighties, ultrasound equipment was primarily used to establish pregnancy length. Thanks to the strongly improved technology of the equipment, it is now possible to diagnose abnormalities like myoma, missed abortion, molar pregnancy and ectopic pregnancy before treatment. Because of the application of sonography during the intervention, the instruments used can often be clearly visualized, possibly reducing the risk of perforations in particular, false routes and incomplete abortions. Ultrasound scanning is also used sometimes at follow-up.

The Royal College of Obstetricians and Gynaecologists (RCOG) holds the view that ultrasonography is not an essential requirement in termination of pregnancy, but that the option must be available to make ultrasound scans in certain circumstances (McGalliard en Gaudoin, 2004). Here we will try to make evidence-based pronouncements on the basis of existing literature about the role of ultrasound scanning in induced abortions.

In our search in Pubmed, three systematic reviews were found, none of which were suitable because they did not deal with termination of pregnancy. Of the 124 other Pubmed articles, the majority was not appropriate for our query. In the end our search resulted in one RCT and 25 observational and comparative studies about the application of ultrasonography in relation to abortion. In February 2010 two more articles followed.

To be able to answer the question a number of sub-questions was defined. These will be answered below.

## 5.2 Establishing a diagnosis

### Guiding question

What is the function of ultrasound scanning in establishing the diagnosis of pregnancy?

### Summary of the literature

Using pre-operative abdominal ultrasound in 120 women, Fakhri et al. (1986) found five instances of missed abortion, one multiple pregnancy, and one ectopic pregnancy. According to the authors, ultrasound scanning is essential to establishing the diagnosis of abnormal pregnancy (missed abortion, twins, ectopic pregnancy, extra-uterine gravidity).

In a prospective trial involving 217 women, Fiala et al. (2003) compared the value of ultrasonography with an hCG indication before and after medical termination of pregnancy. Using ultrasound the authors found no gestational sac in 6 women (2.7%), a gestational sac but no embryonic sac in 44 women (20.3%), both a gestational and an embryonic sac, but no foetus or a CRL < 2 mm in 105 women (48.4%) and a CRL > 2 mm in 62 women (28.6%). The authors claim that ultrasound is not a reliable procedure for establishing pregnancy if no embryonic sac is visible yet, which was true for 50 of the cases in their population (23%). On the basis of a serum hCG test it was always possible to demonstrate pregnancy but impossible to determine its length.

From the retrospective study by Jarallah and Geisson (1985), in which abdominal ultrasound was applied in 753 women, it appeared that 19 (2.5%) turned out not to be pregnant; 52 women (6.9%) had a non-vital pregnancy and 11 women had a multifoetal pregnancy. Incidental findings, like ovary cysts, myoma, IUDs etc., were reported for 27 (3.6%) women.

In a prospective study involving 283 women, McGalliard and Gaudoin (2003) found that, after ultrasound scanning and a pregnancy test, four women (1%) appeared non-pregnant. There were 259 continuing single pregnancies (92%), 3 continuing multiple pregnancies (1%) and 17 missed abortions (6%).

In their retrospective study involving vaginal ultrasound scanning in 140 women, Sinha et al. (2004) found that 15 women showed a missed abortion. Apart from these, two multi-foetal pregnancies, one ectopic pregnancy, one mola pregnancy and one case of uterus bicornis were found.



## Conclusions

### Level 3

From the evidence it appears that anamnesis and physical examination alone are insufficient for detecting abnormal pregnancies. Real time ultrasound scanning during the termination of pregnancy procedure is essential to establish the diagnosis of a multi-foetal pregnancy or abnormal pregnancy.

*C Jarallah en Geisson 1985, Fakh et al. 1986, McGaliard en Gaudoin 2003, Sinha et al. 2004*

## Discussion and evaluation

Jarallah en Geirsson (1985) pointed out the fact that 9.4% of the women referred for a termination of pregnancy were either not pregnant or had no vital pregnancy. Correct diagnostics spared these women from the stigma of having undergone termination of pregnancy. As an aside it should be remarked that a simple pregnancy test will at any rate exclude those who are not pregnant.

## Recommendations

In termination of pregnancy ultrasound must be employed to establish the diagnosis of multi-foetal pregnancy, abnormal pregnancy and pregnancy as such.

### 5.3 Determining pregnancy length

#### Guiding question

What is the role of ultrasound in determining pregnancy length?

#### Summary of the literature

Blanchard et al. (2007) conducted a prospective comparative study into the value of self-estimated LMP (time elapsed since the last menstrual period), clinical findings (over or under 8 weeks since LMP) and ultrasound results in 673 women. The women's estimate (LMP) appeared on average to be 19 days below the outcome of the ultrasound, while the findings of doctors (LMP and internal examination) were still one to two days below the ultrasound outcome. In a prospective study of 120 women considering a first trimester termination of pregnancy Fakhri et al. (1986) compared pregnancy length as determined by pre-operative ultrasound with the stated length of amenorrhoea and the findings of an internal examination. When the findings of the abdominal ultrasound were matched with those of the internal examination there was a difference of less than one week in 81% of the cases; in 13% the difference was one to two weeks; in 6% there was a difference of more than two weeks. Of the women with a difference of more than 2 weeks between ultrasound and internal exam two were very young primigravidae, both hard to examine, two missed abortions, one grand multipara, one uterus myomatous and one case of obesity. The authors conclude that there is a good overall correlation between both methods. The correlation between ultrasound scans and stated length of amenorrhoea was not so good: in 15% a discrepancy of more than two weeks was found.

In the US the extra cost involved in having an ultrasound made before and after medical termination of pregnancy puts up a barrier to the further acceptance of this method. In a prospective multicenter trial, involving 15 centres and including 1,016 women who underwent medical termination of pregnancy at a pregnancy length of 63 days of amenorrhoea, Fielding et al. (2002) therefore compared the outcomes of the anamnesis and internal exam with ultrasound findings. On the basis of an internal examination, experienced clinicians dated the length of pregnancy correctly in 87% of the cases (< 63 days); they underestimated the length of pregnancy in only 1%. In the population in this trial the length of pregnancy was estimated >63 days in 9%, where this was actually only true for 3%. The authors concluded that medical termination of pregnancy may be performed safely without ultrasounds.

Goldstein et al. (1988) conducted a prospective study in 250 women considering a first trimester termination of pregnancy. All women had a stated length of amenorrhoea of twelve weeks or less and a positive pregnancy test. After abdominal

ultrasounds were made, in four women the pregnancy turned out to have progressed beyond twelve weeks.

Jarallah and Geirsson (1985) did a retrospective study of 753 women undergoing termination of pregnancy. Abdominal ultrasounds were made for all women. Only 73% of the women were able to indicate a date from which the length of amenorrhoea could be inferred. In 62% of these women the amenorrhoea length turned out to coincide with the ultrasound findings; 22% was at a later stage, whereas 16% had progressed less far than they had calculated.

McGalliard and Gaudoin (2003) conducted a prospective trial including 283 women. All women underwent vaginal ultrasound scanning, plus an abdominal scanning if, after abdominal palpation, the uterus appeared much larger than the calculated length of amenorrhoea would lead one to expect. First trimester terminations of pregnancy were performed by surgery and second trimester terminations by medication. Of the 262 women with a normal pregnancy 25 could not remember the date of the last menstrual period. Of those who did remember there was a deviation of a week or more in 90 (38%) compared to the ultrasound (in 35 women the pregnancy was at a later stage than predicted by calculated amenorrhoea length, in 55 it was earlier).

In a retrospective study of 140 women who had undergone a medical termination of pregnancy at an amenorrhoea length of under 63 days, Sinha et al. (2004) found a discrepancy between the stated date of their last menstrual period and the findings of a vaginal ultrasound. The authors conclude that vaginal ultrasound scanning should be an essential element in the screening of all women considering medical termination of pregnancy.

### Conclusions

<b>Level 3</b>	<p>It seems likely that, in early pregnancies, there is a clear correlation between the findings from the stated date of the last menstrual period together with an internal exam by experienced clinicians and an ultrasound.</p> <p><i>B Fielding et al. 2002</i></p> <p><i>C Fakh et al. 1986; Blanchard et al. 2007</i></p>
----------------	---

<b>Level 3</b>	<p>It seems likely that there is no clear correlation between stated length of amenorrhoea and the outcome of an ultrasound alone.</p>
----------------	--

	<i>C Jarallah en Geisson 1985; Fakhri et al. 1986; Goldstein et al. 1988; McGalliard en Gaudoin 2003; Sinha et al. 2004; Blanchard et al. 2007</i>
--	--

### **Discussion and evaluation**

Determining pregnancy length before termination of pregnancy is important to select the appropriate method. The risk of a continuing pregnancy after a medical termination of pregnancy with mifepristone and misoprostol increases at a pregnancy length of more than 49 days of amenorrhoea. The technique to be used in first trimester abortion differs from the one used in second trimester termination of pregnancy. Besides, the highest possible degree of precision in determining pregnancy length can be of importance to the woman when she chooses to have termination of pregnancy (unacceptable progenitor, pregnancy too far advanced, etc.).

The relevance of subjective pregnancy symptoms for determining pregnancy length is small (Robinson en Barber, 1977). Only 15% of all women have a regular menstrual cycle of 28 days, which is the basic assumption underlying the LMP approach. It is not surprising, therefore, that there is no clear correlation between the length of amenorrhoea and the findings of ultrasound screening. That these findings, together with an internal exam, do yield a clear correlation with ultrasound data can undoubtedly be attributed to the experience of the doctors involved and the absence or non-availability of an ultrasound scanner. Although the study by Fakhri et al. (1986) took place 25 years after the introduction of ultrasound scanners, their use in termination of pregnancy was still exceptional. Similar remarks can be made about the study by Fielding et al. (2002), however recent. In the US agencies providing medical termination of pregnancy often do not have ultrasound equipment at their disposal and must therefore be skilled at palpation. Dutch abortion clinics do have ultrasound scanners at their disposal and use them to determine pregnancy length. Internal exams are increasingly left out. It may therefore be expected that, if the study by Fakhri et al. were to be repeated in The Netherlands today, the discrepancy between ultrasound findings and internal examination would be much bigger. Fielding et al. (2002) concluded that medical termination of pregnancy could safely be executed without ultrasound screening.. The study group does not agree with this conclusion and feels that, in medical termination of pregnancy in the Dutch situation, ultrasound scanning must always take place, as scanners are available everywhere and scanning contributes to the choice of treatment method.

The tables used in the establishment of pregnancy length by ultrasound are based on known conception date (IVF); thus, ultrasound screening is the golden standard for determining pregnancy length. In a review, Paul et al. (2000) claim that vaginal ultrasound scanning will detect an early pregnancy about a week earlier than abdominal scanning and is more exact (margin of error of  $\pm 3$  days, versus  $\pm 1$  week).

On 4 June 2010 the NVOG approved the guideline 'dating of pregnancies, version 1.0'. This guideline establishes that ultrasound images will be the standard from now on in determining pregnancy length. For the measurement tables included in it the study by Verburg et al. (2008) was used. For every known measure, such as CRL, BPD, HC, femur length and TCD this article specifies the median, and the 5<sup>th</sup> and 95<sup>th</sup> percentiles. For instance, for a CRL of 20mm the median is 9+0 weeks/days of amenorrhoea, with 8+2 as its 5<sup>th</sup> percentile and 9+5 as its 95<sup>th</sup> percentile. For further information we refer to this guideline and the article.

### **Recommendation**

Pregnancy length must always be determined by ultrasound and be documented. Ultrasound will also show if there is a vital intra-uterine pregnancy inside a normal uterus.

## **5.4 Surgical termination of pregnancy**

### **Guiding question**

What is the role of ultrasound during surgical termination of pregnancy?

### **Summary of the literature**

In a randomized trial Acharya et al. (2004) compared 115 women who had undergone abdominal ultrasound screening during suction curettage in the first trimester with 115 women who had not. 1 mg gemeprost was given preoperatively at an LMP > 11 weeks, dilatation was performed up to an opening width corresponding with the length of pregnancy and finally there was sharp post-curettage treatment. In the group without ultrasound the complication rate was 15.9%, in the group with ultrasound 3.7%. There were no statistical differences between both groups as regards complications during the intervention, but there were with respect to immediate post-operative complications. Infection occurred in 7.5% of the cases in the group without ultrasound and in 1.9% of the cases in the group with ultrasound. For post-curettage treatment in connection with retained pregnancy products these figures were 4.7% and 0%, respectively. In relation to the infections the authors remarked that these probably resulted from selective prescription of antibiotics. In addition, the use of ultrasound had a significantly positive effect on the time needed for the intervention, because sharp post-curettage treatment could be skipped, and convalescence time and blood loss improved (also due to skipping sharp post-curettage).

In a retrospective study, Darney and Sweet (1989) compared 353 women undergoing a second trimester termination of pregnancy (D&E) without a pre-operative ultrasound check with 457 women who received a pre-operative abdominal ultrasound check. For one quarter of the women in the first group and one-third in the second a pregnancy length of 20 weeks of amenorrhoea or more was established. Despite this difference the risk of perforation was 1.4 versus 0.2%.

Fakih et al. (1986), mentioned earlier, performed abdominal ultrasounds in 120 women immediately after the abortion. In six cases there were suspicions of incomplete abortions, confirmed by further curettage later. The use of ultrasound directly after the intervention prevents the continuation of incomplete abortions.

Helm et al. (1986) carried out a prospective trial into the value of ultrasound screening directly following the intervention in 50 women undergoing surgical termination of pregnancy in the first or second trimester. Of the 39 first trimester pregnancies 15 (33%) were not empty on ultrasound; this proved unjustified in two

cases. Of the seven second trimester pregnancies the cavum was not fully cleared in four instances (two instances of a foetal caput). The authors conclude that ultrasound scanning during and directly after second trimester termination of pregnancy with D&E makes identification of retained foetal tissue and its removal easier.

### Conclusions

<b>Level 2</b>	<p>It is likely that the use of abdominal ultrasound scanning during and directly after first and second trimester termination of pregnancy (suction curettage) will simplify the identification of retained pregnancy products and will render post-curettage superfluous.</p> <p><i>A2 Acharya et al. 2004</i> <i>C Fakh et al. 1986</i></p>
<b>Level 3</b>	<p>It is likely that the use of abdominal ultrasounds during second trimester termination of pregnancy (D&amp;E) will make the identification of retained foetal tissue and its removal easier.</p> <p><i>C Helm et al. 1986</i></p>
<b>Level 3</b>	<p>It is likely that the use of abdominal ultrasounds during second trimester termination of pregnancy (D&amp;E) reduces the risk of perforation.</p> <p><i>B Darney en Sweet 1989</i></p>

### Discussion and evaluation

The incidence of traces of chorion villi or trophoblasts after a first trimester termination of pregnancy is estimated at less than 5% (Grimes en Gates, 1979) and at 0.3-0.9% after a second trimester intervention with D&E (Grimes et al. 1977). These figures are exclusively based on the apparent need to explore the uterus cavity once again in the second instance. It cannot be excluded that retained tissue often does not give rise to complications as it is expelled spontaneously through the vagina. In the study by Helm et al. (1986) the quality of the medical proceedings may be questioned in a number of respects. Overlooking the foetal caput is generally a

matter of inattentiveness. This, however, does not affect the validity of the conclusion phrased by Helm et al. (1986) – that ultrasound scanning during and directly after second trimester termination of pregnancy with D&E makes identification of retained foetal tissue and its removal easier.

It is unpleasant for a patient to have a transducer pressing her stomach again and again and this is certainly not necessary in most treatments. In very early pregnancies an ultrasound at the start and conclusion of treatment is usually sufficient.

In the selected literature abdominal ultrasound scanning is used, but the study group finds that vaginal ultrasound scanning should be preferred. For many women, however, vaginal scanning may be aggravating, because quite often they are sexually traumatized; the intended termination of pregnancy is already a confrontation in its own right. It is therefore quite common to start with abdominal ultrasound scanning. If greater accuracy is required, a vaginal ultrasound is indicated. The study group finds that, apart from making an ultrasound, inspection of the curettement is necessary.

### **Recommendations**

Pre-operative abdominal ultrasound scanning must be used in the case of complex interventions (like deviant positioning, congenital abnormalities, pathology) and in surgical abortion in the second trimester.

The use of ultrasound scanning during first and second trimester interventions is appropriate

Macroscopic inspection of the curettement must be carried out.



## 5.5 Ultrasound after surgical termination of pregnancy

### Guiding question

What is the role of ultrasound scanning after surgical termination of pregnancy?

### Summary of the literature

Bar-Hava et al. (2001) conducted a prospective study involving 74 women analyzing the “normal” ultrasound scan image after termination of pregnancy. Of these women, 57 had undergone termination of pregnancy at 8-12 weeks of amenorrhoea; 10 had received treatment after an incomplete spontaneous abortion (8-12 weeks of amenorrhoea) and 7 after a missed abortion (at 6-12 weeks of amenorrhoea). Suction curettage was applied in 60 cases, D&E in 14. Vaginal ultrasounds were made after 24 hours in 26 women, after 48 hours in 10 women, on day three or four in 18 women and on day five or six in 20 women. The ultrasound findings were categorized in three groups: A thin, regular midline < 7 mm (N=17), B a thick midline of 7-19 mm (N=37) and C a midline > 20 mm or irregular Ultrasoundgenicity (N=20). The midline in women who were screened within 48 hours was thicker and more irregular than in women who were screened later. No correlation was found with clinical parameters or method of treatment and the findings were similar for women with or without complaints. The most striking outcome was that the uterus cavity was rarely totally empty in the first days after first trimester termination of pregnancy and that modest to large quantities of intra-uterine material of varying Ultrasoundgenicity was found in 57 women (77%). They concluded that the presence of thick heterogeneous material is an acceptable finding, to be expected after a first trimester termination of pregnancy, and that this does not imply that a second curettage must follow straightaway.

In a study discussed before, Fakhri et al. (1986) performed abdominal ultrasound scans on 120 women directly after the abortion. In six cases the images raised suspicions of incomplete abortions, which was confirmed by further curettage. The use of ultrasound directly following the intervention will prevent a continuing incomplete abortion.

In a study of 21 women undergoing first trimester suction curettage, Haddad et al. (1992) found an elliptical sac-like structure in 19 of the 21 women, 4-6 hours after surgery (Ultrasoundgenic edges and hypo-Ultrasoundgenic contents), the so-called pseudo-embryonic sac; the other two women showed a scan image with clearly an empty uterus cavity. After three days this structure was still found in eight women, albeit clearly smaller, and on day five the uterus cavity was empty in all women.

Helm et al. (1986) conducted a prospective study including 50 women into the value of abdominal ultrasound scanning directly after abortion. Of the 39 first trimester pregnancies, 15 (33%) were non-empty on ultrasound; in two cases this proved incorrect.

A prospective study was carried out by Marengo et al. (1988) in 144 women undergoing surgical termination of pregnancy in the first trimester, for the purpose of gaining a better insight into ultrasonographic images directly after termination of pregnancy, to avoid unnecessary re-curettage. Vaginal scanning was applied, 8-36 hours after termination of pregnancy. In 84 women there was a linear-shaped endometrium, in the other sixty this was incomplete or the image was non-homogeneous. Incomplete abortion was only observed in two of these sixty women. A pseudo-embryonic sac was observed eight times. The authors relativize the importance of an ultrasound 8-36 hours after abortion.

Maslovitz et al. (2004) conducted a comparative retrospective study into 69 women who had undergone re-curettage on suspicion of retained traces after first or second trimester surgical termination of pregnancy; repeat curettage took place within 14 days (range 6-43 days) on average. In 59% of the women no trophoblastic tissue was found, histopathologically.

In a prospective study, McEwing et al. (2007) described the ultrasound outcomes of 38 women without complaints after first trimester termination of pregnancy and compared these with the images of 105 women with complaints indicative of retained tissue. Determined were: thickness of the endometrium; irregularities of the cavity; the Ultrasonogenicity of the contents of the uterus cavity and Doppler colour flow. They concluded that there is a poor relation between ultrasound findings and symptoms and between ultrasound findings and symptoms with histological findings.

Mikkelsen en Fielding (1994) carried out a prospective study in 117 women who underwent a first trimester suction curettage, to establish the value of abdominal ultrasound imaging directly after treatment. Repeat curettage was undertaken in five women within four weeks because of pain and blood loss. Retained tissue was only found in three women. They observed that ultrasound imaging subsequent to treatment does not lead to a reduction in the number of cases of tissue retention and should therefore not be recommended.

In the prospective trial by Stone and Elder (1974) abdominal ultrasonography was conducted within 24 hours in 105 women undergoing first trimester suction curettage; retained placenta tissue was found in 33 women. The authors conclude that there is a clear relationship between immediate complications and placenta traces on the ultrasound. Of greater interest is their observation that a uterus cavity which appeared empty on ultrasound appeared not to be empty at all times, as this was the case in two women.

A retrospective study by Tribalat et al. (1987) in 75 women who underwent first trimester suction curettage points out the danger of unnecessary repeat curettage on the basis of the abdominal ultrasound images at 24 hours after the intervention. Linear endometrium was only found in 14 cases, in one case there was a continuing pregnancy, a small residue was found twenty times; in forty cases the images showed a sac-like structure with hypo-ultrasoundgenic contents (pseudo-gestational sac).

## Conclusions

<b>Level 2</b>	<p>It may be assumed that the presence of a pseudo-gestational sac, 4-6 hours after surgery, or the presence of thick heterogeneous material during the first days after treatment is an acceptable finding, to be expected after first trimester termination of pregnancy, especially in the first two days after the intervention. This does not imply that an immediate repeat curettage must be carried out.</p> <p><i>B Tribalat et al. 1987, Bar-Hava et al. 2001, McEwing et al. 2007</i>  <i>C Marenco et al. 1988, Haddad et al. 1992</i></p>
<b>Level 3</b>	<p>It appears likely that the use of abdominal ultrasound imaging immediately upon or shortly after treatment may lead to unnecessary re-curettage or to the conclusion that the uterus cavity is empty.</p> <p><i>C Stone en Elder 1974, Helm et al. 1986, Tribalat et al. 1987,</i></p>

Marenco et al. 1988, Mikkelsen en Fielding 1994, Maslovitz et al. 2004B,

### **Discussion and evaluation**

Contrary to the findings and conclusions above, the study group holds the view that there are good reasons to carry out ultrasonography at the conclusion of the treatment. By ultrasound it is possible to check if the cavity is empty at the end of the treatment. However, the specialist in charge must also use the suction curette to feel if treatment is complete, and inspect the curettement.

When complaints of serious pain, too much blood loss, or continuing symptoms of pregnancy occur in the first weeks after the termination of pregnancy, ultrasound may reveal complications.

### **Recommendations**

There are good reasons to carry out ultrasonography at the conclusion of the treatment, to exclude the presence of retained tissue.

It is advisable to conduct ultrasound scanning when new or lingering complaints are observed during the period of time after the termination of pregnancy, such as severe abdominal pain, loss of too much blood or continuing haemorrhage.

If a woman has no complaints after a termination of pregnancy, ultrasound scanning has little added value. Generally, no abnormalities are found.

If the pregnancy test is still positive after four weeks, it is necessary, however, to conduct ultrasonography.

## 5.6 Ultrasound after medical termination of pregnancy

### Guiding question

What is the role of ultrasound imaging after medical termination of pregnancy?

### Summary of the literature

In a retrospective study by Acharya et al. (2004) of 645 women who underwent medical termination of pregnancy complications arose in 66 women (10.2%). On the ultrasound the uterus was not empty in 98 (15.2%) of the women when they were checked 2-3 weeks later. Of these women, 43 underwent curettage. The authors conclude routine ultrasound imaging at check-up to be an efficient method of identifying continuing pregnancies and for a diagnosis of completed abortion. Vaginal ultrasounds after medical termination of pregnancy at an LMP < 63 days is only an aid with respect to the decision to carry out additional curettage: the clinical presentation after termination of pregnancy is decisive.

Creinin (1996) concludes that a decrease of the serum- $\beta$ hCG of less than 50% at 24 hours after administration of misoprostol makes it unlikely that a complete abortion was achieved.

In a prospective trial including 165 women undergoing medical termination of pregnancy Edelman et al. (2004) found that ultrasound, after a minimum interval of four hours after taking misoprostol, held additional value. An empty cavity (50 cases in total) predicted that no additional curettage was necessary in 96% of the women with an amenorrhoea of <49 days; this figure was 98% at an amenorrhoea <63 days. In this population curettage had to be performed in 31 cases.

In a retrospective cohort study in 437 women undergoing medical termination of pregnancy at an amenorrhoea up to 63 days the endometrial thickness was measured after 7-10 days, using vaginal ultrasound (Cowett et al. 2004). The average thickness was  $4.1 \pm 1.8$  mm (spread: 67-13.4 mm). In view of the spread it is impossible to make pronouncements about treatment success by measurement of endometrial thickness. The decision to start additional treatment must be based on the clinical presentation, unless there is still an embryonic sac.

In their previously mentioned prospective trial involving 217 women undergoing medical termination of pregnancy Fiala et al. (2003) repeated vaginal sonography and the serum- $\beta$ hCG test after 6-18 days. Verification by ultrasound was only possible in those cases in which an initial ultrasound had determined the presence of intrauterine gravidity (yolk sac or crown-rump length). This was true for 167 (77%) of

the women: in 17 of them, (10.2%) complete abortion could not be demonstrated on day 7-12 by sonography alone, because of a non-homogeneous picture. The hCG levels went down to an average of 3% compared with the values before termination of pregnancy (spread 1-44%). The authors conclude the prognostic value in terms of successful expulsion to be 0.995 at a decrease to below 20% or less of the initial values. When the decrease is less than 80%, the negatively prognostic value will be 0.5 and further evaluation needs to take place. In view of the fact that the hCG tests took place after 6-18 days, these figures must be interpreted with care.

In 1,016 women undergoing medical termination of pregnancy Fielding et al. (2002) found a remaining yolk sac in 24 cases at follow-up. In seven cases the experienced clinicians saw no indication for sonography after examination and so would have missed these continuing pregnancies. The authors conclude that if clinical practitioners determine hCG levels in order to identify ectopic or continuing pregnancies medical termination of pregnancy can be carried out safely without ultrasound.

Machtinger et al. (2005) carried out a prospective trial involving 191 women undergoing medical termination of pregnancy at an amenorrhoea of < 49 days. Vaginal sonography was carried out in 170 women after 10-14 days; in 31 women in this group there were suspicions of retained traces of tissue. Of these 31, four received curettage. Four women wished to step out of the trial; in 23 the vaginal sonography was repeated after menstruation. In 9 out of these 23 there were suspected retained traces of pregnancy products, confirmed by hysteroscopy in 7 cases.

Menashe et al. (1995) conducted a study in 20 women undergoing medical termination of pregnancy with mifepristone alone. The success rate was 70%. Vaginal ultrasound correlated well with the clinical picture, in particular as regards the arrest of embryonic cardiac activity. This contrasted with serum- $\beta$ hCG testing in the first seven days; the test results had no prognostic value as regards a successful termination of pregnancy.

The review by Paul et al. (2000) discusses the value of serum  $\beta$ hCG determination and vaginal ultrasound imaging after medical first trimester termination of pregnancy. Elimination of  $\beta$ hCG is characterized by a rapid initial downtrend, followed by a gradual downtrend by around 50% per two days. A retrospective analysis of women participating in four medical abortion trials shows that the average

downtrend in serum-βhCG values in women with a complete abortion rated  $66 \pm 8\%$  24 hours after administration of misoprostol; in all others the decrease rated  $25 \pm 19\%$ . The authors judge that if there is clinical suspicion of a failed termination of pregnancy, vaginal sonography is more effective than repeated determinations of serum-βhCG.

In a prospective trial including 871 women undergoing medical termination of pregnancy with an amenorrhoea of < 63 days (Rorby et al. 2004) measured serum-βhCG on day 8 and 15 and established endometrium thickness on day 15, using vaginal sonography. In this trial, the prognostic value of vaginal ultrasound imaging and repeated serum testing (βhCG) was calculated. The authors conclude neither determinant to be useful as a clinical test, to predict late failures.

Schaff et al. (1995) studied 100 women with an LMP < 56 days who underwent medical termination of pregnancy and found that the average interval before the serum-βhCG had disappeared was 33 days (spread of 4-90 days).

Tsuchudin et al. (2004) conducted a retrospective study of 225 women after a medical termination of pregnancy (amenorrhoea < 49 days). In 40% of these women suspicions of retained tissue persisted after ultrasonography at 2 weeks; this included 50 of the 123 women with a confirmed complete abortion. This percentage went down after a longer waiting interval. Additional misoprostol did not influence this outcome. A policy of waiting and seeing would seem justified when retained products are found in sonography, or an endometrium thickness of < 16 mm.

### Conclusions

<b>Level 3</b>	<p>Vaginal sonography after medical termination of pregnancy is primarily intended to verify if the gestational sac has disappeared.</p> <p><i>B Fiala et al. 2003</i></p> <p><i>C Paul et al. 2000</i></p>
----------------	---

<b>Level 3</b>	<p>It may be assumed that sonography after medical termination of pregnancy leaves a picture which is often difficult to interpret. The endometrium is often thick; sometimes there is no homogeneity in the picture, resembling an incomplete abortion. Ultrasound does not always make it possible to pronounce an expert judgement about success or failure within two weeks after a medical termination of pregnancy.</p>
----------------	---

	C <i>Cowett et al. 2004, Rorby et al. 2004, Tsuchudin et al. 2004, Machtinger et al. 2005</i>
--	---

<b>Level 3</b>	<p>It is plausible to found the decision to start up additional treatment after a medical termination of pregnancy on the clinical picture, unless sonography reveals the presence of a gestational sac. When the uterus is not empty after sonography, a policy of waiting and seeing would seem justified.</p> <p>B     <i>Fiala et al. 2003</i></p> <p>C     <i>Paul et al. 2000, Acharya et al. 2004, Cowett et al. 2004</i></p>
----------------	--

### **Discussion and evaluation**

There is no consensus about what is best practice in verifying the outcome of a medical termination of pregnancy. Some clinical professionals use ultrasound before and after treatment, with rather large differences with respect to the time lapse after treatment, other trust serum-βhCG levels or use a less sensitive pregnancy test (500 IE/ml) at follow-up.

Elimination of βhCG is characterized by a rapid initial downtrend – which in medical termination of pregnancy actually does not start until after the administration of misoprostol – followed by a gradual downtrend of around 50% per two days. An increase of the serum-βhCG level compared to the initial value indicates a continuing pregnancy. In other respects, the available data are conflicting. Creinin (1996) claims that a decrease of less than 50% 24 hours after administration of misoprostol renders a complete abortion unlikely. Menashe et al. (1995) determined serum-βhCG levels in the first seven days and Rorby et al. (2004) on days 8 and 15; both find that this indicator has no prognostic value for a successful termination of pregnancy. Fiala et al. (2003) determined serum-βhCG on day 6 and 18. They claim – with the proviso of the time of determination – that a decrease down to 20% or less of the initial value implies a prognostic value for successful expulsion of 0.995, while a decrease of less than 20% of the initial value implies that an additional evaluation must take place. The importance of serum-βhCG determination and its timing will thus remain hovering in mid-air, for the time being.

Determining serum-βhCG prior to surgical termination of pregnancy or medical termination of pregnancy does not yield essential information for the intended treatment. This particular determination does not yield any information about the length of amenorrhoea, either. A rising serum-βhCG level indicates the need for a surgical intervention, but a continuing pregnancy may also be revealed by



ultrasound. Apart from this, there is also the importance of determining the presence of an ectopic pregnancy, which is not discussed in this framework.

At a week after starting the medical termination of pregnancy it is possible to check if the pregnancy was in fact expelled. This does not imply that treatment may be terminated. There is often evidence of retained tissue; when the woman keeps reporting too much loss of blood or symptoms of a continuing pregnancy, she must report back for an ultrasound check.

The study group feels that if no pregnancy can be demonstrated by ultrasound, it is best not to start a medical termination of pregnancy, but to wait for another week. It may also be a case of extra-uterine gravidity. If treatment is started up, it is necessary to obtain a  $\beta$ -hCG-determination on days 1 and 4, to ascertain if the pregnancy has come to an end.

### **Recommendations**

It is advisable to carry out a sonography after a medical termination of pregnancy, in the case of continuing abdominal pains, excessive blood loss or prolonged bleeding, or continuing symptoms of pregnancy.

It is advisable to carry out sonography at one to four weeks after a medical termination of pregnancy, depending on the stage of the pregnancy.

## 5.7 References

- Acharya G, Morgan H, Paramanatham L, Fernando R. *A randomized controlled trial comparing surgical termination of pregnancy with and without continuous guidance.* Eur J Obstet Gynecol Reprod Biol 2004; 114:69-74
- Acharya G, Haugen M, Brathen A, Nilsen I, Maltau JM. *Role of routine ultrasonography in monitoring the outcome of medical abortion in a clinical setting.* Acta Obstet Gynecol Scand 2004; 83: 390-4
- Bar-Hava I, Aschkenazi S, Orvieto R, Perri T, Shalev J, Dicker D, Ben-Rafael Z, Dekel A. *Spectrum of normal intrauterine cavity sonographic findings after first-trimester abortion.* J Ultrasound Med 2001; 20:1277-81
- Blanchard K, Cooper D, Dickson K et al. *A comparison of women's, provider's and ultrasound assessments of pregnancy duration among termination of pregnancy clients in South Africa.* Int J Gynecol Obstet 2007; 114:569-75
- Cowett AA, Cohen LS, Lichtenberg S, Stika CS. *Ultrasound evaluation of the endometrium after medical termination of pregnancy.* Obstet Gynecol 2004; 103:871-5
- Creinin MD. *Change in serum B-human chorionic gonadotrophin after abortion with methotrexate and misoprostol.* Am J Obstet Gynecol 1996; 174:776-8
- Darney P, Sweet RL. *Routine ultrasonography for second trimester abortion reduces incidence of uterine perforation.* J Ultrasound Med 1989; 8:71-5
- Edelman A, Thomas L, Jensen J. *Transvaginal ultrasound and the success of medical abortion.* Int J Gynecol Obstet 2004; 85:62-3
- Fakih MH, Barnea ER, Yarkoni S, DeCherney AH. *The value of real time ultrasonography in first trimester termination.* Contraception 1986; 33:533-8
- 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; 190-5
- Fielding SL, Schaff EA, Nam B. *Clinicians' perception of sonogram for mifepristone abortion up to 63 days.* Contraception 2002; 66:27-31
- Goldstein SR, Snyder JR, Watson C, Danon M. *Combined sonographic-pathologic surveillance in elective first-trimester termination of pregnancy.* Obstet Gynecol 1988; 71:747-50
- Grimes DA, Cates W. *Complications from legally induced abortion: a review.* Obstetrical Gynecological Survey 1979; 34:177-190
- Grimes DA, Schulz KF, Gates W, Tyler CW. *Mid-trimester abortion by dilatation and evacuation.* N Engl J Med 1977; 296: 1141-5
- Haddad S, Ruach M, Ohel G. *Sonographic demonstration of endometrial fluid collection following termination of pregnancy.* Obstet Gynecol 1992; 5:703-4
- Helm CW, Maxwell DJ, Lilford RJ. *A prospective study of the use of ultrasound in vaginal legal abortion before 20 weeks of pregnancy.* J Obstet Gynaecol 1986; 7:143-5
- Hornstein MD, Osathanondh R, Birnholz JC, Kapnic SJ, Jones TB, Safon LE, Cayea PD, Doubilet PM. *Ultrasound guidance for selected dilatation and evacuation procedures.* J Reprod Med 1986; 31:947-50
- Jarallah Y, Geirsson RT. *Is routine ultrasound before termination of pregnancy worthwhile?* Scott Med J 1985; 30: 232-3
- Machtiger R, Seidman DS, Goldenberg M, Stockheim D, Schiff E, Shulman A. *Transvaginal ultrasound and operative hysteroscopy in women undergoing medical termination of pregnancy as a part of routine follow-up.* Fertil Steril 2005; 84: 1536-8
- Marengo M, Sarramon MF, Berrebi A, Bergis A, Kobuch WE. *Le controle Ultrasonographique en post interruption volontaire de grossesse immediate.* J Gynaecol Obstet Biol Reprod 1988; 17 :51-5
- Markovitch O, Tepper R, Klein Z et al. *Sonographic appearance of pregnancy.* J Clin Ultrasound 2006; 34:278-82

- Maslovitz S, Almog B, Mimouni GS, Jaffa A, Lessing JB, Many A. *Accuracy of diagnosis of retained products of conception after dilatation and evacuation.* J Ultrasound Med 2004; 23: 749-56
- McEwing RL, Anderson NG, Meates JB et al. *Sonographic appearances of the endometrium after termination of pregnancy in asymptomatic versus symptomatic women.* J Ultrasound Med 2009; 28:579-86
- McGalliard C, Gaudoin M. *Routine ultrasound for pregnancy termination requests increases women's choice and reduces inappropriate treatments.* Br J Obstet Gynaecol 2004; 111:79-82
- Menashe Y, Bider D, Shalev J, Pariente C, Serr DM. *Clinical, hormonal and sonographic predictors of successful RU-486 induced abortions.* Gynecol Obstet Invest 1995; 40:108-12
- Mikkelsen AL, Fielding C. *The value of peroperative ultrasound examination in first trimester legally induced abortion.* Clin Exp Obst Gyn 1994; 3:150-1
- NVOG, *Datering van de zwangerschap, versie 1.0*, 04-10-2010, [www.nvog.nl](http://www.nvog.nl)
- Paul N, Schaff E, Nichols M. *The roles of clinical assessment, human gonadotropin assays, and ultrasonography in medical abortion practice.* Am J Obstet Gynecol 2000; 183: s34-s43
- Robinson ET, Barber, JH. *Early diagnosis of pregnancy in general practice.* J R Coll. Gen Pract 1977; 27:335-8
- Rorbye C, Norgaard M, Nilas L. *Prediction of late failure after medical abortion from serial beta-hCG measurements and ultrasonography.* Human Reprod 2004; 19:85-9
- Schaff EA, Eisinger SH, Franks P, Kim SS. *Combined methotrexate and misoprosol for early induced abortion.* Arch Fam Med 1995; 4:774-9
- Sinha P, Pradhan A, Chowdhury V. *Value of routine transvaginal ultrasound scan in women requesting early termination of pregnancy.* Obstet Gynecol 2004; 24:426-28
- Stone M, Elder MG. *Evaluation of sonar in the prediction of complications after vaginal termination of pregnancy.* Am J Obstet Gynecol 1974; 120:890-4
- Tribalat S, Ballardur A, Lewin D. *Images Ultrasoundgraphiques le lendemain d' une interruption volontaire de grossesse.* J Gynecol Obstet Biol Reprod 1987 ; 16 :100-1001
- Tschudin S, Zanotelli D, Bitzer j, Holzgreve W. *Erfahrungen mit dem medikamentösen Schwangerschaftsabbruch, insbesondere nachkontrolle, nachbehandlung und nachfolgende Kontrazeption.* Geburtsh Frauenheil 2004; 64:1299-1304
- Verburg B, Steegers E, de Ridder M, Snijders R, Smith E, Hofman A, Moll H, Jaddoe V en Witteman J, *New charts for ultrasound dating of pregnancy and assesment of fetal growth: longitudinal data from a population based cohort study,* Ultrasound Obstet Gynaecol 2008; 31: 388-396

# Chapter 6 Rhesus factor

## Guiding question

When must rhesus factor determination take place and what is the treatment in the case of Rh-?

### 6.1 Introduction

In the case of blood group antagonism a pregnant woman may become immunized by blood group antigens of the foetus. Isoimmunisation is started against antigens which the foetus inherits from its father and which are absent in the mother. In rhesus antagonism a rhesus negative woman produces antibodies during her pregnancy against her rhesus positive child. In most cases this concerns rhesus D. Around 85% of the population is rhesus-D positive, the other part rhesus-D negative. Out of 4,972 cases of pregnancy isoimmunisation, Van Went (1963) only found 70 (1.4%) with antibodies other than anti-Rh(D), while in 46 of those 70 anti-Rh(D) was also present; so, isoimmunisation by an agent other than anti-Rh(D) only exclusively occurred in 24 cases (0.48%). As early as 1948, Levine suspected that the production of antigens is induced by Rh(D) positive foetal erythrocytes which end up in the circulation of the mother via transplacental channels. This phenomenon was termed foetomaternal transfusion (FMT). Around week 12 of embryonic development syncytium cells develop into the endothelial lining of the arteries; at that point the mother's blood starts to penetrate the lacunae system. In this way placental circulation comes into place. The pumping activity of the embryonic heart and thus its blood circulation starts at about four weeks. Rh(D) antigen was already demonstrated in a foetus of 38 days (Bergstrom c.s. 1967). It is open to question if the antigen is already immunogenic at that point, however. Theoretically a transplacental haemorrhage in a rhesus negative woman brings along the risk of rhesus isoimmunisation at this point of embryonic development. Rhesus subgroup isoimmunisations (against subgroups C, c, E and e) and also isoimmunisations against other blood group antigens (Kell, Duffy, Lewis e.d.) do not proceed differently from Rh (D) isoimmunisation, but their frequency is much lower. During a first FMT of a Rh(D) negative mother and a Rh(D) positive foetus the onset of antigen production is probably very slow: antigens are usually not found until between the 3<sup>rd</sup> and 6<sup>th</sup> month after delivery. Once primary immunisation has set in (primary response) the body will respond to minute quantities of Rh(D) positive blood with a rapid increase in antigen production (the so-called booster reaction). In a next pregnancy the antibody titer will rise relatively early and may turn both mother and child gravely ill. This is the reason why the rhesus factor is determined in every

pregnant mother. A search was conducted in Medline and Embase with respect to termination of pregnancy, using controlled key terms and free text terms (starting 1966 in Medline and 1980 in Embase up to December 2009). Explode "Abortion-Induced"/all subheadings was used as a controlled key term. This topic was also searched using free text terms like pregnancy termination and induced abortion. The theme of rhesus antagonism was added via the controlled key terms "Rh-Isoimmunisation"/all subheadings or Immunoglobulin-administration-and -dosage. The outcome was restricted to English, Dutch, German and French language sources. Five articles were selected on the basis of this literature search. The authors also had articles in their possession which they had collected on this subject over the years. A total set of 15 articles was available which met the criteria, on which evidence tables could be based showing the risk of foetomaternal transfusion in termination of pregnancy expressed as a percentage of positive KB tests and the risk of rhesus isosensitization in termination of pregnancy in relation to method, amenorrhoea and prophylaxis.

## **6.2 Summary of the literature**

### *Factors which influence the frequency of rhesus isoimmunisation*

The first precondition for isoimmunisation is rhesus antagonism (after all, the foetus may be Rh(D) negative). Among Caucasians, around 15% is Rh(D) negative, in the African population around 7.5% and among Asians about 3.5%. Isoimmunisation turns out to be more restricted than what the figures would lead one to expect. The Rh(D) antigens are exclusively found in erythrocytes; rhesus isoimmunisation in the course of pregnancy can therefore only be caused by FMT. The FMT must, however, be of sufficient volume. Mollison (1971) estimates the minimum quantity of Rh(D) positive blood to cause isoimmunisation of a Rh(D) negative receiver to be 0.1-0.25 ml. The chances of isoimmunisation appear to be rising with the volume of FMT (Borst-Eilers, 1972). The maximum isoimmunisation percentage is reached after haemorrhages of 1 ml or more and lies at 60-65%. Thus, not every FMT is followed by isoimmunisation: the antigen must have immunizing power and the mother must be capable of forming antibodies, which is only the case in 2/3 of all Rh(D) negative women. Apart from that, immunological hypo-reactivity during the pregnancy and ABO-incompatibility play a role (Querido 1977).

### *Demonstrating foetomaternal transfusion*

By using the Kleihauer-Betke (KB)-test (Kleihauer, 1957) it can be demonstrated which erythrocytes in the maternal blood primarily hold HbF. However, HbF erythrocytes need not always be of foetal origin; besides, not all foetal erythrocytes contain HbF, either exclusively or mainly (Querido 1977). The percentage of HbA and

HbF is assessed with HPCL after lysis. In adults the proportion is 95/5; in a foetus this is 5/95 up to 10/90, depending on its age. Implied is the proportion inside each cell. The KB test can distinguish a foetal cell from an adult cell with a great degree of certainty. Apart from this, when interpreting the KB test it is important to take into account the presence or absence of natural or acquired antibodies against foetal erythrocytes in the mother's blood, in view of the survival time of foetal erythrocytes. The technical execution of the test has not been standardized, nor has the method of counting, rendering comparisons between the results of different authors difficult to make. A raised alpha foetoprotein level in the maternal serum appears to be a more sensitive and reliable indicator than the KB test (Lachman 1977). The KB test is not sensitive enough to demonstrate FMT of  $\leq 0.1$  ml. Flow cytometrics is a novel and more sensitive method.

#### *Foetomaternal transfusion in termination of pregnancy*

In a prospective trial, Jorgensen (1969) studied 227 women with respect to the incidence of FMT after a termination of pregnancy. Before the intervention, all women tested negative on the KB test. After spontaneous abortion, no FMT higher than 0.1 ml was found; after suction curettage in one case only (1.2%); after curettage also in a single case (6.7%); after hypertonic saline four cases (5.9%) and after rupture of the membranes (punctio ovi) three cases (25%). Leong (1979) studied 75 women undergoing suction curettage at a pregnancy length up to 8 weeks of amenorrhoea on the presence of foetal erythrocytes, using the KB test 15 minutes before surgery and 30 minutes after surgery. Before surgery, the KB test was positive in two cases (2.6%) and in twelve cases after surgery (15.5%). At six weeks of amenorrhoea there was no positive KB test, neither before nor after surgery. Murray (1970) studied 483 women on the incidence of FMT before and directly after spontaneous and surgical abortion, and again after a time interval. Before abortion, the KB test was positive in 54 cases (11.6%). Of the 243 cases in which the pregnancy was ended by means of suction curettage, it was ended before the 14<sup>th</sup> week of amenorrhoea, in all but six cases. In the suction curettage group, 39 women tested positive on the KB test before the intervention and 39 after the intervention. In the group of women with a spontaneous abortion, 21 women tested positive on the KB test before the abortion and 22 after the abortion. On the basis of these findings the authors conclude that it makes no difference whether the abortion was spontaneous or induced.

Queenan (1971) studied 606 women on the presence of FMT after termination of pregnancy: 404 women underwent termination of pregnancy by suction curettage (384 women up to 13 weeks and 20 women at between 13 and 16 weeks of

amenorrhoea) and 202 women (13 up to 23 weeks of amenorrhoea) by hypertonic saline solution. None of these women had any foetal cells in their blood before treatment. The FMT was monitored with the KB test 24 hours after the termination of pregnancy; FMT was defined as the presence of two or more foetal cells per 50,000 maternal cells (which corresponds with an FMT of 0.2 ml). In the entire suction curettage group FMT could be demonstrated in 7.2%; in the suction curettage group up to 13 weeks this figure was 6.0%. In the group receiving the hypertonic saline solution FMT could be demonstrated in 20.2%.

Borst-Eilers (1972) studied the frequency of FMT in 72 women before and after termination of pregnancy. In twelve cases no assessment was possible. Of the other 60, 50 underwent suction curettage, 8 curettage and 2 sectio parva. In just three cases, the number of HbF erythrocytes was considerably higher after the intervention than before (5 versus 1; 11 versus 2 and 10 versus 3). An FMT of over 0.1 ml thus only occurred in two cases.

#### *Isoimmunisation and prevention in termination of pregnancy*

Jorgensen (1969) conducted a prospective trial in 30 Rh(D) negative women whose pregnancy was terminated. The group consisted of 8 primigravidae and 22 multigravidae. In one primigravida (13%) and two multigravidae (9%) antibodies were demonstrated 6-12 months later (overall percentage: 10%). No antibodies had been found in any of the women before termination of pregnancy. The primigravida was curettaged at 15 weeks of amenorrhoea; after the intervention, the KB test was positive (FMT >1.5 ml). The two multigravidae were curettaged at 10 and 14 weeks of amenorrhoea.

Murray c.s. (1970) carried out a prospective trial involving 23 Rh(D) negative multiparae after termination of pregnancy. In three instances isoimmunisation was found. The KB test after the abortion was negative.

In the study by Queenan (1971) discussed above, 66 women were Rh(D) negative: 15 were given anti-D immunoglobulin after termination of pregnancy; 3 had already become isosensitized. Of the remaining 48 women nobody was isosensitized before the intervention. Follow-up of 25 women after four months showed that one multipara had become isosensitized (had developed antibodies); she had undergone suction curettage at nine weeks of amenorrhoea and tested negative on a KB test after her termination of pregnancy.

Murray (1971) conducted a comparative prospective study including 96 Rh(D) negative women (48 primigravidae and 48 multigravidae). The KB test was administered both before and after termination of pregnancy. After 6-9 months she found antigens in 3 primigravidae and 6 multigravidae. Of these nine cases showing

antibodies five had undergone suction curettage (four out of a group of 27 multiparae and one in a group of 27 primiparae), three had undergone saline treatment and one a hysterotomy abortion.

177 Rh(D) negative women undergoing termination of pregnancy were studied by Murray (1972). A KB test was administered to 146 women before and after the termination of pregnancy. 96 women were monitored for isosensitization: 44 had an amenorrhoea length of <12 weeks, 40 > 12 weeks while in 12 women their pregnancy length was uncertain. Of the entire group, seven (6.2%) tested positive on the KB test with an FMT of > 0.1 ml. However, only two of the patients (2%) appeared isosensitized at a pregnancy length of seven and ten weeks, respectively. Both women tested negative on the KB test after surgery.

Vischer (1972) carried out a prospective comparative trial in 57 Rh(D) negative women with Rh(D) positive partners after spontaneous abortion. Their pregnancy length was 8-24 weeks of amenorrhoea; after an incomplete abortion curettage was carried out. In the double blind part of the study, 19 women received 300 µg anti-d while 29 did not. In a follow-up study of nine women none were given anti(Rh)D immunoglobulin. At check-up after three and six months no antibodies were found. The authors find that Rh-immunoprophylaxis is unnecessary after a spontaneous abortion <12 weeks of amenorrhoea. An important argument in this context is that it is assumed that foetal necrosis and placenta degradation occur 4-5 weeks before the spontaneous abortion sets in.

Goldman (1972) conducted a study of 170 Rh(D) negative women after a spontaneous or an induced termination of pregnancy. 48 women in all (29 in their first and 19 women in their second trimester) were given 200 µg anti-D immunoglobulin, while 22 did not. In the group thus treated no isosensitization occurred. Isosensitization did occur in two non-protected women after spontaneous abortion; this was also the case for three women who underwent surgical termination of pregnancy. According to the authors, the risk of FMT is greater after surgical termination of pregnancy compared to spontaneous abortion.

Keith (1977) researched 315 Rh(D) negative women undergoing a first trimester termination of pregnancy. Seventeen women received 300 µg anti-D immunoglobulin and 298 women 50 µg. No isosensitization could be found in any of the women at six months. In the first trimester 50 µg immunoglobulin is sufficient to prevent isoimmunisation.

Bennebroek Gravenhorst (1986) c.s. monitored serum AFP levels in 103 women directly before and after termination of pregnancy, at an amenorrhoea length between 12 and 19 weeks. FMT increased with pregnancy length; in 6-8% of the



women the quantities ranged between 1 and 3.5 ml. Administration of 75 µg of anti-D immunoglobulin proved enough to prevent isosensitization.

Hensleigh (1977) studied 187 rhesus negative women with a pregnancy length of 5-14 weeks of amenorrhoea. FMT occurred in 27%, based on the KB test. There was a subdivision in three groups. Each group received a different dose of anti-D immunoglobulin: 499 µg, 155 µg and 73 µg, respectively. Isosensitization was found in none of the patients.

Urquhart (1990) compared 20 women undergoing medical termination of pregnancy with 20 women undergoing vacuum aspiration. Age and pregnancy length were the same in both groups. Serum-AFP was monitored before mifepristone was taken, 48 hours later before taking misoprostol and again at 4 hours after taking misoprostol. In the case of vacuum aspiration serum-AFP was monitored before the administration of anaesthesia and immediately after surgery. In the medical termination of pregnancy group not a single patient presented an increase in serum-AFP between administration of mifepristone and administration of misoprostol. After taking misoprostol the AFP level rose to 25% above the starting value in three patients after four hours (15%). In the vacuum aspiration group an increase of 25% was found in twelve patients (60%). Thus, FMT occurs more frequently after vacuum aspiration than after medical termination of pregnancy. This does not imply that isosensitization will develop more frequently, too. According to the authors, all Rh(D) negative women must be given anti-d immunoglobulin; in medical termination of pregnancy at the moment when misoprostol is taken.

Jabara carried out a literature study of the years between 1964 and 2003, on rhesus antagonism and termination of pregnancy. They concluded that the evidence supporting the administration of anti-d immunoglobulin in the first trimester is very thin, but that there is theoretical evidence for the necessity to do so nonetheless.

Mollison (1971) estimated that at least 0.1-0.25 ml of foetal blood is needed to effect isosensitization. It may be assumed that 1000 IE (200µg) of anti-D will neutralize positive full blood (= 10 ml Erythrocyte concentrate). 20 ug anti-D immunoglobulin will suppress immunogenic problems caused by 1 ml of blood; 50 ug anti-D immunoglobulin will therefore offer protection against 2.5 ml of blood, a quantity bigger than the entire blood volume in a foetus in the first trimester. This quantity was already established by the WHO in 1970. Research by Kiss c.s. (1974), the Working Party (1975) and Keith (1977) also proves that a dosage of 50 ug anti-D immunoglobulin is adequate in the first trimester. For the second trimester the dosage should be between 50 and 200 ug (WHO 1970, Bennebroek Gravenhorst 1981, Bennebroek Gravenhorst, 1986). The latter quantity is adequate protection after delivery (i.e. it will protect against FMT of 20 ml).

## Conclusions

<b>Level 3</b>	<p>The KB test appears to be reliable in demonstrating HbF. This test is a measure of foetomaternal transfusion. FMT is a precondition to rhesus isosensitization. When interpreting the findings derived from the literature both false-positive and false-negative outcomes of the KB test must be taken into account.</p> <p><i>C Kleihauer 1957, Querido 1977</i></p>
<b>Level 3</b>	<p>It appears likely that practically no foetal cells pass through the placenta barrier during the first trimester of pregnancy, not even after a spontaneous abortion. The frequency of FMT (and so the risk of isosensitization) rises with pregnancy length; theoretically, FMT may be found from 52 days of amenorrhoea onward. Not every instance of FMT is followed by isosensitization.</p> <p><i>B Queenan 1971</i> <i>C Borst-Eilers 1972, Bennebroek Gravenhorst 1986</i></p>
<b>Level 3</b>	<p>It appears likely that Rh isosensitization may also occur without prior demonstration of FMT as measured by the KB test (false-negative KB outcome). It takes a few weeks before a primary response can be demonstrated.</p> <p><i>B Murray 1970, Queenan 1971</i> <i>C Murray 1972</i></p>
<b>Level 2</b>	<p>It appears likely that the risk of sensitization is negligible in the case of spontaneous abortions at under eight weeks of amenorrhoea. After eight weeks, the risk is 3-4%; in the second trimester it is 6-8%.</p> <p><i>A2 Visscher 1972</i></p>
<b>Level 3</b>	<p>Foetomaternal transfusion more frequently occurs in induced termination of pregnancy, compared to spontaneous abortions.</p> <p><i>B Jorgenson 1969, Goldman 1972</i></p>

<b>Level 2</b>	<p>In the case of an induced termination of pregnancy it is likely that immunoglobulin at a dose of 50 ug (250 IE) is adequate in the first trimester; a dose of 75 ug (375 IE) is adequate in the second trimester</p> <p>A2    <i>Hensleigh 1977</i></p> <p>B      <i>Keith 1977</i></p> <p>C      <i>Kiss 1974, Working Party 1975, Bennebroek Gravenhorst 1981, Bennebroek Gravenhorst 1986</i></p>
----------------	---

### 6.3 Discussion and evaluation

Medical termination of pregnancy is no spontaneous abortion. Lacking are the most important characteristics of spontaneous abortion: foetal necrosis and placenta degeneration some weeks before expulsion. It is advisable to follow the same policy in medical termination of pregnancy as in surgical termination of pregnancy. The anti-D immunoglobulin may be administered on the same day as the mifepristone. Critical remarks are warranted with respect to the study by Leong et al. (1979). Firstly, LMP and gestation are mixed up. Next, the authors claim that they measured foetal erythrocytes rather than HbF. The numbers recorded by the authors do not match the percentages they published.

According to Urquhart (1990) the optimal administration of anti-D immunoglobulin is during the intake of misoprostol, but as anti-D immunoglobulin is effective up to 21 days after administration, it may well be given at the moment of taking mifepristone. Anti-D immunoglobulin must always be given within 48 hours after termination of the pregnancy. Administration of anti-D immunoglobulin beyond 48 hours after exposition is probably less effective, but still proven to be effective up to 13 days after exposition and is recommended up to one month after exposition (Bowman 1985, Samsonen Mollison, 1975).

Dutch abortion practice shows that we may refrain from administering anti-D under specific circumstances (e.g. absolutely no wish to have a child). It is an absolute prerequisite that the possible consequences are discussed with the woman.

As anti-D-vaccine is expensive and is made of human blood, it is advisable to put doses of 50 µg (250 IE) and 75 µg (375 IE) immunoglobulin on the market.

In the NVOG guideline the following recommendation was adopted: Rhesus negative women must be given anti-D in the case of a termination of pregnancy, with the exception of a medical termination of pregnancy before week 10. This recommendation and the doses specified above have been taken over from the 1998 IGZ<sup>10</sup> report. Doses of 50 µg (250 IE) were not available at that time.

<sup>10</sup> National Health Inspectorate of The Netherlands

Discussion arose in the study group about the pregnancy stage at which anti-D should become obligatory. The literature lists only one study in which the presence of Rh(D)-antigen was demonstrated at 52 days of amenorrhoea (Bergstrom).

### **Recommendations**

Up to 7/0 weeks (49 days) of amenorrhoea there is no need to administer anti-d immunoglobulin.

Starting at 7/0 weeks (49 days) of amenorrhoea Rh(D) negative women undergoing termination of pregnancy must be protected with an adequate dose of anti-d, of 250 IE in the first and 375 IE in the second trimester, with the exception of already isosensitized women.

## 6.4 References

- Bennebroek Gravenhorst J. *De preventie van Rh(D) immunisatie mbv anti Rhesus(D) immunoglobuline*. GHI Bulletin. Leidschendam. 1981
- Bennebroek Gravenhorst J, Beintema-Dubbeldam A, van Lith D.A.F., Beekhuizen W. *Elevation of maternal alpha-fetoprotein serum levels in relation to fetomaternal haemorrhage after second trimester pregnancy termination by aspirotomy*. Br. J. Obstet. Gynaecol. 93, 1302-4, 1986
- Bergstrom, H., Nilsson, L.A., Nilsson, L., en L. Ryttinger. *Demonstration of Rh antigens in a 38 day-old fetus*. Amer. J. Obstet. Gynec. 99, 130, 1967
- Borst-Eilers, E. *Rhesusimmunisatie: ontstaan en preventie*. Acad. Proefschrift, Utrecht, 1972
- Bowman JM. *Controversies in RH prophylaxis. Who needs RH immunoglobulin and when should it be given?* Am. J. Obstet. Gynecol 1985: 151:289-94
- Goldman, J.A., Eckerling B. *Prevention of RH Immunization after abortion with anti-Rh(D)-immunoglobulin*. Obstet. Gynecol. 40, 366-70, 1972
- Hensleigh, P.A., Leslie W., Dixon E, Hall E, Kitay D.Z., Jackson J.E. *Reduced dose of Rh(D) immunoglobulin following induced first-trimester abortion*. Am. J. Obstet. Gynecol. 129, 413-6, 1977
- Jabara, S. en K.T. Barnhart. *Is Rh immune globulin needed in early first-trimester abortion*. Am. J. Obstet. Gynecol. 129, 623-7, 2003
- Jorgensen, J. *Rhesus-antibody development after abortion*. Lancet II, 1253, 1969
- Keith, L., Bozorgi N. *Small dose anti-Rh therapy after first trimester abortion*. Int. J. Gynaecol. Obstet. 15(3) 235-7, 1977
- Kiss, D en B. Szoke. *Praevention der Rh-Isoimmunisation in Verbindung mit Spontan-abortus und Schwangerschaftsunterbrechungen*. Zentralbl. Gynaekol. 96, 398, 1974
- Kleihauer, E., Braun, H. en K. Betke. *Demonstration vom fetalem Haemoglobin in den Erythrocyten eines Blutausschnitts*. Klin. Wschr. 35, 687, 1957
- Lachman, E., Hingley, S.M., Bates, C. e.a.. *Detection and measurement of fetomaternal haemorrhage: serum alpha-fetoprotein and the Kleihauer technique*. BMJ 1, 1377, 1977
- Leong, M., Duby, S. en R.A.H. Kinch. *Fetal-maternal transfusion following early abortion*. Obstet. Gynecol. 54, 424-6, 1979
- Levine, P. *The mechanism of transplacental iso-immunization*. Blood 3, 404, 1948
- Mollison, P.L. *The role of Rh antibodies in causing haemolytic disease of the newborn and in preventing it*. J. Clin. Path. 24, 479, 1971
- Murray, S., Barron, S.L. en R.A. McNay. *Transplacental haemorrhage after abortion*. Lancet I, 631, 1970
- Murray, S. en S.L. Barron. *Rhesus iso immunization after abortion*. BMJ 3, 90, 1971
- Murray, S. en S.L. Barron. *Transplacental haemorrhage in induced abortion*. Lancet I, 1972, 815-7
- Queenan, J.T, Shah, S, Kubarych, S.F. en B. Holland. *Role of induced abortion in rhesus immunisation*. Lancet I, 815-7, 1971
- Querido, L. *Abortus en rhesusprophylaxis*. Stimezo, Dan Haag, 1977
- Samson, D. en P.L. Mollison. *Effect on primary Rh immunisation of delayed administration of anti-Rh*. Immunology 1975 :28:394-397
- Urquhart, D.R., Templeton A. *Reduced risk of isoimmunisation in medical abortion*. Lancet, 914, 1990
- Visscher R.D. en H.C. Visscher. *Do Rh-negative women with an early spontaneous abortion need Rh immune prophylaxis*. Am. J. Obstet. Gynecol. 15, 158-65, 1972
- Van Went, J.J. *Rhesusimmunisatie*. Acad. Proefschrift, Amsterdam, 1963
- WHO Report 486: *Prevention of Rh sensitisation*. Geneva, 1970
- Working Party on the use of anti-D immunoglobulin. *Controlled trial of various anti-D dosages in suppression of Rh sensitisation following pregnancy*. Brit. Med. J. 2, 75, 1975

## Appendix 1 Search strategy

The foundation of this guideline rests on evidence from published scientific research. Relevant articles were traced by carrying out systematic searches. Medline was analysed with respect to the years between 2000 and 2010. An orientative search was also directed at the Cochrane Library; a specific search was carried out with respect to existing guidelines and in (inter)national guideline clearinghouses which could be consulted online.

The languages were limited to English and Dutch. In addition, articles were extracted from reference lists in the requested literature and submitted by study group members. This yielded additional articles related to some of the guiding questions. All searches were undertaken between December 2009 and January 2010.

For all guiding questions a uniform phrasing of the intervention was used.

1. exp Abortion, Induced/
2. ("pregnancy termination\*" or "induced abortion\*" or "therapeutic abortion\*").af.
3. 1 or 2
4. (pregnancy adj3 termination).ab,ti.
5. 3 or 4

In addition. specifications were used for each of the guiding questions.

Guiding question	Specification	Found	Criteria
<b>1. First trimester treatment</b>	4 first trimester.ab,ti. (12810) 5 pregnancy trimester, first/ (11029) 6 early.ab,ti. (820909) 7 4 or 5 or 6 (833866) 8 3 and 7 (5391) 9 Vacuum Curettage/ (779) 10 (vacuum adj5 aspiration).ab,ti. (3) 11 (vacuum adj5 curettage).ab,ti. (1) 12 (vacuum adj5 curettage).ab,ti. (154) 13 (vacuum adj5	Medline (OVID), Cochrane Library 14 SR 87 RCTs	systematic review/meta-analysis /RCTs/ between Jan. 2000 to 2010 English, Dutch, French and German

Guiding question	Specification	Found	Criteria
	aspiration).ab,ti. (832) 14 (vacuum aspiration or suction or "dilatation and curettage").ab,ti. (12757) 15 (surgical adj2 abortion).ti,ab. (373) 16 or/9-15 (13490) 17 (medical adj2 abortion).ti,ab. (834) 18 exp Abortifacient Agents/ (46303) 19 (misoprostol or mifegyne or cytotec).ti,ab. (3112) 20 17 or 18 or 19 (47164) 21 16 and 20 (659) 22 7 and 21 (415) 49 limit 22 to (yr="2004 -Current" and (Dutch or English or French or German)) (132) 50 Filter RCTs > (56) 51 Filter SR > (10) Cochrane (93)		
<b>2a. Second trimester treatment</b>	4. ("second trimester abortion" or "late abortion").ab,ti. 5. Pregnancy Trimester, Second/ 6. 3 and 5 7. 4 or 6 8. exp curettage/ or "dilatation and curettage"/ 9. Dilatation/ 10. Misoprostol/ 11. Mifepristone/ 12. Oxytocin/ 13. Oxytocin/ 14. Ambulatory Surgical Procedures/	9 SR 103 RCTs	Systematic reviews RCTs Starting 2005 Dutch, English, German, French

Guiding question	Specification	Found	Criteria
	15. (surgery or sugical).ab,ti. 16. misoprostol.ab,ti. 17. currettage.ab,ti. 18. curettage.ab,ti. 19. cervical dilatation.ab,ti. 20. cervical priming.ab,ti. 21. or/8-20 22. 7 and 21 23. limit 22 to (yr="2005 -Current" and (dutch or english or french or german))		
<b>2b Complications of second trimester treatment</b>	77 ((Early or late) adi complication*).ti,ab. (11097) 78 complications.fs. (1348289) 79 77 or 78 (1356966) 81 adverse effects.fs. (1115542) 82 79 or 81 (2333206)	3 SR 21 RCT 44 various	
<b>2c Cervical priming</b>	1. exp Abortion, Induced/ 2. ("pregnancy termination*" or "induced abortion*").af. 3. 1 or 2 4. ("second trimester abortion" or "late abortion").ab,ti. 5. Pregnancy Trimester, Second/ 6. 3 and 5 7. 4 or 6 20. cervical priming.ab,ti. 25. vaginal touch.mp. 26. exp Palpation/ 27. 7 and 26 28. digital vaginal examination*.ab,ti. 29. vaginal examination*.ab,ti. 30. physical examination*.ab,ti. or exp Physical Examination/ 31. 25 or 29 or 30 32. 7 and 31 33. 20 and 32 34. 3 and 31	17 various	



Guiding question	Specification	Found	Criteria
	<p>35. 20 and 34</p> <p>36. gyneacologic* examination*.ab,ti.</p> <p>37. gynecologic* examination*.ab,ti.</p> <p>38. 36 or 37</p> <p>39. 31 or 38</p> <p>40. 3 and 39</p> <p>41. 20 and 40</p> <p>42. Cervical Ripening/</p> <p>43. 40 and 42</p> <p>44. (cervical adj4 ripening).ab,ti.</p> <p>45. (cervix adj4 ripening).ab,ti.</p> <p>46. (cervix adj4 priming).ab,ti.</p> <p>47. (cervical adj4 priming).ab,ti.</p> <p>48. 19 or 20 or 42 or 44 or 45 or 46 or 47</p> <p>49. 40 and 48 &gt; 11 refs.</p> <p>Embase: 'induced abortion'/exp OR (induced NEAR/2 abortion):ab,ti OR (pregnancy NEAR/2 termination):ab,ti AND ('physical examination'/exp OR vaginal NEAR/3 examination* OR gynecological NEAR/3 examination* OR gynaecological NEAR/3 examination*) AND ('uterine cervix ripening'/exp OR (cervix NEAR/3 priming):ab,ti OR (cervical NEAR/3 priming):ab,ti OR (cervical NEAR/3 ripening):ab,ti OR (cervix NEAR/3 ripening):ab,ti</p>		
<b>3. Prophylactic antibiotic policy</b>	<p>6. Antibiotic Prophylaxis/</p> <p>7. "prophyla*".ab,ti.</p>	<p>Medline (OVID)</p> <p>10 SR</p>	<p>systematic review/meta-analysis</p>

Guiding question	Specification	Found	Criteria
	<p>8. Anti-Bacterial Agents/ or Azithromycin/ or Azithromycin.ab,ti. or Metronidazole/ or Metronidazole.ab,ti. 7 or 8 9 and 6</p> <p>9. exp Anti-Bacterial Agents/ or Azithromycin/ or Azithromycin.ab,ti. or Metronidazole/ or Metronidazole.ab,ti. or exp Bacterial Infections/pc [Prevention &amp; Control] (500733)</p>	<p>28 RCT 52 other trials</p>	<p>/RCTs/ other comparative studies</p> <p>from 2000 to 2010 English, Dutch, German, French</p>
<p><b>4. Ultrasound</b></p>	<p>7. exp *Ultrasonography/ 8. (ultrasound or sonograph* or Ultrasound).ti. 9. 7 or 8 10. 5 and 9 11. abortion, therapeutic/ or pregnancy reduction, multifetal/ 12. 10 not 11 13. Ultrasonography, Prenatal/ 14. 10 not 13 15. 12 or 14 16. limit 15 to (dutch or english) 17. Search filter systematic reviews 45. 16 and 44 &gt; 2 References (Probably not relevant) 46. Search filter RCTS 69. 16 and 68 &gt; 7 References 70. exp epidemiologic studies/ 71. 16 and 70 72. limit 16 to (clinical trial, all or clinical trial or comparative study or consensus development</p>	<p>2 SR 7 RCTS 29 various trials</p>	

Guiding question	Specification	Found	Criteria
	conference or consensus development conference, nih or controlled clinical trial or evaluation studies or government publications or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or research support, nih, extramural or research support, nih, intramural or research support, non us gov't or research support, us gov't, non phs or research support, us gov't, phs or "review" or technical report or validation studies)		
<b>5. Rhesus antagonism</b>	4. Rh Isoimmunization/ 5. Rh Isoimmunization.af. 6. exp Immunoglobulins/ad [Administration & Dosage] 7. "rhesus immunisation".af. 8. or/4-7 9. 3 and 8 10. "Rh-Hr Blood-Group System"/ 11. 3 and 10 12. 9 or 11 13. 9 not 11 14. 11 not 9 15. limit 12 to yr="2006 -Current"  Result: 2 References.  Search embase: 3 References 'induced abortion'/exp OR (induced NEAR/2 abortion):ab,ti OR (pregnancy NEAR/2 termination):ab,ti AND ('immunoglobulin'/exp/dd_do,dd_a d OR 'rhesus isoimmunization'/exp OR 'blood group and rhesus	Medline (2) and Embase (2)	Various designs

Guiding question	Specification	Found	Criteria
	antagonism'/exp OR rhesus:ab,ti)		

Search filter Systematic reviews (adapted from SIGN)

(<http://www.sign.ac.uk/methodology/filters.html>)

1. meta-analysis/ or meta-analysis as topic/
2. (meta adj analy\$).tw.
3. (systematic\* adj review\$1).tw.
4. (systematic adj overview\$1).tw.
5. exp "Review Literature as Topic"/
6. or/1-5
7. cochrane.ab.
8. embase.ab.
9. medline.ab.
10. (psychlit or psyclit).ab.
11. (cinahl or cinhal).ab.
12. cancerlit.ab.
13. or/7-12
14. selection criteria.ab.
15. data extraction.ab.
16. "review"/
17. 15 or 14
18. 16 and 17
19. Comment/
20. Editorial/
21. Letter/
22. Animals/
23. Humans/
24. 22 not (22 and 23)
25. 21 or 19 or 20
26. 25 or 24
27. 6 or 18 or 13
28. 27 not 26

Search filter RCTs (adapted from SIGN)

(<http://www.sign.ac.uk/methodology/filters.html>)

1. exp clinical trial/ or randomized controlled trial/

2. exp clinical trials as topic/ or randomized controlled trials as topic/
3. Random Allocation/
4. Double-Blind Method/
5. Single-Blind Method/
6. (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt.
7. or/1-6
8. clinic\$ trial\$1.tw.
9. (clinic\$ adj trial\$1).tw.
10. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
11. Placebos/
12. placebo\$.tw.
13. randomly allocated.tw.
14. (allocated adj2 random\$).tw.
15. or/8-14
16. 7 or 15
17. Letter/
18. Animals/
19. Humans/
20. 18 not (18 and 19)
21. 16 not 20

## **Appendix 2 Terms and definitions**

### **Abortus provocatus**

(Induced) termination of pregnancy, induced abortion

### **Abortion figure**

The number of induced abortions per 1,000 women in the child bearing age (15-44 years).

### **Abortion ratio**

The number of induced abortions per 1,000 live born children in a particular year.

### **Amenorrhoea length**

The period of time starting from the first day of the last menstrual period. This time indicator is often used to specify pregnancy length. The manner in which this is done is described under 'pregnancy length'.

### **Dutch national abortion register (Lar)**

In the Dutch National Abortion Register (LAR) abortion clinics collect characteristics of and data from abortion patients on a voluntary basis. 14 of the 17 abortion clinics collaborate in the LAR; hospitals do not contribute to the LAR. Although no full coverage is achieved for this reason, the LAR is a valuable additional source of data to the inspectorate's registration, as relations between individual data can be obtained.

### **Early abortion**

Early termination of pregnancy, up to 16 days' absence of menstruation (amenorrhea length up to 44 days). Early abortion is usually medical.

### **First trimester abortion**

Termination of pregnancy up to 91 days of amenorrhoea.

### **Pregnancy length**

The nominal length of pregnancy, calculated from the first day of the last menstruation (in a regular four weeks' cycle and assuming there are no indications justifying a discussion of terms) or possibly calculated starting 14 days preceding ovulation.

**Second trimester abortion**

Termination of pregnancy beyond 91 days of amenorrhoea up to the (legal) viability line.

**Spontaneous abortion**

Non-induced termination of pregnancy, miscarriage

## Appendix 3 Statement of interests

**Statement about a possible conflict of interests and embargo with respect to the guideline ‘Counselling of women considering termination of pregnancy’, developed at the initiative of the Dutch Association of Abortion Specialists, with the support of the Department of Support in Professional Quality of the Dutch Order of Medical Specialists**

24 August 2008

Re: Guideline ‘Treatment of women undergoing termination of pregnancy’

Dear Sir / Madam,

In connection with your contribution to the development of the guideline ‘Treatment of women undergoing termination of pregnancy’ we kindly request you to fill out the statement on the annexed page (reproduced below).

In the domain of science it has been recognized over the past few years that conflicts of interests cannot always be avoided. The Dutch Order of Medical Specialists thus takes steps to assure full transparency in this matter.

You are therefore requested to declare on the annexed form if you (have) maintained a (financially supported) connection with commercial enterprises, organizations or institutions within the past five years, connected with the subject of the guideline ‘Counselling of women considering termination of pregnancy’.

The details of your statement will be open to anyone requesting this information at the Department for Support in Professional Quality’s secretariat.

### **Embargo**

The texts of the draft version(s) of this guideline will be under embargo during the full course of its development.

This implies that it is not permitted to pass on passages from the draft guideline, or the full draft text, to other parties without the written consent of the commissioner of this guideline. This proviso also includes annexes and addenda, such as evidence-based tables.

The undersigned declares by his/her signature to agree to the above.

.....  
(name)

.....  
(place, date) (signature)



**Statement about conflicts of interests**

Did you have interests over the past five years which may interfere with the study group’s decision making with respect to the interpretation of scientific evidence and the drafting of recommendations, or do you foresee such interests during the course of development of the guideline?

Yes / No

If affirmative, can you describe from what activities these interests derive and which organizations or enterprises are concerned? Examples of activities may be found in consultations, advisory roles, (re)training, courses and the support of scientific research.

- 1. ....
- 2. ....
- 3. ....

If you have more than three entries, please use separate page.

The undersigned declares to have truthfully submitted the above information and to be prepared to communicate all mutations of the above to the study group’s chairman and secretary.

Re: guideline ‘Treatment of women undergoing termination of pregnancy’

Name: .....

Participant on behalf

of: .....

(place, date) (signature)

## Appendix 4 Evidence tables

Guiding question Priming in 1<sup>st</sup> trimester suction curettage

Reference	Type of study	Characteristic elements	Intervention	Control group	Outcome indicators Follow up	Results	Quality	Evidence level
Oppegaard KS, 2005	RCT	Women with intact pregnancy 7-12 weeks preferring suction curettage excl: other pregnancy length, no Norwegian or English, allergic to misoprostol n=338 (calc 340)	Misoprostol vaginally morning intervention 400 mcg	Misoprostol orally evening before intervention 400 mcg	Dilatation Complications acceptability Contact after 60 days	Dilatation no difference Parity sole factor More blood loss in oral group (OR 10.4) Vaginal administration acceptable (only asked in this group)	no blinding big sample reasonable	B
Saxena P, 2005	Prospective clinical trial	Women between 6-12 weeks of pregnancy n=100 (118 asked) Many exclusion criteria	Misoprostol sublingually 400mcg	Misoprostol vaginally 400mcg	Dilatation Pain Intervention length Blood loss	Dilatation in sublingual group more simple (9 vs 7, p<0.0002) and shorter 3.51 minuten vs. 4.68 (p<0.0001) Side effects and complications no difference Sublingual more acceptable (also because taking at later time)	- no randomisation - no calculation of sample size - logistically illogical -only multiparae Thus: poor	B

Guiding question: 2<sup>nd</sup> trimester - Cervix Priming

Reference	Type of study	Characteristic elements	Intervention	Control group	Outcome indicators Follow up	Results	Qualityit	Evidenc e level
A.Goldberg, 2005	RCT	Healthy pregnant women > 18 yrs n=84 12+6 to 15+6 excl:>1 s.c., mult.pregn, iufd, myoma >3cm, lis excision, coagulation problem, iud, allergy, breastfeeding Suction curettage possibly combined with forceps	misoprostol on intervention day after vaginal screening on day prior to intervention	laminaria day prior to interv. followed by placebo on day of intervention	Time of procedure Direct completion Dilatation at the start Acceptabilit y	procedure shorter through laminaria, esp. in nulli (p<0.001) completion: no difference dilatation at start 33 vs 43 French (=11 and 14 mm resp.) (p<0.001) Doctors preferred laminaria Misoprostol patients more satisfied	Good	A2
A.Edelman, 2005	RCT (geblindeerd )	Healthy pregnant women >18 yrs, 13-15+6, n=62 (calc 72) 16-20+6, n=63 (calc 72) Excl refusal no sedation allowed contraindication misoprostol	misoprostol buccally 60-90 minutes before interv. and laminaria 1 day before intervention	placebo buccally 60-90 minutes before interv. and laminaria 1 day before intervention	4mm difference in dilatation	no significant difference found; appears only useful >19 weeks 13-15+6 46 fr vs 45 fr p=0.68 16-20+6 50.9 vs 48.9 p=0.16	Good	A2
Carbonell, JL et al 2007	prospective randomized open clinical trial	n=900 1 mif + 600 miso sublingually 2 mif + 600 miso vaginally 3 600 miso sublingually 4 600 miso vaginally subsequent D&E 12.2 to 19.9 weeks (BPD 46) in healthy women; abortion on social indication Dilapan used when	1 misoprostol vaginally 2 mifepristone	1 misoprostol sublingually 2 no mifepristone	Dilatation? Operation time Cervix priming by mifepriston e	mifepristone does have effect: dilatation with mifepristone 12. 5mm vs 8.5 without (sign); operation time 11.0 min vs 13 min (sign) route misoprostol not cervix priming: rigicity from 65% to 13% with Misoprostol: therefore less laminaria used	bias by dilapan; why no placebo introduced?	B

		cervix unripe on day of treatment						
Patel et al, 2006	retrospective descriptive	Different regimes in 19 different centres adequacy, (serious) adverse events, side effects n= 2218 12 to 23 6/7 weeks	All women second trimester, surgical abortion		rates of (serious) adverse events adequate safe patient satisfaction treatment over in 1 session	adverse events overall 19.39/100 serious adverse events overall 0.45 % (primarily blood loss>500ml) adequate 75 % patient not satisfied 2.3% one session 99.8%	Good	C

Guiding question: 2<sup>nd</sup> trimester – D&E versus medical

Reference	Type of study	Characteristic elements	Intervention	Control	Outcome indicators Follow up	Results	Quality	Evidence level
PA Lohr, 2009	systematic review	Comparing surgical and medical induced abortion RCTs induced abortion > 16 weeks	D & E	medical	2 articles	1. D&E better than intra-amniotic Prosta F2alfa 2. D&E seems better than mifepristone/ misoprostol, but n=18	Good	A2
Grossman et al 2008	Pubmed review	key words second trimester abortion mid-trimester abortion dilation and evacuation mifepristone and misoprotol (only English) RCTs, comp cohort, cohort studies and consecutive case studies > 400	safety surgical versus medical abortion		Uterus perforation or rupture bleeding requiring transfusion incomplete surgical evacuation needed cervix laesion infection other complication	1 RCT: more pain and more adverse events in the medical group 1 retrospective cohort medical generally later in pregnancy, but more adverse events in medical group especially incomplete abortions : OR adverse event surgical 0.1 5 case studies >400  Both methods show low complication rates, D&E is becoming safer		A

Guiding question: 2<sup>nd</sup> trimester - medical

Reference	Type of study	Characteristic elements	Intervention	Controle	Outcome indicators Follow up	Results	Quality	Evidenc e level
Dickinson, 2002	Double blind RCT	n=150 14-30 weeks Foetal abnormalities	I. 200 mcg Misoprostol vag. every 6 hours during 24 hours up to 48 hours max. II. 400 mcg vag. every 6 hours up to 48 hours max. III.600 mcg vag. followed by 200 mcg vag. every 6 hours up to 48 hours	See Intervention	Abortion <24 hours Nausea, vomiting, diarrhoea, pain, use of narcotics. retained placenta	Group I: time to abortion longer than in other groups (18.2 hrs vs 15.1 and 13.2 hrs, p=0.035), smaller perc abortion< 24 hrs (p=0.013) higher perc. Abortion after 48 hrs (p=0.021). No significant difference as to side-effects	?	A2
Bhattachar yya, 2006	Prospective case control	14-20 weeks, single foetus excl: previous s.c., allergy prostaglandins, serious hypertension, heart/vascular disease kidney problems, jaundice n=138	Loading dose misoprostol 600 mcg, then 200 mcg 3 hrly vaginally (max x4)	Misoprostol 400 mcg 4 hrly vaginally (max x5)	Success after 48 hrs Dosis needed Interval until abortion Adverse events	No difference after 48 hrs Less needed in loading dose group No difference in interval, except in parity>3 Less fever in loading dose group	No blinding Good size	B
M.I.Nor Azlin,2006	Prospective case control	14-26 weeks, n=54 Excl: multifoetus, allergy or contraindication to medication	Misoprostol vaginally every 12 hrs 4 x	Gemeprost 1 mg vaginally 3 hrly max 5 x	abortion within 24-48 hrs failure after 48 hrs pain relief needed costs	All differences favouring misoprostol, but all N.S. misoprostol much cheaper, which is significant	No blinding	B
J. Chai et al 2009	Open randomized two centre trial	18 years and older, n=141 12-20 weeks excl: long list	Mifepristone 200 mg and simultaneous start of Misoprostol 600 microgram vaginally, followed by 400 microgram per 3 hrs , doses max.	Mifepristone 200 mg , start misoprostol after 36-38 hrs (standard schedule)	Success rate after 24 hrs (expulsion of foetus) Induction up to abortion interval	Induction up to abortion shorter under standard: 4.9 vs 10 hrs (p<0.0001) 98.6% delivered within 12 hrs under standard, versus	Sample size based on results research in first trimester	B

			needed misoprotol schedule repeated after 24 hrs		Side effects	73.2% (p<0.0001) 24 hrs 100 vs 91.5% p=0.028 Side-effects: difference shivering and fever favours standard, otherwise not		
Oi Shan Tang et al 2005	Double blind placebo controlled	18 yrs and older N=118 12-20 weeks (gestation) excl: chronic medication; IUD, breast feeding, multifoetus, heavy smokers	200 mg mifepristone 36-48 hrs later followed by 400 microgram misoprostol sublingually and 2 tablets placebo per os every 3 hrs 5 doses max. in 24 hrs; possibly to be repeated after 24 hrs	Same except all placebo sublingually and misoprostol per os	Success rate after 24 hrs Time induction-abortion Side effects	Success rate after 24 hrs 91.4% vs 85%: thus relative risk 1.075. Induction to abortion time 5.5 hrs vs 7.5hrs p=0.0009; more fever in sublingual group p<0.0001	N=120 may measure 20% difference Conclusion that sublingual superior is not quite warranted	A?
B. Yilmaz et al 2007	Randomized prospective trial	n=81 IUD or congenital abnormality, healthy women 20-40 years, single foetus 14-24 weeks, no dilatation before and hemodynamically stable Excl: scarred uterus, blood loss, Hb<10 mg/dl, allergy and broken membranes	800 microgram Misoprostol moistened with physiological salt every 6 hrs, max. 3 times per 24 hrs; possibly repeated within 48 hrs	Again, but without physiological salt	Time induction-abortion Success rate after 24 hrs Success rate after 48 hrs Dosage of Misoprostol Retained placenta Hb-decrease Side-effects	No statistically significant differences found	N=76 can measure a difference of 18.6% Vaginosis not excluded, possibly affecting vaginal PH	B
B. Yilmaz et al 2005	Prospective, double blind randomized controlled trial	n=66 population as above	As above (B)	Again, but moistened with 3 ml acetic acid 5% (A)	Time induction till abortion Success within 48 hrs Quantity Misoprostol Retained placenta Hb-decrease	Induction-abortion time group A 8 hrs vs group B 14 hrs (p<0.001) Group A 96.7% within 24 hrs vs 78.1% in group B (p<0.001) Also less misoprostol group A (p<0.05) No	Sample size on basis of pilot, difference 30% Women with vaginitis not in study	B

					Side-effects	other statistically significant differences; all women delivered within 48 hrs		
N. Bhattacharjee et al 2008	Randomized comparative study	n=300 single foetus 13-20 wks contra-indications isoprosto: allergy, anemia, irritable colon, cardiovascular diseases, bronchial asthma	400 microgram misoprostol sublingually at intervals of 3 hrs, max 5 doses in 24 hrs (A)	Again, vaginally (B)	Complete abortion rate at 24 and 48 hrs Induction to abortion (fetus)interval Side effects Women's preference	24 hrs: A 64.03%; B 61.59%; p=0.767 48 hrs: A 79.14%; B 82.01; P=651 Interval A 14.1; b 14.5 P=0.066 (NS) Side effect NS Preference for sublingual p<0.0001	Good sample size: looking for 20% difference no blinding	B
A. Karsadig et al 2009	Open randomized clinical study	n=49 16-28 weeks incl: foetal abnormalities excl: asthma, hemorraghic complaints, allergy, heart disease, scarred uterus, IUVD, hydrops	200 microgram misoprostol sublingually every 6 hrs max. 4 doses in 24 hrs With Bishop 7 oxytocine i.v. (A)	Again vaginally (B)	Reduced blood supply through umbilical cord Vaginal delivery within 24 hrs Time till abortion	No differences in flow Within 24 hrs: A:24, B: 13 p=0.0008 Interval A 12.8h, B 22 h; p=0.0001	Sample size looking for 25% difference saturation umbilical cord Slightly cryptic	?
N. Jansen et al 2008	Prospective randomized study	n=16 single f. 16-24 weeks, cong res. or genetic res. excl: allergy to medication and scarred uterus	200 milligram mifepristone, after 48 hrs 200 microgram misoprostol vaginally every 3 hrs till expulsion (A): if no delivery after 3 days on to standard)	Dilapan, followed next day by sulproston i.v. (B, standard) after 3 days interval, then repeat	Induction till expulsion time (starting misoprostol vs sulprostone	A 17.8 hrs; B 45.1 hrs NS p=0.3	50% reduction of interval for sample size calc.	
Von Hertzen et al 2009	Multiclinic 7 countries Randomized and placebo controlled	n=680 13-20 weeks healthy women, single foe. Hb higher than 100mg/dl excl. various diseases	400 misoprostol sublingually every three hrs up to 5 doses per 24 hrs Repeated after 24 hrs	Again, vag. Repeated after 24 hrs sublingually	Success within 24 hrs complete and incomplete Again after 48 hrs Time till	After 24 hrs success higher in vaginal group After 48 hrs equal More fever vaginally Vaginally more success in nulliparae,	Sample size based on less than 10 % difference	B



					abortion Side-effects Women's opinion	not multip.		
H.Hamoda et al, 2005	Open randomization	n=69 Intact single pregn. 13-20 weeks Excl <16 jaar, serious asthma, haemorrhagia, heart disease, smoking>35 jaar and ECG absent breastfeeding, allergy	Mifepristone 200 milligram 36-48 hrs later followed by 600 microgram sublingually, followed by 400 microgram subl every 3 hrs, max. 5 doses (A)	Again, only loading dose Misoprostol 800 microgram vag.	Abortion within 15 hrs after first misoprostol Induction up to abortion interval Acceptability of the route for woman Side effects Acceptability of the route for staff	Efficacy the same, but power not good Side effects: differences small More analgesia use in sublingual group	Sample size based on difference of 2 hrs between the groups (70)	B
E. Caliskan et al, 2009	Prospective, randomized, controlled trial	n=162 15-22 weeks excl: allergy for prostaglandins, serious asthma, cervix already open 4 mm, vag, blood loss at intake, non-cooperative	100 microgram sublingually every 2 hrs Max. 12 doses (A)	200 microgram sublingually every two hrs max. 12 doses (B)	Abortion rate after 12 and 24 hrs Induction abortion time Total quantity Misoprostol needed side-effects	After 12 hrs: A 43.2% vs B: 48.1%; p=0.52 After 24 hrs: A 92,6% vs B:91.4%, p=0.77 Induction-abortion time A885 min vs B912, p=0.72 More misoprostol in group B: 1274±592 µgr vs A 614±432 µgr p=0.000	Sample size based on assumptions, as results the same due to difference smaller than 15% (144)	B

Guiding question: 2<sup>nd</sup> trimester - foeticide in 2<sup>nd</sup> trimester D&E

Reference	Type of study	Characteristic elements	Intervention	Control	Outcome indicators Follow up	Results	Quality	Evidence level
Elimian, 1999	Retrospective chart review	Single foetus pregnancies 18-24 weeks, induction by PGE2 N=68	Foeticide with KCl intracardially N=22	No foeticide N=46	Average dose PGE2 Time till expulsion foetus	Significantly less PGE2 in foeticide 2 doses vs 3 doses (p<0.00!) Time until expulsion shorter in foeticide 570 minutes vs 890 minutes p<0.006	Good	B

Guiding question: 2nd trimester - scarred uterus

Reference	Type	Characteristic elements	Intervention	Control	Outcome indicators Follow up dhrs	Results	Quality	Evidence level
V. Berghella 2009	systematic review	retrospective chartanalysis search medline, scopus, popline (medical abortion)	complications use of misoprostol in TOP (16-28 weeks) in women with sectio caesarea in anamnesis 1 s.c. n=461 1 of 2 n=507	None	Uterus rupture from 1998	1 s.c.: 0.4% (CI.008-1.67) uterus rupture	good (in view of the possibilities )	C/D
Ido Ben-Ami, 2009	retrospective cohort	TOP in 2nd trimester Single pregn.17-24 weeks excl: multiples adherent placenta no, one or more s.c. (D&E)	sectio in anamnesis 1 s.c. 59 2 or more 36	no s.c. 545	Uterus rupture	0	Numbers too small	B
Goyal V., 2009	systematic review	Risk of uterus rupture after use of misoprostol in women with s.c. in anamnesis (medical abortion) 16 articles	sectio in anamnesis n=722	no s.c. n=3,556	- uterus rupture - number needed to harm	s.c. + 0,28 s.c. - 0,04 number needed to harm: 414	Good	B?
Dickinson Jan E. 2005	retrospective cohort	TOP for foetal abnormality 14- 28 weeks, 2 equal time cohort, wit hor without s.c. in anamnesis medical TOP with misoprostol (different regimes)	n=720 of which 101 with a s.c. in anamnesis	101 vs 619	quantity misoprostol used, demographics , time until delivery, rupture or hysterectomy	No difference quantity of misoprostol; in s.c. group older and higher parity and gravidity. Pregn. up to 9 wks, time until delivery not different, no ruptures or hysterectomy in both groups	limited	C
Tarim E. et al, 2004	case reports	TOP for foetale indications, all	n=29 h/o vaginal delivery	Delieverd before and	Differences with respect	Except age and number of	limited	C/D?

		medical with 200 microgram per hr., max 6 tabl pd	n=16 nulliparae n=12 1 s.c.	how?	to complications / side effects	pregnancies no differences found		
Daskalkis et al. 2005	retrospective analysis of case records	TOP between 17 and 24 weeks, medical with misoprostol excl:cardiovascular cond., allergy/c.i. prostaglandins, multiple pregn., myectomy or other uterus surgery	108 women with s.c. in anamnesia and 216 controls (next two on the list) without s.c.	haemorrhage, postabortal infection, retained placenta,uterine rupture	Differences?	Non-significant difference found (one rupture in control group)	Limited (no hypothesis)	C
Bhattacharjee, N. 2007	prospective case control; controls matched for age, parity and pregnancy length	TOP 13-26 weeks, different indications, medical using misoprostol	n=160, 80 with s.c.	complications	differences in complications	No difference	Limited (no power, since no sample size calculation)	? B2

Guiding question: 2<sup>nd</sup> trimester - late complications

Reference	Type of study	Characteristic elements	Intervention	Control	Outcome indicators Follow up	Results	Quality	Evidence level
Jackson JE et al, 2006	retrospective chart analysis with simultaneous cohort	Wanted pregnancies; first pregnancy after D&E, no multiples or foetal abnormalities n=85 2 next pregnancies timewise of same age (2yrs) without D&E in anamnesis n=170	Past D&E 12-24 weeks	none D&E 12-24 weeks gehad	pregnancy outcome, viz. prematurity, placenta abnormality, multiple complications	Lower birthweight but NSGA at delivery lower (p=0.001) more preterm delivery (<37 weeks) but NS <34 weeks 0-1 cerclage 2-1 abnormal placenta 4-4 c.s fewer but NS haemorrhage 2-4 uterine rupture 0-1 overall 10-12 (NS)	good?	C
Winer et al, 2009	Prospective case control	Admission for late spontaneous abortion, premature delivery or prematurely ruptured membranes all before 37 weeks n=245 (1) 2 next deliveries at over 37 weeks (n=490) (2) exc: multiple pregnancies, other treatment course to effect induced abortion	induced abortion in anamnesis?	Same	odds ratio	more admissions in group 1 than group 2, but after correction for age number of pregnancies OR 1.33 (CI 0.81-2.17)	good	B
Turok et al, 2008	Retrospective cohort	major complications 1. D&E in academic hospital n=83 2. medical abortion in academic hospitals n=89 3. D&C in private outpatient clinic n= 253  Price also considered  abortion 13-24 weeks period of 5 years in hospital 1 year in private clinic	hypothesis: more complications in hospitals  a long list		odds ratio	clinic much fewer complications (and cheaper) Apples and oranges in a way	limited	C

		Indications hospital: iuvd, foetal abnormalities or maternal illness indicatiions clinic: 98% social						
Nucatola et al 2008	retrospective chart analysis	6,620 elective surgical abortions 12-16 weeks with misoprostol priming (68 months)	complications ?		complications	3 perforated uterus (0.45 per 1,000 abortion) 1 haemorrhage due to placenta accreta = complication of the pregnancy) Not different from literature		C
Lohr, 2008	Literature review (descriptive)	Modern methods D & E in second trimester	n.a.	n.a.	Safety Pros and cons Acceptability Complications	D&E is safe, efficient and cost-effective as a method to effect second trimester termination of pregnancy for women who have access	Non-systematic, expert opinion	D

Guiding question Antibiotic policy

Reference	Type	Characteristic elements	Intervention	Control	Outcome indicators	Results	Quality	Evidence level
Prager en Oyer 2009	Guideline	Unknown guideline	AB for all patients after an AAP		Duration follow up	antibiotics prescribed to all patients after surgical abortion		
Reeves 2009	RCT	N=40 women 2 groups. First group 4 hrs before D&E, Second group the night before D+E??	doxycycline D&E with two dosage schedules	The 4 hour group receive doxycycline	Reduction of nausea and vomiting after use of doxycycline in second group	Less vomiting and nausea, but results in lower serum Levels at the time of D & E. infection difference?		A2
Fjerstad 2009	Retrospective analysis	gender F. 3- ?? pregnant women		buccal Administration of misoprostol	Reduction of serious infections	The number of serious infections after medical abortion went down 93% after a shift from vaginal to buccal administration of misoprostol		B
May 2007	RCT	N=140 routine prophylaxis with antibiotics compared with no routine-prophylaxis	Routine antibiotic prophylaxis	No prophylaxis	No differences found between routine AB-prophylaxis or no AB.	There is not enough evidence to evaluate a policy of antibiotic prophylaxis for women with an incomplete abortion.??		A2
Foy 2004	RCT	N= 249 patienten	N= 249 patienten	N=255	Respecting the five most important Recommendations guidelines (primary outcomes) and costs	No effect observed for all important Recommendations		A2
Miller 2004	RCT	Self-report data	N=2,552	N=1,764	no significant differences between groups	No decrease in complications post-abortion .		A2
Wildeboer 2003	RCT	pharmaco-economic model calculations	71 patients had been treated, Suction curettage	N=800 7 ds 100mg 2dd1doxycycline	N=720 3ds 100mg 2dd1 doxy	no significant difference of infection risks?		A2
Welte 2002	Pharmaco-economic model calculations	Group of women 15-34 years old.	screening	No screening	Screening of 15-34-year old women	From a pharmaco-economic perspective		C

					would save costs, compared to no screening	a CT screening programme for sexually active women in Amsterdam is advisable.		
Crowley 2001	RCT	1 <sup>st</sup> trimester treatment abortion, group 1  group 2	N=273	N=	There was no difference in risk of transfer to hospital and the frequencies of self-reported symptoms was not different across both groups	Weak indications that metronidazol reduces the risk of infection of upper bronchia and genitals after first trimester AAP??		A2
Grimes 2001	RCT	4 studies (women from Kenia, Nigeria, US and Turkey) Effectiveness of prophylactic antibiotics Administration before implantation of IUD			IUD is safe to use, with or without the use of prophylactic antibiotics. prevalence of infection no difference ?			A2
Larsson 2000	RCT	clindamycine 2% cream or placebo	N=1,102	N= placebo	Treatment with clindamycine cream in women with a normal lactobacillus flora showed no difference compared to the non-treated group.	No difference		A2



Guiding question: abnormal ultrasound findings in establishing the diagnosis of pregnancy

Reference	Type of Study	Characteristic elements	Intervention	Control	Outcome	Results	Assessment	Evidence level
Fakih 1986	prospective	N=120	Sonography pre-operative	-	5x missed ab. 1x gemelli 1x eug	Sonography pre-op.essential for diagnosing abnormal pregn.		C
Jarallah 1985	retrospective	N=753	Abdominal sonography	-	19 x non-preg. 52x non-vital 11x multiples 27 other	Incidental findings in 27 women		C
McGalliard 2003	prospective	N=283	Sonography and pregnancy test	-	4 women Non-pregnant	259 pregn. women 3 multiples 17 missed abortion		C
Sinha 2004	retrospective	N=140	Vaginal sonography		15x missed abortion	2x gemelli 1x ectopic 1x mola 1x uterus bicornus		C

Guiding question pregnancy length: comparing ultrasound with LMP/VT findings

Reference	Type of Study	Characteristic elements	Intervention	Control	Outcome	Results	Assessment	Evidence level
Blanchard 2007	prospective	N=673 8 weeks AM	Comparing reported LMP With ultrasound		Estimate of LMP 19 days below ultrasound	Medical abortion possible without ultrasound		C
Fakih 1986	prospective	N=120 1 <sup>st</sup> trimester	Comparing reported LMP and VT With ultrasound		Between ultrasound and Vt, differences: 89% <1 week 13% 1-2 weeks 6% >2 weeks	No positive correlation Between ultrasound and LMP; good correlation between ultrasound and LMP plus VT		C
Fielding 2002	prospective multicenter	N=1,016 Pregnancy <63 days' AM	Medical abortion		Adequate overall parallel between LMP and VT versus ultrasound	VT:87% correct 9% incorrect		B
Goldstein 1988	prospective	N=250 1st trimester	Surgical abortion		4 women with LMP<12 weeks Appeared longer pregnant after Ultrasound			C
Jarallah 1985	retrospective	N=753	Abdominal ultrasound before abortion		73% knew LMP	62% equal to ultrasound, 22% Further and 16% less far		C
McGalliard 2003	prospective	N=283	1st trimester surgical 2nd trimester medical		In 90 out of 262 women No difference between LMP and ultrasound > 1week			C
Sinha 2004	retrospective	N=140	Medical abortion <63 days		Discrepancy between LMP and sonography in 19.3%			C

Guiding question: Findings after application of peri-operative and immediate post-operative sonography

Reference	Type of study	Characteristic elements	Intervention	Control	Outcome	Results	Assessment	Evidence level
Achary 2004	rct	N=230 1 <sup>st</sup> trimester	Suction curettage 115 with ultrasound 115 without		15.9% complications without, 3.7% with sonography	Post curettage in 4.7% without 0% with sonography		A2
Darney 1989	retrospective comparative	N=353 N=457 2 <sup>nd</sup> trimester	D+E with and without peri-operative ultrasound		Perforation risk 1.4% without Sonography	Perforation risk 0.2% with sonography		B
Fakih 1986	prospective	Postabortum sonography N=120	Surgical abortion with or without post-operative ultrasound		In 6 women image of incomplete abortion	Confirmation by curettage; Sonography immediately after intervention timely warning of incomplete abortion		C
Helm 1986	prospective	N=50	Surgical abortion, followed by sonography		33% uterus not empty, 7x not empty in 2 <sup>nd</sup> trimester	Peri-operative sonography good check on emptiness of uterus cavity	Large residues should not be overlooked in curettement	C

Guiding question: Ultrasonographic findings after 1st trimester surgical abortion

Reference	Type of study	Characteristic elements	Intervention	Control	Outcome	Results	Assessment	Evidence level
Bar-Hava 2001	Prospective	N=74	Ultrasound at different times after abortion		Findings not different between women with and without complaints	Cavum not empty first days after 1 <sup>st</sup> trimester treatment in 77%		B
Fakih 1986	Prospective	N=120	Ultrasound directly postabortum		6x image of incomplete abortion	Confirmed by curettage. Ultrasound directly after abortion prevents incomplete abortion		C
Haddad 1992	Prospective	N=21 1 <sup>st</sup> trimester	Ultrasound after suction curettage		After 4-6 hrs pseudo embryonic sac in 19 women	All cavities empty after 5 days		C
Helm 1986	Prospective	N=50 1 <sup>st</sup> trimester	Ultrasound directly Postabortum		In 33% cavum not empty	In 2 cases empty after all		C
McEwing 2007	Prospective comparative	N=143 1 <sup>st</sup> trimester	Ultrasound in 38 women without complaints and 105 with complaints		Poor correlation between ultrasound findings/symptoms	Poor correlation between ultrasound findings/histological findings		B
Marengo 1988	Prospective	N=144 1 <sup>st</sup> trimester	Surgical abortion and ultrasound directly postabortum		After 8-36 hrs in 60 women non-homogeneous picture	In 2 of 60 incomplete abortion. Ultrasound post-abortum of relative importance		C
Maslovitz 2004	retrospective	N=69	Ultrasound after 6-43 days		Re-curettage due to suspected retained tissue	Pathological in 59% No trophoblast tissue		C
Mikkelsen 1994	Prospective	N=117 1 <sup>st</sup> trimester	Suction curettage and ultrasound directly postabortum		Re-curettage in 5 women due to pain and blood loss	Retained tissue in 3 women		C
Stone 1974	Prospective	N=105 1 <sup>st</sup> trimester	Suction curettage within 24 hrs abd. ultrasound		Retained tissue in 6 women	Clear relation between immediate complications and placenta residue on ultrasound	Quite a few complications >30%	C
Tribalat 1987	retrospective	N=75 1 <sup>st</sup> trimester	Suction curettage		Linear endometrium in 14 cases	1x continuing pregnancy; 20x small residu; 40x pseudo-embryonic sac		C

Guiding question Ultrasoundbevindingen op verschillende tijdstippen na medical abortion

Referentie	Type of study	Characteristic elements	Intervention	Control	Outcome	Results	Assessment	Evidence level
Acharya 2004	retrospective	N=645 LMP <63 days	Vaginal Ultrasound After 2-3 weeks		15.2% sonographically non empty, 43 x curettage	Vaginal sonography only aid, clinical picture determines		C
Cowett 2004	retrospective cohort	N=437 <63 days	Monitoring endometrium thickness after 7-10 days		Average thickness 4.1+1.8 mm.	Assessing endometrium thickness no measure of treatment success		C
Edelman 2004	prospective	N=165	Vaginal ultrasound after 4 hrs after taking misoprostol		Vaginal ultrasound has added value 31x curettage	Empty cavum predicts in 95% that there is no need for curettage		C
Fiala 2003	prospective	N=167	Vaginale Ultrasound na 6-18 dagen+serum $\beta$ -HCG		Complete abortion could not be demonstrated in 10.2%	Decrease $\beta$ -HCG to 20%: successful; Decrease <80%: further evaluation needed		B
Machtin ger 2005	prospective	N=170 A.m. <49 days	Vaginal ultrasound after 10-14 days		Suspected residues in 31	4 x curettage; waiting for menstruation in 23; residue in 9		C
Markovitch 2006	prospective	N=36	Vaginal ultrasound after 6 hrs and 14 days		Re-curettage on the basis of clinical picture			C
Rorby 2004	prospective	N=871 <63 days	Serum $\beta$ -HCG after 8 and 15 days Endometrium thickness Assessment after 15 days		Monitoring endometrium thickness and determination of $\beta$ -HCG not useful	Both determinations no test for predicting late failure		C
Tsuchud in 1987	retrospective	N=225 < 49 dagen	Vaginal ultrasound after 14 days		Suspected residue in 40%	Percentage went down after longer waiting interval. Extra Misoprostol no influence.		C

Guiding question: Rhesus factor, risk of foetomaternal transfusion related to abortion expressed as percentages positive KB tests

Author	Study	Number of women	Pos. KB test pre-op. (> 0.1 ml)	Method	Pos. KB test post-op when neg KB test preop	Conclusion	Remarks	Evidence level
Jorgensen 1969	Case series N=227	47 85 15 80	0 0 0 0	Spontaneous Suction curettage Curettage Otherwise	0 (0%) 1 (1.2%) 1 (6.7%) 7 (8.6%)	No FMT after spontaneous abortion; after suction curettage in 1.2% and after other methods 8.6%		B
Leong c.s. 1979	Case series N=75	75	2	Suction curettage	10 (13.7%)	No FMT before 6 weeks a.m.		B
Murray c.s. 1970	Case series N=483	91 243 73 76	21 39 11 7	Spontaneous Suction curettage Saline Otherwise	1 (1.4%) 0 (0%) 1 (1,6%) 0 (0%)	No difference in frequency of FMT between spontaneous and induced abortion	Suction curettage up to 14 weeks' amenorrhoea	B
Queenan c.s. 1971	Case series N=606	404 202	0 0	Suction curettage Saline	7.2% 20.2%	Frequency FMT rises with pregnancy length	Suction curettage up to 16 weeks' amenorrhoea	B
Borst-Eilers 1972	Case series N=72	12 50 8 2	Not determined 0 0 0	Suction curettage Curettage Sectio parva	Group undefined ; Total of 2 (3.3%)	In 2 cases FMT more than 0.1 ml but less than 0.16 ml		

Guiding question: Rhesus factor - Risk of rhesus isosensitization due to abortion, related to method, amenorrhoea and prophylaxis

Author	Study	Neg KB test Pre-op	Pos KB test Post-op	Prophylaxis	Isosensitization, number of cases	Amenorrhoea	Method and numbers	Remarks	Evidence level
Jorgensen 1969	Case series N=30	30	1	None	3 (10%)	10 14 15	Suction curettage (1) Curettage (1) Curettage (1)		B
Murray c.s. 1970	Case series N=23	23	0	None	3	10 12 18	Suction curettage (1) Suction curettage (1) Hysterotomie (1)		B
Murray c.s. 1971	Case-control N=96	96	0	None	9	Incomplete data	Suction curettage (5) Saline (3) Hysterotomie (1)		B
Murray c.s. 1972	Case series N=177	44 40 12	7 of the 96 tested	None	2	7 and 10	< 12 weeks >12 weeks unknown	Both sensitizations had negative KB test post-op.	C
Queenan c.s. 1971	Case series N=43	25 18	0 0	None Anti-d	1 0	7	Suction curettage (1)	Prophylaxis after 6 weeks am	B
Visscher c.s. 1972	RTC N=57	29 19 9	29 19 9	None 300 ug anti-d None	0 0 0		Spontaneous Spontaneous Spontaneous	No immunoprophylaxis in the case of spontaneous abortion < 12 weeks	A2
Goldman c.s.	Controlled	122 48		None 200 ug anti-d	2 0	1 <sup>st</sup> trim. 2 <sup>nd</sup> trim.	Spontaneous (1)	FMT bigger in surgical	B

1972	clinical trial N=170					1 <sup>st</sup> trim. 2 <sup>st</sup> trim.	Spontaneous (1) Surgical(1) Surgical (2)	than spontaneous abortion. Risk increases with gestation length	
Keith c.s 1977	Controlled clinical Trial N=315	17 298		300 ug anti 50 ug anti	0 0	1 <sup>st</sup> trim. 1 <sup>st</sup> trim.		50 ug anti-d is sufficient in 1 <sup>st</sup> trim.	B
Bennebroek Gravenhorst c.s 1986	Case series N=103		FMT 1-3.5 ml In 6-8%			2 <sup>nd</sup> trim.		75 ug anti-d is sufficient in 2 <sup>nd</sup> trim.	C
Hensleigh c.s 1997	RCT N=187		FMT in 27%		0 (of N=134 control group)	5-14 weeks		Group with 73 ug anti-d too small for statistical analysis	A2