Maarit Niinimäki

MEDICAL COMPARED WITH SURGICAL MANAGEMENT IN INDUCED ABORTIONS AND MISCARRIAGES
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**Abstract**

Each year approximately 11,000 induced abortions are performed in Finland, the majority of these women being younger than 25 years of age. Medical abortion with the antiprogestin mifepristone and the prostaglandin analogue misoprostol is increasingly being used instead of surgical method (dilatation of cervix and uterine evacuation with instruments). Similarly, miscarriages can be treated with medical or surgical management. Still, clinical outcomes of the medical treatment of miscarriage are not well established, and various different regimens exist.

The aim of this study was to investigate the frequency and risk factors of repeat abortions and immediate post-abortal complications, focusing especially on the impact of the method of abortion. National health registries were used as a data source. Another part of the study was aimed at comparing the efficacy, acceptability and cost-effectiveness of the medical and surgical treatment of miscarriage.

In national cohort, the risk of repeat abortion was associated with sociodemographic characteristics (parity, previous abortion, low socioeconomic status, being unmarried but cohabiting or single), but not with the method of abortion. The risk of repeat termination of pregnancy decreased with age, among women living in rural area, and when intrauterine devices or sterilization were planned for future contraception.

The overall incidence of adverse events was 4-fold greater in the medical compared to the surgical abortion cohort. Hemorrhage and incomplete abortion were more common following medical abortion, but the incidence of infections did not differ.

Medical and surgical treatment of miscarriage were compared in a randomized setting; the efficacy of the treatment did not differ. Medically treated patients were less satisfied with the treatment and had experienced more pain.

In the cost analysis, the primary costs of the surgical treatment were higher, but more unexpected events and complications increased the secondary costs in the medical group.

In summary, medical abortion offered a good alternative to surgical method without increasing the risk of repeat abortions, but with an increased risk of short-term adverse events. The medical method was efficient in treating miscarriages, and the majority of women were satisfied with the treatment. Neither of the methods was economically superior in treating miscarriage.

*Keywords:* cost-effectiveness analysis, curettage, medical abortion, mifepristone, miscarriage, misoprostol, patient satisfaction
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Abbreviations

ACOG American College of Obstetricians and Gynecologists
CEA cost-effectiveness analysis
CDC Centers for Disease Control and Prevention
CI confidence interval
COC combined oral contraceptives
CRL crown-rump length
CRP C-reactive protein
Cu-IUD copper-releasing intrauterine device
D&C dilation and curettage
FDA Food and Drug Administration
hCG human chorionic gonadotropin
HR hazard ratio
ICD-10 International Classification of Diseases
ICER incremental cost-effectiveness ratio
LNG-IUS levonorgestrel-releasing intrauterine system
NA not applicable
NS non significant
OR odds ratio
O&G obstetrics and gynecology
PG prostaglandin
RCOG Royal College of Obstetricians and Gynaecologists
RCGP Royal College of General Practitioners
RCT randomized controlled trial
SD standard deviation
TVS transvaginal scan
WHO World Health Organization
List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:


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1 Introduction

Termination of pregnancy is one of the most common gynecological procedures. Even if the overall rate of induced abortions in Finland is low, this procedure is annually performed on approximately 11,000 women. Furthermore, most women seeking abortion are younger than 25 years of age (National Institute for Health and Welfare 2009), and thus at the beginning of their reproductive life span. Minimizing the risks of serious complications for predominately young and healthy women who choose to terminate their pregnancies is of clear public health importance (Bartlett et al. 2004).

Although surgical abortion is a safe procedure in experienced hands and proper facilities, safe surgical abortion cannot necessarily be offered in developing countries. Optimally, women should be provided with a choice of methods (Honkanen et al. 2004). Based on these needs, development of a pharmacological method for termination of pregnancy has been an important achievement in gynecology.

The studies focusing on termination of pregnancy are valuable not only to evaluate the safety of the procedures, but also to find strategies aimed at decreasing the number of unwanted pregnancies. This may be achieved with focused contraceptive counseling and by defining the risk groups for repeat induced abortions. Once the woman had made her decision, unimpeded access to induced abortion efficiently prevents illegal abortions.

In Finland, medical abortion was approved for general use in 2000 and within a few years it became the dominant method over surgical abortion (National Institute for Health and Welfare 2009). Medical abortion is easily adopted (Suhonen et al. 2003), and with increasing experience more flexible regimens, including home administration of misoprostol, have become available in many hospitals.

It has been estimated that one in six pregnancies ends in miscarriage (Hemminki & Forssas 1999). Still, the available evidence on its medical treatment is limited and opinions as to proper management of spontaneous miscarriage differ widely (Ankum et al. 2001). Defining the optimal treatment is challenging, as the results of the studies are confused with various regimens, various types of miscarriages and diverse ways of defining clinical outcomes.

This study was conducted to investigate the impact of the medical method in two common gynecological entities: induced abortions and miscarriages. The
medical method was compared with the traditionally used surgical method emphasizing different aspects: safety, efficacy and the experiences of the women undergoing one of these managements. Both a clinical and epidemiological approach was used. As the economical aspect is increasingly affecting the choices in health care, the study was complemented with cost-analysis.
2 Review of the literature

2.1 The role of abortion in family planning

2.1.1 The trends in pregnancy termination worldwide

The number of induced abortions is an indicator of the incidence of unintended pregnancies, and thus reflects access to professional family planning and the availability of reliable methods of contraception. Still, the availability of modern contraception can reduce, but never eliminate the need for abortion (Grimes et al. 2006). Unintended pregnancies do not only concern developing countries. For instance in the United States, nearly half of all pregnancies are unintended (Finer & Henshaw 2006), and 22% of all pregnancies (excluding miscarriages) end in the termination of pregnancy (Jones et al. 2008).

The worldwide incidence of safe abortions was estimated by using official national reporting systems, nationally representative surveys, and published studies in 2003. The estimated number of abortions in 2003 was 42 million, compared with 46 million in 1995. The abortion rate was decreasing in both developed (39 vs. 26 per 1,000 women aged 15–44) and developing (34 vs. 29 per 1,000 women aged 15–44) countries between 1995 and 2003. The highest abortion ratio was seen in Eastern Europe (105 for every 100 live births) (Sedgh et al. 2007).

2.1.2 Unsafe abortions

Unsafe abortions are defined by WHO (World Health Organization) as abortions performed by people lacking the necessary skills or in an environment that does not fulfill minimal medical standards, or both. These include abortions in countries where the law is restrictive and abortions that do not meet legal requirements in the countries where the law is not restrictive (WHO 2009a). The latest worldwide report in 2003 indicated that half of all induced abortions (about 20 million) were unsafe. Of these unsafe abortions 97% were performed in developing countries (Sedgh et al. 2007). Abortions performed by unskilled providers and/or in insufficient medical circumstances are a serious threat to women’s life and health. Worldwide, an estimated 5 million women are
hospitalized every year for treatment of complications related to unsafe abortions
(Singh 2006). Moreover, 68,000 women are estimated to die annually from unsafe
abortions, and millions more are injured, many of them permanently (WHO 2004).
The main causes of death are hemorrhage, infection and poisoning. The strategies
for primary prevention of morbidity and mortality related to unsafe abortions
include reduction in the need for unsafe abortion through contraception,
legalization of abortion on request, the use of safer techniques (e.g. vacuum
aspiration or medical methods) and improvement of provider skills (Grimes et al.
2006).

2.1.3 Termination of pregnancy in Northern Europe

In Europe (with the exception of Eastern Europe), the overall abortion rates are
low (12–17 per 1,000 women aged 15–44). Abortion is legally available, although
unsafe abortions may occasionally occur due to poor information or access to safe
medical services (Sedgh et al. 2007). Among the Nordic countries (Denmark,
Finland, Iceland, Norway, Sweden) Finland has the lowest abortion rates (in 2007
9.0 per 1000 women aged 15–49) (National Institute for Health and Welfare
2007a) (Fig. 1).

It is generally believed that abortions are not performed outside the public
health care system in Finland. According to the current Act on Induced Abortions
in Finland, women need permission with a legal indication for termination of
pregnancy, but the legislation is interpreted liberally. The legislation on access to
induced abortion in the Nordic countries is shown in Table 1 (National Institute
collects the annual numbers of abortions and other abortion-associated trends in
the Registry of Induced Abortions (National Institute for Health and Welfare
2007b).

<table>
<thead>
<tr>
<th>Country</th>
<th>Access to induced abortion in the first and second trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>On request up to 12th week &gt;12 weeks, with the permission of regional authority</td>
</tr>
<tr>
<td>Finland</td>
<td>With the permission of one/two physicians up to 12th week &gt;12 weeks, with the permission of national authority</td>
</tr>
<tr>
<td>Iceland</td>
<td>With the permission of one/two physicians up to 12th week &gt;12 weeks, with the permission of national authority</td>
</tr>
<tr>
<td>Norway</td>
<td>On request up to 12th week &gt;12 weeks, with the permission of regional authority</td>
</tr>
<tr>
<td>Sweden</td>
<td>On request up to 18th week &gt;18 weeks, with the permission of national authority</td>
</tr>
</tbody>
</table>


The current legislation in Finland dates from 1970 and 1985. According to the current Act on Induced Abortions, termination of pregnancy can be allowed up to 20 weeks of gestation for social, medical or ethical reasons (24 weeks in cases of a medical condition of the fetus). Social reasons include considerable strain on...
living or other conditions, age below 17 or above 40 years at conception, or four previous deliveries (Finlex 2009).

The most common indication for termination of pregnancy in Finland is a social reason; in 2007 90.7% of abortions were performed for this indication. The number of induced abortions has been stable since 2000; the range has varied between 10,230 and 11,165 (National Institute for Health and Welfare 2009). Since the year 2002, the largest age-group with induced abortions has been women aged 20–24 years (18 by age group per 1,000 women of the same age) (National Institute for Health and Welfare 2007b) (Fig. 2).

![Fig. 2. Induced abortions by age, per thousand women of the same age, 2000–2007 (*in 2008 preliminary data) (National Institute for Health and Welfare 2009).](image)

In a national program of sexual and reproductive health, the Ministry of Social Affair and Health has set a goal to reduce abortions among women under 25 years of age to the same level as in the mid-1990s, and to reduce repeat abortions by the year 2011 (Ministry of Social Affair and Health 2007).
2.2 Methods in termination of pregnancy

2.2.1 Surgical methods

The surgical methods of abortion include vacuum aspiration (also called vacuum curettage or uterine aspiration) and sharp curettage (dilation and curettage, D&C). Vacuum aspiration is safer and less painful than D&C, and in many countries the most widely used method for terminating pregnancy in the first trimester (Wen et al. 2008). The high efficacy of vacuum aspiration, with complete abortion rates between 95 and 100%, has been well reported in several trials (Hakim-Elahi et al. 1990, Wen et al. 2008). According to Finnish guidelines, surgical method is predominantly used when the duration of gestation is between 7 and 12 menstrual weeks (Finnish Gynecological Association's task force 2001).

In Finland, surgical termination of pregnancy is mostly performed in general anesthesia (Finnish Gynecological Association's task force 2001). Paracervical block with 10–20 ml 1% lidocain, widely used in the United States, (Stubblefield et al. 2004) and conscious sedation (e.g. with fentanyl and benzodiazepins) (Lichtenberg et al. 2001) are alternative methods of analgesia. In paracervical block pain relief is not necessarily sufficient; in a large study, 34% of patients undergoing first-trimester vacuum curettage under paracervical block reported pain to be “severe” or “very severe” (Smith et al. 1979). In paracervical block pain relief is more beneficial if a higher volume of local anesthesia is used (Allen et al. 2006). Recommendations by the Royal College of Obstetricians and Gynaecologists (RCOG) considers suction termination to be safer under local anesthesia than under general anesthesia. According to the RCOG guidelines, if conscious sedation is used in stead of general anesthesia to reduce pain and anxiety, it should only be undertaken by trained practitioners (RCOG 2004). Cervical dilation is accomplished with conventional tapered dilators, hygroscopic dilators, or medication (e.g. misoprostol or gemeprost) (Stubblefield et al. 2004).

Induced abortion with a surgical method is a relatively safe operation carrying a low rate of major morbidity (RCGP/RCOG 1985). The overall incidence of major complications in surgical abortion is less than 3% (Goldberg et al. 2004), increasing with advanced duration of gestation; the lowest major complication rate occurs at 7–8 menstrual weeks (0.3 per 100 abortions) (Grimes & Cates 1979). Excessive bleeding is the most frequent immediate complication. For first trimester abortions, anesthesia is an important determinant of blood loss.
Local anesthesia has been associated with a lower rate of blood loss than general anesthesia (Hakim-Elahi et al. 1990).

2.2.2 Medical methods

The regimen of mifepristone followed by a suitable prostaglandin analogue (usually misoprostol) has become increasingly available and is now the gold standard for pharmacologically induced first-trimester abortion. Where mifepristone is not accessible, various misoprostol regimens are being used (Faundes et al. 2007). Before mifepristone was approved for termination of pregnancy in the United States, the combination of methotrexate and misoprostol was used, though approximately only 0.7% of abortions were performed with this protocol (Creinin et al. 2003).

In different surveys, the following main reasons were given as to why women choose medical termination of pregnancy: 1) avoiding general anesthesia, 2) perceived to be safer, 3) perceived to be more natural, 4) more privacy and autonomy, 5) less invasive (Henshaw et al. 1993, Winikoff et al. 1997, Honkanen & von Hertzen 2002). Some typical characteristics of the medical and surgical methods of induced abortions are shown in Table 2.

Table 2. Comparison of the methods of induced abortion in the first trimester (< 84 days of gestation) modified from National Guidelines of Induced Abortions 2007 by the Finnish Gynecological Association (Finnish Gynecological Association’s task force 2001).

<table>
<thead>
<tr>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>In all durations of gestation (mostly &lt;63 days)</td>
<td>Duration of gestation 49 - 84 days</td>
</tr>
<tr>
<td>Outpatient / Home</td>
<td>Outpatient / Day-surgery</td>
</tr>
<tr>
<td>No anesthesia</td>
<td>General anesthesia</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>Invasive</td>
</tr>
<tr>
<td>Bleeding up to 14-28 days</td>
<td>Scant bleeding</td>
</tr>
<tr>
<td>Surgical evacuation in 5% for incomplete abortion</td>
<td>Re-evacuation in 3% for incomplete abortion</td>
</tr>
<tr>
<td>Sick-leave 1-3 days</td>
<td>Sick-leave 1-3 days</td>
</tr>
<tr>
<td>Hormonal contraception can be initiated immediately, intrauterine device after the first menstruation</td>
<td>Hormonal contraception can be initiated immediately, intrauterine device during the procedure</td>
</tr>
</tbody>
</table>
Mifepristone (RU486) is a synthetic 19-norsteroid with progesterone and glucocorticoid antagonist properties. To the human progesterone receptor, mifepristone has an affinity more than twice as great as progesterone (Heikinheimo et al. 1987). Without activating the receptor mifepristone effectively inhibits the corresponding agonist (e.g. progesterone or cortisol) from receptor binding. The agonist is then eliminated from the target cells or metabolized in situ. Mifepristone has a prolonged half-life of about 20 hours (Mahajan & London 1997).

Mifepristone also has high affinity in glucocorticoid receptors (Heikinheimo 1997). The antiglucocorticoid effect is mediated at central level, resulting in inhibition of the feedback control of cortisol on the pituitary-adrenal axis (Bertagna et al. 1984). Peripheral antiglucocorticoid effects are seen in inhibition of cutaneous cortisol-induced vasoconstriction (Gaillard et al. 1985).

There are several mechanisms how mifepristone administration leads to termination of pregnancy (Fig. 4). In the uterus, mifepristone is associated with extracellular matrix degradation which results in bleeding (Papp et al. 2000). Mifepristone has a direct effect on the decidua by initiating synthesis of prostaglandin F2α, which seems to have a luteolytic effect in humans (Somell et al. 1990). It also induces cervical ripening and cervical dilation with a linear dose-response relation between 50–600 mg mifepristone (Lefebvre et al. 1990). Impaired synthesis of placental hormones and proteins (human chorionic gonadotropin, human placental lactogen, progesterone and pregnancy-associated
plasma protein-A) have been shown in cell cultures of first and third trimester placentas. *In vivo* decline in circulating levels of these hormones might increase the abortifacient properties of mifepristone (Bischof *et al.* 1986, Das & Catt 1987).

Throughout the pregnancy, the uterus is inactive, most likely due to the inhibitory effect of progesterone on myometrial contractility (Csapo *et al.* 1973). Thus antagonism of progesterone action by mifepristone increases uterine contractility. It has been suggested that the increased uterine activity observed after mifepristone administration may be due to stimulation of endogenous prostaglandin (PG) production and inhibition of PG metabolism (Swahn & Bygdeman 1988, Norman *et al.* 1991a, Norman *et al.* 1991b). Mifepristone sensitizes the myometrium to the contraction-inducing activity of prostaglandins (Swahn & Bygdeman 1988), both endogenous and exogenous ones, such as misoprostol. Human studies performed in women with induced abortions have suggested that uterine contractility increases only after 24–36 hours of mifepristone administration (Swahn & Bygdeman 1988). A summary of the mechanisms mifepristone has in termination of pregnancy is shown in Fig. 4.

![Mechanisms of mifepristone-induced termination of pregnancy](image)

**Fig. 4. The mechanisms how mifepristone induces to termination of pregnancy.**

The four officially approved indications for mifepristone are: I early termination of pregnancy up to 63 days gestation with prostaglandins, II in combination with PGs for termination of pregnancy beyond the first trimester, III softening and dilation of the cervix prior to mechanical cervical dilation for pregnancy termination in the first trimester, IV labor induction in fetal death *in utero* during
the third trimester of the pregnancy (Sitruk-Ware & Spitz 2003). Besides the medical abortion, cervical ripening caused by mifepristone (mostly with prostaglandins) may also help in the management of other clinical situations such as preparation of labor induction at term or post term (Stenlund et al. 1999, Wing et al. 2000), and in cases of intrauterine fetal death in the first or second trimester of the pregnancy (Wagaarachchi et al. 2002a, Vayrynen et al. 2007). There are many other potential indications, for instance postcoital contraception (Webb et al. 1992, Ashok et al. 2002b), treatment of endometriosis (Jiang et al. 2002), leiomyomas (Fiscella et al. 2006, Engman et al. 2009) or breast cancer (Poole et al. 2006).

Misoprostol

![Fig. 5. 2D skeletal formula of misoprostol.](image)

Misoprostol (Fig. 5), a synthetic analogue of prostaglandin E₁ (PGE₁), is officially licensed to be used for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs. Misoprostol in not registered for use during pregnancy, but in most countries physicians may use licensed medications outside the recommendations given in the license with appropriate informed patient consent. The main applications have been for termination of pregnancy and the induction of labor (Bygdeman 2003).

Misoprostol is available as a tablet stable in room temperature and is significantly cheaper than PGE₂ and other analogues (Bygdeman 2003).

The pharmacokinetics of misoprostol is dependent on the route of administration. Pharmacokinetic evaluation of oral and vaginal administration of misoprostol has demonstrated that misoprostol is absorbed more rapidly following oral intake, resulting in a higher peak serum level (Danielsson et al. 1999, Zieman et al. 1997). However, vaginal administration results in greater uterine contractility, and the intensity of contractility continues to increase for at
least 4 hours (Danielsson et al. 1999). It has been suggested that adding water to the tablets before vaginal administration would increase the absorption of misoprostol. However, no confirmation for this suggestion has been found in pharmacokinetic or clinical studies (Ngai et al. 2000, Tang et al. 2002).

Sublingual route (holding pills under the tongue) leads to uterine contractions that are initially stronger than after vaginal administration, but the contractions start diminishing 2–3 hours after administration (Aronsson et al. 2004). According to a recent randomized controlled trial (RCT) buccal (holding pills in the cheek) administration of 0.8 mg misoprostol seems to be a good option in early termination of pregnancy (duration of gestation less than 63 days); the success rate was even higher (96.2%) than with the oral route (91.3%, p = 0.003), and the success rate remained unaffected in advanced duration of gestation (unlike in oral administration) (Winikoff et al. 2008).

Contraindications and side effects of medical abortion

There are few absolute contraindications to medical abortion. These are suspected ectopic pregnancy, chronic adrenal failure, severe asthma uncontrolled by therapy, inherited porphyrias, and allergy to mifepristone or any component of the product (Davey 2006). Some other circumstances that are not absolute contraindications require special attention: long-term corticosteroid therapy, hemorrhagic disorder, use of liver-enzyme-inducing drugs (such as many antiepileptic drugs), severe anemia or pre-existing heart disease or cardiovascular risk factors. Age alone is not a contraindication for medical abortion; it can safely be provided to adolescents or women over 35 years of age (von Hertzen et al. 2006).

Mifepristone is well-tolerated and only minor side-effects, such as mild uterine pain, nausea and vomiting, have been described (Kovacs et al. 1984). The side effects of medical abortion can theoretically be classified into three categories: pregnancy-related symptoms (nausea, vomiting, breast tenderness, fatigue, dizziness, headache), drug-related side-effects (diarrhea, fever, rash and change in blood pressure) and side effects related to the abortion process (lower abdominal pain) (Honkanen et al. 2004). All these side effects normally resolve within a few days (Gemzell-Danielsson et al. 2007).
2.3 Introduction of the medical method into clinical practice

2.3.1 Medical abortion worldwide

Prostaglandins were known to terminate early pregnancy already by the 1960s. Wider use of prostaglandins was prevented by the side effects (nausea, vomiting, diarrhea, fever and severe pain). As the role of progesterone in maintaining pregnancy was revealed by showing that removal of the corpus luteum in early pregnancy resulted in termination of pregnancy (Csapo et al. 1972, Csapo et al. 1973), further studies to find antiprogestin for clinical use were initiated. Mifepristone (initially called RU-486), the first antiprogestin used in practice, was described at the beginning of the 1980s in France by Roussel-Uclaf (Herrman et al. 1982).

The abortifacient potential of mifepristone was shown in several studies, but the maximal effectiveness was below 80% in several studies (Kovacs et al. 1984, Couzinet et al. 1986, Birgerson & Odlind 1987). The invention of mifepristone and its capability to increase the sensitivity of the pregnant uterus to prostaglandins (Bygdeman & Swahn 1985) led to extensive studies to find a feasible prostaglandin to be used in combination with it. The combination of mifepristone with prostaglandin was proven to be more efficient than monotherapy with mifepristone in termination of pregnancy (Bygdeman & Swahn 1985, Cameron & Baird 1988, Swahn & Bygdeman 1988). In 1988 a combination of mifepristone and prostaglandin E1 analogues was licensed in France to be used in medical abortion. The E-series prostaglandins, principally gemeprost and misoprostol, have mostly been used because they stimulate uterine smooth muscle more than gut or vascular muscle, which are stimulated more by the F-series prostaglandins (Meckstroth & Darney 2003).

Medical abortion was approved in the United Kingdom in 1991 and in Sweden in 1992 in pregnancies up to 63 days (Fiala & Gemzel-Danielsson 2006). In the United States the Food and Drug Administration (FDA) approved mifepristone to be used together with a prostaglandin for terminating pregnancies up to 49 days in 2000. In most European countries mifepristone has been approved since the year 2002 (Jones & Henshaw 2002).

Deviating from the original officially proved FDA regimen, the commonly used dosage of mifepristone is 200 mg (instead of 600 mg) and that of misoprostol 0.4–0.8 mg vaginally (instead of 0.4 mg perorally). The interval
between administration of mifepristone and misoprostol has also been decreased to 6–24 hours (instead of 36–48 hours). Additionally, the regimen is generally used up to 63 days instead of 49 days of gestation (Creinin et al. 2006a).

WHO’s reproductive health strategy, approved by the World Health Assembly in 2004, identified elimination of unsafe abortions as one of five priorities, which will also help to achieve the Millennium Development Goal for reduction in maternal mortality. In the year 2006, WHO included the combination of mifepristone and misoprostol in the list of Essential Medicines (WHO 2009b).

2.3.2 Medical abortion in Finland

In Finland, medical abortion by using a combination of mifepristone and misoprostol was officially accepted for clinical use in termination of pregnancy with duration of gestation up to 63 days in the year 2000. The first national guideline was published in 2001 recommending the regimen of mifepristone perorally and misoprostol sublinguinally or vaginally 2 days later, and the guidelines were later updated to be more flexible (Finnish Gynecological Association's task force 2001). The method was rapidly adopted in the whole country. In the year 2007, 64% of all abortions were performed using medical method (National Institute for Health and Welfare 2007b). At the same time, in Sweden 61% (Socialstyrelsen 2009) and in the UK 35% (Department of Health 2009) of all abortions were performed using the medical termination of pregnancy. While the medical regimen has become the predominant method in Finland, the annual rates of induced abortions have remained stable between 8.9–9.4 per 1,000 women aged 15–49 (National Institute for Health and Welfare 2007b). The fast uptake of the medical abortion in Finland reflects the flexible medical system, which offered women a free choice soon after the method was introduced. Training of health care providers (e.g. doctors, midwives, nurses) has been shown to be crucial for this fast uptake (Fiala & Gemzel-Danielsson 2006).
2.4 Clinical outcomes in medical termination of pregnancy

2.4.1 Efficacy

The efficacy of medical abortion is usually defined as the termination of pregnancy with complete expulsion of the conceptus without the need for surgical procedure (Spitz et al. 1998). The highest rates of complete medical abortion, reported from centers with extensive experience on medical abortion, are up to 98% (Ashok et al. 1998, Ashok et al. 2002c).

Several studies suggest the success rate of medical abortion to be dependent on the duration of gestation (Spitz et al. 1998, Allen et al. 2001, Rorbye et al. 2003). With the regimen of mifepristone 400 mg and misoprostol 0.4 mg orally, pregnancy was terminated in 92% with duration of gestation ≤ 49 days, in 83% with duration of gestation 50–56 days, and in 77% with duration of gestation 57–63 days (Spitz et al. 1998). Other studies using mifepristone and misoprostol given vaginally have not shown a significant decrease in effectiveness up to 63 days of gestation (el-Refaey et al. 1995, Ashok et al. 1998). The high efficacy of the medical method in advanced duration of gestation in 63–84 days and in the second trimester has been shown (Ashok et al. 2002a, Hamoda et al. 2005). Some researchers even claim that ultrasound examination is not necessary prior to medical termination of pregnancy to define the duration of gestation, as the method is efficient in both the first and second trimester (Fielding et al. 2002). To identify ectopic or postabortal ongoing pregnancies the monitoring of hCG (chorionic gonadotropin) levels was proposed (Fielding et al. 2002). When compared with ultrasound examination, serum hCG measurement is more effective in the follow-up to confirm successful medical abortion (Fiala et al. 2003).

In some studies parous women have had lower complete abortion rates after medical abortion compared with nulliparous women (Bartley et al. 2000, Ashok et al. 2002c), even with a correlation between the increasing number of deliveries and incomplete abortion (Child et al. 2001). Previous induced abortions have also been associated with lower complete medical abortion rates (Allen et al. 2001, Ashok et al. 2002c).

Several studies have proved the efficacy and the safety of mifepristone to be equal at doses of 200 mg and 600 mg in the termination of pregnancy (WHO Task Force 2000, Kulier et al. 2004). According to a meta-analysis, mifepristone alone...
is less effective than the combined regimen of mifepristone and prostaglandin. In that meta-analysis, four studies out of five indicated that a combined regimen is more effective than prostaglandin alone (Kulier et al. 2004). Earlier studies suggest that vaginal administration of misoprostol following mifepristone abortions would be more effective than oral administration of the same dose (el-Refaey et al. 1995, Ho et al. 1997), and may be associated with less side effects (Kulier et al. 2004).

The use of medical abortion can be rapidly adapted by physicians (Suhonen et al. 2003). Thus, the experience of the physicians performing medical abortion may be an important factor in determining the success of the procedure, as reflected by the rate of surgical intervention (Vitner et al. 2009). In the hazard analyses in which demographic factors were adjusted, significant differences persisted across study sites, indicating the difference in providers’ tendency to perform surgical (re-)evacuation (Hedley et al. 2004).

2.4.2 Acceptability

When choosing the method of termination of pregnancy, being given a choice is perceived as extremely important by the majority of women (Slade et al. 1998). Previous studies have also shown that women are more likely to find a method acceptable if they have chosen it themselves (Henshaw et al. 1993, Slade et al. 1998). Medical abortion has been found to be highly acceptable (80–90%) by women (Schaff et al. 2000, Honkanen et al. 2004). The majority of women undergoing medical abortion would choose the same method in the future (89%) and would recommend the medical method for a friend (88%) (Honkanen & von Hertzen 2002).

In a comparative study conducted in the United States, women undergoing medical abortion reported significantly greater satisfaction than women undergoing surgical abortion (Jensen et al. 2000). A Danish partially randomized study (volunteers were randomized, and the rest of the women made their own decision of the method of abortion) did, however, find the medical method to be more painful, and satisfaction with care to be inversely correlated with the intensity of pain and other side effects (nausea, vomiting and dizziness) (Rorbye et al. 2005). A multicenter study analyzing the predictors of narcotic analgesic use during medical abortion indicated that the need for narcotic analgesics correlated directly with gestational age. The relative risk of using narcotic analgesics
decreased among women with previous births and older age (Westhoff et al. 2000).

2.4.3 Immediate complications

The most frequently reported adverse events associated with medical abortion are bleeding and infections (Gary & Harrison 2006). Mifepristone-related severe adverse event reports to FDA were analyzed over a 4-year span. Overall, of the 637 adverse events reported, 39% were bleeding and 11% infectious complications. The third most common class of adverse events was undiagnosed ectopic pregnancy (Gary & Harrison 2006). In earlier studies an average of 10% of the patients with medical abortion complained of excessive bleeding (Sitruk-Ware 2006), but a large trial showed curettage for excessive bleeding to be relatively rare (0.5–1.0%) (Ulmann et al. 1992).

Because medical abortion is a noninvasive procedure, there is an expectation that infection after medical abortion could be less frequent than after surgical abortion (Shannon et al. 2004). Still, the risk is present due to the retained products of conception. In a prospective study performed in Scotland, women who chose surgical abortion were more likely to receive antibiotics for suspected endometritis than those who chose medical abortion (9.6% vs. 1.2%; p = 0.0001) (Cameron et al. 1996). A systematic review of the infections diagnosed or treated after medical abortion found the incidence to be low, 0.92%. The frequency of infections varied among regimens: the frequency of infection after treatment with mifepristone and vaginal misoprostol was 1.3%, and after mifepristone and oral misoprostol 0.2%. Regional differences in the reported frequency of infections, however, may indicate that the diagnosis and treatment of infection depends heavily on medical practice and physician behavior (Shannon et al. 2004).

Most studies focusing on the short-term complications of induced abortion have been small or have not compared the two dominant methods of abortion (medical or surgical). In a large register-based study, 5% of the subjects had a complication (bleeding, infection or re-evacuation) following surgical abortion during a short-term follow-up of two weeks (Zhou et al. 2002). In a previous meta-analysis comparing medical and surgical termination of pregnancy in the first trimester, no difference in pelvic infection or ongoing pregnancies was noted between the methods. Evidence for a different rate of other potential side effects
or complications between the two abortion techniques could not be confirmed as the trials included were small (Say et al. 2005).

Only few RCTs have been performed to compare the success rate and complications between medical vs. surgical abortion (Henshaw et al. 1994, Ashok et al. 2002a, Rorbye et al. 2004). In a previous partly randomized study no difference in the number of complications was observed (Rorbye et al. 2004). However, the rate of complete abortion was significantly higher in the surgical group (98% vs. 94%), but the surgically treated patients also had a higher incidence of antibiotic treatment than the patients undergoing medical abortion (Rorbye et al. 2004). In another RCT, the abortion was complete in 98% following surgical and in 95% following medical abortion. Moreover, no differences in the rates of major complications were observed (Ashok et al. 2002a).

The rate of ongoing pregnancies has been reported to be less than 1% (Hausknecht 2003, Suhonen et al. 2003) following medical abortion. However, the incidence of ongoing pregnancies was higher when vaginal gemeprost was used instead of vaginal misoprostol (Bartley et al. 2001).

A few cases of fatal toxic shock syndromes associated with medical abortion have been reported in North America. The cause of infection in these cases has been Clostridium sordellii, a gram-positive anaerobic bacillus. These patients had a rapidly progressive illness with necrotizing endomyometritis (Cohen et al. 2007). However, fatal septic shocks are very rare; the incidence of fatal Clostridium sordellii infections has been estimated to be 1/100,000 (Fischer et al. 2005). Despite the concern, there is no evidence that the route of misoprostol administration affects the risk of Clostridium sordellii infection (Winikoff 2006, Cohen et al. 2007).

2.4.4 Repeat abortions

Repeat abortions are not rare; for instance in 2007 in Finland, 35% of the women seeking abortion had had at least one previous abortion (National Institute for Health and Welfare 2009). In the United States, about half of the women seeking abortions have already had a prior abortion (Jones et al. 2006). As medical termination of pregnancy is well-tolerated among women (Jensen et al. 2000, Honkanen & von Hertzen 2002, Ho 2006), the question of whether or not it is associated with an increased risk of repeat abortion has occasionally been raised.
Several studies have involved assessment of the characteristics of women seeking repeat abortion (St John et al. 2005, Fisher et al. 2005, Prager et al. 2007). Women seeking repeat abortion tend to be older than those having their first induced abortion, as older women have had a longer period of exposure to the risk of having an unintended pregnancy (Jones et al. 2006). Age, however, is thought to be more of a confounder than a true risk factor (Prager et al. 2007). In addition, parity has emerged as a risk factor of repeat abortion, although, like age, it is more of a confounding factor (St John et al. 2005). Histories of physical or sexual abuse (Fisher et al. 2005) and alcohol and drug abuse (Prager et al. 2007) have also been associated with repeat abortion in cross-sectional studies. In a recent prospective Finnish study, young age, parity, a history of previous abortion and smoking emerged as risk factors of repeat abortion following medical termination of pregnancy (Heikinheimo et al. 2008).

Contraceptive choices of women seeking repeat abortion differ from those of first-time aborters; women seeking repeat abortions have more often been reported to have used some method of contraception (Westfall & Kallail 1995), such as oral contraceptives (Fisher et al. 2005) or depot medroxyprogesterone acetate (Prager et al. 2007). However, in a Danish study women seeking a third abortion tended to use less efficient contraceptive methods (or none at all) than women undergoing their first or second termination of pregnancy (Osler et al. 1997).

To prevent another unwanted pregnancy in the future, preabortion counseling should include discussion on contraceptive needs. If possible, the use of the chosen method should begin immediately after the abortion (von Hertzen et al. 2006). Still, a recent Scottish RCT comparing the efficacy of specialist contraceptive counseling with standard care showed no difference between the groups in the number of women using contraception 4 months after the induced abortion (53 vs. 49%) or in the incidence of repeat abortions within 2 years (15 vs. 10%) (Schunmann & Glasier 2006).

2.4.5 Long-term sequelae

The long-term safety of surgical abortion in the first trimester is well established. Several studies have concluded that a surgical abortion in the first trimester does not increase the risk of ectopic pregnancy, spontaneous abortion, preterm birth, or low birth weight in subsequent pregnancies (Atrash & Hogue 1990, Frank et al.
But not all the studies are congruent; a French multicenter study found an association between previous (surgically) induced abortion and very (and extremely) preterm deliveries, premature rupture of the membranes and antepartum hemorrhage (Moreau et al. 2005). It has been suggested that induced abortion is not an independent risk factor for adverse obstetric outcome, but a previous abortion is associated with marked health-behavior risks (Raatikainen et al. 2006).

Limited information is available regarding the effects of medically induced abortion on subsequent pregnancies. In a recent registry-based study performed in Denmark, medical abortion in the first trimester was not associated with a significantly increased risk of ectopic pregnancies, spontaneous abortion, preterm birth or low birth weight as compared to women with previous surgical abortion (Virk et al. 2007). A history of medically induced abortion was not associated with low birth weight in subsequent pregnancy compared to primigravid women (Yimin et al. 2004) or women with previous surgical abortion (Chen et al. 2004) in Chinese studies. The incidence of placental complications (abruptio placenta, placenta previa, placenta accreta and retained placenta) were studied among nulliparous women with a history of previous medical abortion. The medical abortion itself was not associated with placental complications, but other factors related to medical abortion (gestational age > 6 weeks, a curettage after abortion, and a longer interpregnancy interval) increased the risk of abruptio placenta compared with women with no history of induced abortions (Zhu et al. 2009).

In a two-year follow-up after medical abortion or vacuum aspiration in a partially randomized study, the groups did not differ significantly in terms of general, reproductive or psychological health (Howie et al. 1997). Choosing to terminate a first unwanted pregnancy rather than deliver does not increase the risk of depression (Schmiege & Russo 2005). Women with a previous pharmacological abortion had high conception rates and also high risk of unintended pregnancy during the one-year follow-up (Creinin 1999).

### 2.4.6 Mortality

The estimate of mortality associated with surgical abortion method is 1/1,000,000 (Bartlett et al. 2004), with medical abortion 1/100,000 (Grimes 2005), with miscarriage 1/100,000 (Saraiya et al. 1999) and with a term delivery 1/10,000 (Christiansen & Collins 2006).
In a register-based study performed in Finland, women who underwent an induced abortion had a pregnancy-associated mortality rate from natural causes that was one third higher than that of women who had given birth. After excluding terminations for medical reasons (mostly performed in the second trimester of pregnancy), the pregnancy-associated mortality from all natural causes declined from 22.3 to 15.9 per 100,000 induced abortions, which was lower than the mortality after giving birth. (Gissler et al. 2004). In another study mortality rates after induced abortions were higher from all external causes when compared to the mortality among nonpregnant women, owing to elevated suicide and homicide rates (Gissler et al. 2005).

As the risk of abortion-related mortality increases with the gestational age, it has been estimated that 87% of deaths in women who choose to terminate their pregnancies after 8 weeks of gestation might have been avoidable if these women had had access to abortion services before 8 weeks of gestation (Bartlett et al. 2004).

2.5 Medical method in treating miscarriages

In population-based studies, miscarriage has been shown to be common, with about 15% of women reporting at least one miscarriage during their reproductive life span (Hemminki & Forssas 1999). For most of the 20th century, D&C was the commonly accepted approach for uterine evacuation following early pregnancy failure in order to minimize the risk of infection and hemorrhage. In recent decades, it has been questioned if immediate evacuation by surgical intervention was necessary for uncomplicated cases of early pregnancy failure (Macrow & Elstein 1993, Ballagh et al. 1998). Three different methods for treating miscarriage are currently accepted: surgical, medical (commonly with mifepristone, misoprostol or both) or expectant management (Sotiriadis et al. 2005).

The combination of two highly effective abortifacients, mifepristone and misoprostol, appeared to be effective and safe, not only in inducing abortions but also in treating miscarriages (el-Refaey et al. 1992, Wagaarachchi et al. 2001). Misoprostol alone has also been used in the treatment of miscarriages. Existing studies demonstrate that the use of misoprostol is more effective than expectant (non-intervention) management for early pregnancy failure (Ngai et al. 2001, Bagratee et al. 2004).
2.5.1 *Impact of the type of miscarriage*

Different types of miscarriages are defined in the medical literature (Table 3). “Complete abortion” means that all the products of conception are expelled, while “incomplete miscarriage” means that some of the products of conception still remain in the uterus. The presence of uterine bleeding or lower abdominal pain and ultrasound images of irregular heterogeneous echoes in the midline of the uterine cavity (> 15 mm) are often used to define “incomplete abortion” (Nielsen et al. 1999, Luise et al. 2002).

The criteria for “silent miscarriage” or “early fetal demise”, as defined according to RCOG, are well established. A fetal pole with a crown-rump length (CRL) of more than 6 mm with no heart beat being demonstrated or a CRL less than 6 mm with no change on rescan 7 days later is diagnostic for silent miscarriage (RCR/RCOG 1996).

A gestational sac with a diameter of more than 20 mm without an embryonic pole or yolk sac inside or a diameter less than 20 mm with no change 7 days later is diagnostic for anembryonic pregnancy (RCR/RCOG 1996). In clinical practice, TVS examination is very important in differentiating various types of miscarriages. Sometimes miscarriages may be diagnosed with minimal or no symptoms (e.g. bleeding or abdominal pain) (Tang & Ho 2006).

The success of treatment is evidently dependent of the type of miscarriage. This is particularly true for expectant management; the complete abortion rates were 85-91% for incomplete abortions, 33–76% for missed miscarriage, and 66% for anembryonic pregnancies (Ngai et al. 2001, Luise et al. 2002, Bagratee et al. 2004). Among women with incomplete miscarriage, medical management does not seem to offer greater success than expectant management, but it may offer an alternative management in early fetal demise (Trinder et al. 2006).
Table 3. Different types of miscarriages as diagnosed with TVS.

<table>
<thead>
<tr>
<th>Type of miscarriage</th>
<th>Synonyms</th>
<th>TVS definition</th>
<th>Clinical signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anembryonic pregnancy</td>
<td>Blighted ovum</td>
<td>Gestational sac &gt;20 mm without embryo, or no change in 7 days</td>
<td>No symptoms &lt;-&gt; bleeding, abdominal pain</td>
</tr>
<tr>
<td>Missed miscarriage</td>
<td>Silent miscarriage or early fetal demise</td>
<td>CRL &gt; 6 mm without signs of fetal heart activity</td>
<td>No symptoms &lt;-&gt; bleeding, abdominal pain</td>
</tr>
<tr>
<td>Incomplete abortion</td>
<td>Incomplete miscarriage</td>
<td>Irregular heterogeneous mass &gt; 15 mm in the uterine cavity</td>
<td>Bleeding, abdominal pain</td>
</tr>
<tr>
<td>Complete abortion</td>
<td>----</td>
<td>&lt; 15 mm echo in the uterine cavity</td>
<td>Bleeding, abdominal pain</td>
</tr>
</tbody>
</table>

2.5.2 Other factors affecting efficacy

Besides the type of miscarriage, the success rate may be influenced by gestational age, parity (Creinin et al. 2006b), the time interval between treatment administration, definition and assessment of effectiveness and the regimen used in the treatment. The effectiveness of the medical treatment also depends on the time interval to follow-up (Weeks & Alia 2001). To avoid unnecessary interventions the assessment of success should be delayed for at least 7 to 10 days (Gemzell-Danielsson et al. 2007).

The reported efficacy of medical method in treating early pregnancy failures varies between 50 and 90% (Nielsen et al. 1997, Demetroulis et al. 2001, Wagaarachchi et al. 2002b). Treatment with misoprostol has been found to be superior to expectant management in treating miscarriages in many studies (Ngai et al. 2001, Muffley et al. 2002, Wood & Brain 2002, Bagratee et al. 2004). With the regimen of vaginal misoprostol alone, a success rate of more than 80% in early pregnancy failure was achieved in RCTs (Demetroulis et al. 2001, Zhang et al. 2005). According to a meta-analysis, surgical treatment was significantly more effective than medical or expectant choice when the main outcome was complete abortion. When compared to medical method, surgical evacuation had approximately 1.5 times the success rate (risk ratio 1.44, p < 0.001) (Sotiriadis et al. 2005).

The route of administration affects the complete expulsion rate. Oral misoprostol 0.8 mg was compared with the some dosage administered vaginally: efficacy was similar, but the mean time to expulsion was significantly longer in
the oral group (Ngoc et al. 2004). Sublingual misoprostol had equivalent efficacy compared with vaginal misoprostol in inducing complete miscarriage, but it was associated with more frequent diarrhea (Tang et al. 2003, Ngoc et al. 2004).

The role of mifepristone in the regimen of medical treatment in miscarriages is unclear. Pre-treatment with mifepristone is expected to increase the success rate, because it is known to increase uterine smooth muscle contractility (Gemzell-Danielsson et al. 1993). Protocols combining mifepristone and PG analogues for the treatment of early pregnancy failure have showed a success rate varying between 52 and 84% (Table 4) (el-Refaey et al. 1992, Nielsen et al. 1997, Nielsen et al. 1999, Wagaarachchi et al. 2001, Wagaarachchi et al. 2002b, Chia & Ogbo 2002, Gronlund et al. 2002, Coughlin et al. 2004). In a prospective cross-over study comparing medical treatment with mifepristone and misoprostol, misoprostol alone, or surgical choice in the treatment of early fetal demise pre-treatment with mifepristone did not increase the success rate (74% vs. 71%) compared with misoprostol alone (Gronlund et al. 2002). Few RCTs have been conducted to compare medical treatment (including mifepristone) with other choices. A combination of 400 mg mifepristone and 0.4 mg oral misoprostol showed no advantage compared with expectant management (Nielsen et al. 1999), whereas in another small trial mifepristone 600 mg alone was more effective than expectant management (Lelaidier et al. 1993). In a RCT comparing mifepristone or misoprostol with administration of repeated doses of misoprostol when needed, no benefit in using mifepristone as a pre-treatment was observed in the management of women with early pregnancy failure (Stockheim et al. 2006).
<table>
<thead>
<tr>
<th>Study Group</th>
<th>Design</th>
<th>N</th>
<th>Entry Criteria</th>
<th>Regimens</th>
<th>Follow-up</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Refaey et al (UK)</td>
<td>Prospective</td>
<td>60</td>
<td>Missed abortion or anembryonic pregnancy</td>
<td>600 mg mifepristone, 0.6 mg misoprostol</td>
<td>4h, 10 to 14</td>
<td>95%</td>
</tr>
<tr>
<td>Nielsen et al (Sweden)</td>
<td>Prospective</td>
<td>60 medical</td>
<td>Missed abortion, no clinical symptoms</td>
<td>400 mg mifepristone, 0.4 mg misoprostol orally</td>
<td>6 days</td>
<td>52%</td>
</tr>
<tr>
<td>Nielsen et al (Sweden)</td>
<td>RCT</td>
<td>31</td>
<td>Threatened or inevitable miscarriage</td>
<td>400 mg mifepristone, 0.4 mg misoprostol orally</td>
<td>5 days</td>
<td>82% medical</td>
</tr>
<tr>
<td>Wagaarchchi et al (UK)</td>
<td>Prospective</td>
<td>220</td>
<td>Missed miscarriage or anembryonic pregnancy</td>
<td>200 mg mifepristone, 0.8 mg misoprostol vaginally</td>
<td>14 days</td>
<td>84%</td>
</tr>
<tr>
<td>Wagaarchchi et al (UK)</td>
<td>Prospective</td>
<td>56</td>
<td>Missed miscarriage or anembryonic pregnancy</td>
<td>200 mg mifepristone orally, 0.4 mg misoprostol sublingually</td>
<td>14 days</td>
<td>84%</td>
</tr>
<tr>
<td>Chia and Ogbo (UK)</td>
<td>Prospective controlled</td>
<td>100 medical</td>
<td>Missed abortion</td>
<td>200 mg mifepristone, 0.6 mg misoprostol orally</td>
<td>7 days</td>
<td>84% medical</td>
</tr>
<tr>
<td>Gronlund et al (Denmark)</td>
<td>Prospective cross-over</td>
<td>56 mifepristone and misoprostol</td>
<td>Missed abortion</td>
<td>600 mg mifepristone, 0.6 mg misoprostol vaginally in two doses</td>
<td>8 days</td>
<td>74% mifepristone and misoprostol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73 misoprostol 49 surgical</td>
<td></td>
<td></td>
<td></td>
<td>71% misoprostol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73 misoprostol 49 surgical</td>
<td></td>
<td></td>
<td></td>
<td>96% surgical</td>
</tr>
<tr>
<td>Coughlin et al (UK)</td>
<td>Prospective</td>
<td>44 mifepristone</td>
<td>Missed abortion or blighted ovum</td>
<td>600 mg mifepristone, 200 mg mifepristone and 0.4 mg misoprostol orally</td>
<td>10 days</td>
<td>84% mifepristone and misoprostol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 mifepristone and misoprostol</td>
<td></td>
<td></td>
<td></td>
<td>82% mifepristone and misoprostol</td>
</tr>
<tr>
<td>Stockheim et al (Israel)</td>
<td>RCT</td>
<td>58 mifepristone</td>
<td>Missed abortion or blighted ovum</td>
<td>600 mg mifepristone, 0.8 mg misoprostol orally</td>
<td>10 to 14</td>
<td>66% mifepristone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57 misoprostol</td>
<td></td>
<td></td>
<td></td>
<td>74% misoprostol</td>
</tr>
</tbody>
</table>

Table 4. Studies on management of miscarriages with mifepristone and misoprostol modified from a review (Chen & Creinin 2007).
2.5.3 Other outcomes

Immediate complications

In a RCT comparing medical and surgical treatment of early pregnancy failure side-effects during and immediately after treatment were similar. Severe abdominal pain was reported in 5% and 2.5% of medically and surgically treated patients, respectively. Moderate vaginal bleeding occurred in 10% vs. 2.5% in the medical and surgical group, but the difference was not statistically significant (Demetroulis et al. 2001). In a meta-analysis comparing medical and surgical management, the groups did not differ in the incidence of pelvic inflammatory disease, blood transfusions, emergency curettages or bleeding. In that study the incidence of major complications was relatively low (Sotiriadis et al. 2005). A RCT of women with early fetal demise had a success rate of 84% in medical treatment with mifepristone and vaginal misoprostol. Of the women participating, 5% required blood transfusions in the medical group (Chia & Ogbo 2002).

A multicenter study (miscarriage treatment (MIST) trial) comparing the incidences of gynecological infections among miscarriage patients treated with the expectant, medical or surgical methods showed no difference between the groups. The overall incidence of infections was rather low (2–3%), reassuring that surgical evacuation of the uterus is not necessary in miscarriages to avoid infections, as was believed earlier. More unplanned admissions and curettages occurred after expectant and medical management than after primary surgical management in that study (Trinder et al. 2006).

Acceptability

Similarly as in induced abortions, a possibility to choose the method of treatment is considered highly important among women with a miscarriage. A previous study assessing the treatment of uncomplicated miscarriages with expectant or surgical management demonstrated that patients having the possibility to choose the type of treatment were more satisfied (84–88%) than those who were randomized to treatment groups (55–74%) (Wieringa-de Waard et al. 2004). In a meta-analysis comparing medical and surgical management of miscarriages satisfaction did not differ between the groups (Sotiriadis et al. 2005). A qualitative
study comparing medical, surgical or expectant treatment of miscarriages concluded that no one single treatment is the best choice for all women, but that all the methods have different benefits and problems from women’s point of view (Smith et al. 2006).

**Long-term sequelae**

Fertility outcome following medical management of early pregnancy failure is limited. A cohort of women participating in a RCT of medical or surgical evacuation of miscarriage were followed up for a median of 6 years. The long-term conception rate and pregnancy outcomes did not differ between the groups (Tam et al. 2005).

### 2.6 Economical aspects

#### 2.6.1 Economical aspects in termination of pregnancy

Despite the widespread use of medical termination of pregnancy, there is limited understanding of the costs of this method. The economical evaluation can be discussed as cost to the patient, cost to the provider or cost to society. A review over pharmacoconomics of medical abortion indicates that medical abortion is an expensive process both for providers and for the patient. The actual cost is estimated to be in the same range as for surgical abortion. In comparison, however, pregnancy and childbirth are still more expensive. Nevertheless, the personal decision of whether or not to continue a pregnancy should not be based on primary costs (Murthy & Creinin 2003).

In a descriptive study conducted in the United States, the average patient costs were $351, consisting of direct medical costs (pregnancy test, charges), direct nonmedical costs (childcare, travel, lodging) and productivity losses (time away from work and other activities). Three quarters of these costs were direct medical costs, and the majority of the women were not aware of whether their insurance covers abortion or not. The authors concluded that costs are a barrier to access to abortion for some women and that it is important to evaluate the costs of each method (Van Bebber et al. 2006). Creinin et al. measured the time that each staff member spent with a patient in medical or surgical abortion. Mid-level providers (e.g. nurses) spent much more time with patients undergoing a medical
abortion. As for physicians, twice as much time was spent with patients having a surgical procedure. According to this study, the differential hourly wage between mid-level providers and physicians determines the true cost of providing abortion. Surgical abortion was reported to require 0 to 10% more personnel costs than medical abortion (Creinin 2000).

In some countries the cost of mifepristone is a barrier to its use. The calculations to compare direct and indirect costs of medical abortion using a combination of mifepristone and misoprostol, or misoprostol alone were made in both developing (India) and developed (the United States) country settings. In these calculations, because of the higher efficacy with the regimen of mifepristone and misoprostol, such regimens are less expensive or only minimally more expensive than those using misoprostol alone (Creinin et al. 2005).

2.6.2 Economical aspects in treating miscarriages

As described earlier, several treatment options of early pregnancy failure are available to the clinician and the patient. The option selected depends on many factors, including efficacy, ease of administration, cost, follow-up and patient preference (Rocconi et al. 2005). Most studies of economical evaluation have been made concerning the complications and success rate, not taking into account the qualitative aspects. Previous studies have suggested medical treatment as a cost-saving alternative to surgical treatment using a decision model (You & Chung 2005) or in clinical trials using sensitivity analysis (Hughes et al. 1996, Graziosi et al. 2005). A large RCT (the MIST trial) comparing expectant, medical and surgical methods found the net costs per woman to be highest in the surgical group. In that study societal perspective (cost of hospital and community health and social services, the costs borne by women themselves and their informal carers, and the costs of lost production) was used in the analysis (Petrou et al. 2006).

In the MIST trial, where the focus in cost-effectiveness estimates was on the number of infections avoided, the net societal costs per woman were approximately £1086, £1410 and £1585 for expectant, medical and surgical management, respectively. The type of miscarriage had a significant effect on the costs; in incomplete miscarriages the mean cost difference between the methods was £238, whereas in missed miscarriages the difference was £155. This large study perceived various economical aspects, and sensitivity analysis was also
used (Petrou et al. 2006). In another previous study using a decision tree to simulate three different methods, the traditional surgical treatment of miscarriage has been found to be the most expensive choice compared to expectant or medical management in uncomplicated spontaneous abortions (You & Chung 2005). A decision model comparing strategies for managing abnormal early pregnancies concluded that manual vacuum aspiration is the most cost-effective method. In that study, D&C was more cost-effective than the medical method using a single dose of vaginal misoprostol, despite the clearly higher primary costs of the treatment. The efficacy of the medical treatment was estimated to be 81%. However, unplanned events were not taken into account (Rocconi et al. 2005).
3 Purpose of the present study

Repeat induced abortions are a common problem. However, research data on the risk factors for repeat abortions is limited. As medical abortion is well accepted, the question whether medical abortion increases the risk of repeat abortions has been raised. The complications of medical induced abortions have mostly been studied in relatively small clinical settings. The aim of the study was to investigate the incidence of adverse events and their risk factors within 6 weeks of termination of pregnancy using national registries with a large cohort of women.

Medical treatment of miscarriages using a combination of mifepristone and misoprostol has not been evaluated in a randomized controlled trial. Some studies on economical assessment of medical and surgical treatment of miscarriages have been performed. In previous studies, efficacy has been estimated by using only quantitative measurements. The present study was planned to compare two methods of treatment by using both quantitative (complete evacuation rates) and qualitative (patient preferences and satisfaction) aspects and the actual institutional prices.

The specific aims are as follows:

1. To define the frequency and risk factors of repeat abortions in a nationwide cohort of women with medical or surgical termination of pregnancy, and especially the impact of the method of abortion.
2. To study the incidence and risk factors of immediate complications of medical and surgical induced abortions in a nationwide cohort by using Finnish health registries (Abortion Registry, Hospital Registry, Cause-of-Death Registry).
3. To compare the efficacy and patient satisfaction of the medical method (using mifepristone and misoprostol) with surgical method in treating patients with a miscarriage in a randomized setting.
4. To evaluate the true costs of the medical and surgical management of miscarriages by using provider’s aspect and institutional prices in the cost-effectiveness analysis (CEA). Specific attention was paid to qualitative aspects in the CEA.
4 Subjects and methods

4.1 Study population

4.1.1 Women with induced abortions

A study of repeat abortions

The cohort consisted of 40,360 women undergoing induced abortion in Finland between January 1, 2000 and December 31, 2005 (the index abortion). The data were collected from the Finnish Abortion Registry. The detailed criteria for inclusion and exclusion in the study have been described in the original publication I.

The method of index abortion was divided into two categories. The medical method included induced abortions performed with mifepristone alone, or with a combination of mifepristone and misoprostol or other prostaglandins. The surgical method included induced abortions performed using either dilation and curettage, or vacuum aspiration. The subjects were divided into two study cohorts (medical or surgical termination of pregnancy) based on the method used in the index abortion.

A study of immediate complications

The study included all women undergoing termination of pregnancy in Finland between January 1, 2000 and December 31, 2006 as retrieved from the Abortion Registry. Total number of women included was 42,619. The inclusion and exclusion criteria have been described in the original publication II. The method of abortion was described similarly as in the study on repeat abortions. Only the first termination of pregnancy for each woman during the study period was included.

4.1.2 Women with miscarriage

The study was carried out at Department of Obstetrics and Gynecology at Oulu University Hospital between February 4, 2003 and December 8, 2004. The number of women included in the study was 98. Women aged 18 or more with a
positive pregnancy test (either urine or serum human hCG) and any type of miscarriage were included. The detailed criteria for inclusion and exclusion in the study are described in the original publication III.
Table 5. Summary of the subjects and methods of studies I-IV.

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
<th>Study Design</th>
<th>Data Source</th>
<th>Study Period</th>
<th>Number of Subjects</th>
<th>Time of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Repeat abortions after induced abortions (duration of gestation 63 days or less)</td>
<td>Prospective cohort</td>
<td>Abortion Registry - linked with Cause-of-Death Registry</td>
<td>2000-2005 (index abortion)</td>
<td>Medical abortion n = 19,841</td>
<td>Until the first repeat abortion or until December 31, 2006 (range 1 to 6 years)</td>
</tr>
<tr>
<td>II</td>
<td>Immediate complications after induced abortions (duration of gestation 63 days or less)</td>
<td>Prospective cohort</td>
<td>Abortion Registry - linked with Cause-of-Death Registry and Hospital Registry</td>
<td>2000-2006</td>
<td>Medical abortion n = 22,368 Surgical abortion n = 20,251</td>
<td>42 days after index abortion</td>
</tr>
<tr>
<td>III</td>
<td>Efficacy and patient satisfaction in medical vs. surgical treatment of miscarriages</td>
<td>Randomized controlled</td>
<td>Patients with miscarriage in University Hospital of Oulu, Department of O&amp;G</td>
<td>2003-2004</td>
<td>Medical n = 49 Surgical n = 49</td>
<td>2 months after treatment of miscarriage</td>
</tr>
<tr>
<td>IV</td>
<td>Cost-effectiveness in medical vs. surgical treatment of miscarriages</td>
<td>Randomized controlled</td>
<td>Patients with miscarriage in University Hospital of Oulu, Department of O&amp;G</td>
<td>2003-2004</td>
<td>Medical n = 49 Surgical n = 49</td>
<td>2 months after treatment of miscarriage</td>
</tr>
</tbody>
</table>
4.2 Study design

4.2.1 Repeat abortions (Study I)

The setting was a population-based cohort study. The data concerning women with induced abortion were retrieved from the Abortion Registry (National Institute for Health and Welfare 2007b). The data include background information such as pregnancy history, occupation, residence, municipality and marital status. Data concerning current pregnancy, such as method of contraception used before the pregnancy, gestational duration at termination of pregnancy, indication as well as method of pregnancy termination and planned future contraception were used. Social status and type of residence were defined as described in the original publication I. The subjects were followed up until the first repeat abortion, or until December 31, 2006. Thus, the minimum follow-up time was 1 year. The data were linked with those in the Cause-of-Death Registry of Statistics Finland (Statistics Finland 2009) to determine the time of follow-up for the subjects who died (n = 102) during the follow-up period in this cohort.

4.2.2 Immediate complications following induced abortions (Study II)

This cohort study was based on three national registries: the Abortion Registry (National Institute for Health and Welfare 2007b) and Care Registry for Health Institutions (later: Hospital Registry) compiled by the National Institute for Health and Welfare (National Institute for Health and Welfare 2007c), and the Cause-of-Death Registry of Statistics Finland (Statistics Finland 2009). The study subjects were collected from the Abortion Registry using the inclusion criteria described previously, after which the other registries were linked with the cohort. Background information (pregnancy history, occupation, residence, municipality, marital status, duration of gestation in current pregnancy) was retrieved from the Abortion Registry. Social status and type of residence were defined as described in original publication II.

Information on the study subjects was linked with the Hospital Registry concerning all hospital inpatient episodes (all hospitals) and outpatient visits (public hospitals) occurring within 42 days after termination of pregnancy. All the diagnoses (based on the ICD-10, International Statistical Classification of Diseases and Related Health Problems) (WHO ICD-10 2009) and codes for
surgical procedures (based on the classification by the Nordic Center for Classifications in Health Care) (NCCHC 2009) found in the cohort were evaluated to select those considered to be of clinical importance.

The complications were divided into seven categories: I hemorrhage, II post-abortal infections, III incomplete abortions, IV injuries or other reasons for surgical operation, V thromboembolic disease, VI psychiatric morbidity and VII death. The classification was based on that reported in the Joint Study of the Royal College of General Practitioners and the RCOG (RCGP/RCOG 1985) and modified for the present study.

The Cause-of-Death Registry maintained by Statistics Finland contains data from death certificates and includes all deaths of Finnish citizens and permanent residents of Finland classified according to ICD-10 codes (WHO ICD-10 2009). All the early deaths were classified as direct, indirect or unrelated according to Deneux-Tharaux et al. (Deneux-Tharaux et al. 2005).

4.2.3 Clinical miscarriage trial (Study III)

The study was a prospective controlled randomized trial. All the clinicians (residents or consultants) were advised to recruit suitable patients for the study in the gynecological outpatient clinic. Clinical examination and TVS was performed on each patient to confirm eligibility criteria before recruiting. Data about previous pregnancies, deliveries, miscarriages and induced abortions were collected. Subjects were randomized into medical and surgical treatment.

In the medical treatment group, all the patients received mifepristone 200 mg orally. All the patients were advised to return to the clinic after 24–72 hours for a second visit, during which a nurse applied misoprostol 0.8 mg in the posterior fornix of the vagina. The observation time in the outpatient clinic after the administration of misoprostol was 4 hours minimum. The patients were routinely given prophylactic oral analgesia before administration of misoprostol. During the observation, analgesia was given at patient’s request and the amount of bleeding was recorded. Both the need of analgesia and the amount of bleeding were subjectively estimated by the nursing staff.

In the surgical treatment group, curettage was performed in intravenous propofol anesthesia following our clinical practice within 0–5 days of the primary examination. Preoperative vaginal misoprostol (0.4 mg) was administered at least 2 hours before the procedure for ripening the cervix, if considered necessary. All the patients were given an intravenous opiate and non-steroid anti-inflammatory
drug during the operation. Postoperative observation in the day-care unit was 2 hours minimum after the procedure. Additional analgesia was given if needed during the procedure or at patient’s request while under observation.

At the treatment visit (curettage or misoprostol treatment) all patients were given a questionnaire to be returned on the follow-up visit 5–6 weeks later. The patients were asked questions of experienced pain: “How strong was the most intensive experience of pain during the procedure”. The intensity of pain during the procedure was classified as “none or mild” or “moderate or intensive”. Satisfaction with the treatment was inquired with two questions (“Would you choose the same method again” and “Are you satisfied with the treatment”).

The clinical outcome was evaluated by confirming a urine pregnancy test (u-hCG) 5–6 weeks after treatment at the follow-up visit. The treatment was considered successful when no subsequent interventions (curettage) were needed after primary treatment. The time of total follow-up was 2 months. The complications during this period were obtained as described by physicians in the individual case histories in the hospital records.

4.2.4 Economic evaluation of the miscarriage treatments (Study IV)

The clinical outcome of the study as well as the data concerning patient satisfaction were retrieved from our randomized study comparing medical and surgical treatment of miscarriages (study III). Hospital records were used to obtain detailed information of the complications, unplanned visits and treatments in the hospital.

The primary outcome of the study was to compare the costs between the medical and surgical treatment group (the primary costs), and the costs caused by the complications of the treatment (the secondary costs). Any hospital treatment (out- or inpatient) for pain, abnormal bleeding or infection (clinical signs or elevated infection parameters in laboratory tests) treated with oral or intravenous antibiotics was considered a complication. The routine recommendation for the duration of sick leave was two days, but the need was always estimated on an individual basis. Information regarding the eventual number of sick leave days was collected from the hospital records.

The costs were calculated using institutional prices, charges to the county for the out- and inpatient visits and procedures. Analyses were made from the aspect of the service provider, i.e. the communities. Only direct hospital costs were analyzed, because they give a relevant idea of the differences between the two
treatments. Direct hospital costs consisted of the clinical management pathway for producing the treatments and additional costs occurring during the treatment period. All the costs were calculated for the year 2007. Neither the costs nor effects were discounted, because both occurred during the first year.

When neither treatment is dominant, the convention is to examine the incremental cost-effectiveness ratio (ICER). The ICER measures the additional costs for achieving an extra unit of effectiveness by adopting the experimental treatment over the standard (Willan & O'Brien 1999). The ICER was calculated for the treatment by dividing the total costs (DC) by effectiveness (DE) defined as DC:DE. Effectiveness was measured by using the outcomes of study III. The incremental costs were compared with incremental effectiveness (success rate, experience of pain and patient satisfaction).

4.3 Ethical aspects

The studies on the cohort of women with induced abortions (studies I and II) and on women with a miscarriage (studies III and IV) were conducted following the approval of the ethics committee of Northern Ostrobothnia Hospital District in 2005 and 2002, respectively. The Ministry of Social Affairs and Health and Statistics Finland gave their permission to use the confidential personal-level data from the registries. The Data Protection Ombudsman was notified of the data linkage before the analyses, as required by the national data protection legislation.

Of the women with induced abortions, the data linkage within the Abortion Registry and between other data sources was achieved by using the women’s unique personal identification numbers. Before the analysis, personal identification numbers were removed from the data to ensure privacy protection.

Women with a miscarriage were treated with two generally accepted methods and the volunteers to participate the study were randomized after informed consent. The data have been analyzed in unidentifiable form by using serial numbers for participants.
4.4 Statistical methods

4.4.1 Studies on induced abortion

All data were analyzed by using the Statistical Program for Social Sciences (SPSS Inc., Chicago, IL, USA). The differences between the cohorts of medical and surgical abortion were assessed by using Student’s t-test (study I and II), the $X^2$-test and the two-sample test of proportions (study I) and the chi-square test for categorical variables (study II). The chi-square test for trend was used for variables that involved ordered categories (study II). Kaplan-Meier curves were constructed by using the log-rank test (study I). Cox regression analyses were performed to identify the risk factors of repeat abortions and the estimated risks are presented as Hazard Ratios (HRs) with 95% confidence intervals (95% CIs). Logistic regression analyses were performed to adjust for the differences in background characteristics in the comparisons of medical and surgical abortions (study II). Furthermore, logistic regression was used to identify risk factors for complications. The estimated risks are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs). Variables that showed a statistically significant association with repeat abortion or complications in univariate analysis were further entered in multivariate analysis.

4.4.2 Studies on miscarriage

All data were analyzed by using the Statistical Program for Social Sciences (SPSS Inc., Chicago, IL, USA). Power calculation was based on the assumption that the success rate in surgical treatment would be 95% and in medical treatment 70%, as was the average in previous literature. At alpha of 0.05 (2-tailed significance) and beta 0.15, the required sample size was 40 in both groups. The baseline demographics and clinical characteristics were defined by using Student’s t-test. The statistical differences between the groups were calculated by using Fisher’s exact test. The limit of statistical significance was set at $p \leq 0.05$ in all studies.
5  Results

5.1  Repeat abortions (Study I)

Fig. 6 shows the proportions (%) of medical and surgical abortions in the study cohort between 2000 and 2005. In addition, the general annual abortion rate (/1,000 women aged 15–49 years) in Finland is shown (National Institute for Health and Welfare 2009). The use of medical abortion increased from 8.5% in 2000 to 73.9% in 2005, and the annual abortion rate varied between 8.9 and 9.4/1,000 women aged 15–49 years.

The total number of women undergoing induced abortion between 2000–2005 and fulfilling the inclusion criteria was 40,360. Of these, 19,841 had medical abortion and 20,519 had surgical abortion. The follow-up time (mean ± SD) for the cohort undergoing medical abortion was 3.0 ± 1.5 years, and 4.3 ± 1.9 years for women undergoing surgical abortion (p < 0.001). The follow-up time for the whole cohort was 3.7 ± 1.8 years.

The characteristics of the women in the cohort are described in detail in the original article I. The cohorts differed statistically in several respects. Notably, the duration of gestation was shorter at the time of abortion among the women in the medical vs. the surgical group. More subjects in the medical group were of an unknown social status (37%) compared with those in the surgical group (22%).

Fig. 6. Annual proportion of medical (open bars) and surgical (black bars) abortions in the study cohort between 2000 and 2005. In addition, the corresponding annual abortion rates (per 1,000 women aged 15–49 years) in Finland are shown on the right hand axis.
A subgroup analysis was performed among primigravid women. The primigravid women were younger (21.3 ± 5.3 vs. 26.6 ± 7.6 years, p < 0.001), more often single (84.9% vs. 63.1%, p < 0.001) and more often students (46.4% vs. 26.8%, p < 0.001) when compared to the entire cohort.

Overall, 14.2% of the subjects requested a repeat abortion within the follow-up time. The incidence of repeat abortion per 1,000 women per follow-up year differed significantly only for the year 2001, shown in Table 2 in the original publication I (34.9/1,000 in the medical group vs. 39.5/1,000 in the surgical group; p = 0.04). In addition, the total numbers of repeat abortions per follow-up year per 1,000 women differed between the two cohorts, being 40.4/1,000 in the medical group and 37.9/1,000 in the surgical group (p = 0.01).

The time interval to repeat abortion in relation to the index abortion was recorded. The time intervals were similar in the two cohorts. In Kaplan-Meier analysis the cumulative risk of repeat abortions in the medical and surgical groups in relation to the index abortion did not differ statistically significantly (data not shown).

To define the risk factors of repeat abortions, uni- and multivariable analyses were performed for the medical and surgical groups (Table 3 in the original publication I) and for both groups together (Fig. 7). The risk factors of repeat abortion were largely similar following both medical and surgical abortion. In multivariable analyses, advancing age was associated with decreasing risk, and previous abortion(s) with an increased risk of repeat abortion in both groups. Moreover, being single or parous increased the risk of repeat abortion in the medical cohort. In the surgical abortion cohort, the risk was also increased among women belonging to the social class “others”. When compared with an urban environment, living in a rural area was associated with a decreased risk of repeat abortion among women undergoing medical abortion.

When compared with planned use of combined oral contraceptives (COCs) for post-abortion contraception, the risk of repeat abortion in multivariable analysis was decreased if sterilization was planned for future contraception in both cohorts.
Fig. 7. Hazard ratios for repeat abortion among the entire cohort.
Fig. 7 shows the hazard ratios (and 95% CIs) for repeat abortion derived from multivariable analysis of both groups combined. The risk of repeat abortion increased with parity, previous abortion(s), having the socioeconomic status of “others”, or being single or cohabiting (compared with married women). However, the risk of repeat abortion decreased with advancing age and was lower among those living in a densely populated or rural area (compared with an urban environment) and when a levonorgestrel-releasing intrauterine system (LNG-IUS), a copper-releasing intrauterine device (Cu-IUD) or sterilization was planned for future contraception (compared with planned use of COCs). As derived from univariable analysis, the method of the index abortion (medical vs. surgical) was not associated with an altered risk of repeat abortion.

When primigravid women were analyzed separately, advancing age was associated with a decreased risk of repeat abortion. The method of the index abortion, social or marital status, type of residence or planned method of contraception did not have an effect on the risk of repeat abortion. Among primigravid women undergoing medical abortion, the risk of repeat abortion was increased (1.74, 1.09–2.78) among blue-collar workers. Of the other variables analyzed, marital status, type of residence, gestational duration and planned contraception did not have an effect on the risk of repeat abortion in either cohort. When both cohorts of primigravid women were combined, only older age was associated with a significantly altered risk of another abortion (Table 6).
Table 6. Uni- and multivariate analysis of the risk factors of repeat abortions among primigravid women.

<table>
<thead>
<tr>
<th>Age category</th>
<th>OR (univariate)</th>
<th>95% CI</th>
<th>OR (multivariate)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 20</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td>0.72</td>
<td>0.66-0.79</td>
<td>0.68</td>
<td>0.62-0.75</td>
</tr>
<tr>
<td>25-29</td>
<td>0.46</td>
<td>0.40-0.54</td>
<td>0.43</td>
<td>0.37-0.51</td>
</tr>
<tr>
<td>30-34</td>
<td>0.33</td>
<td>0.26-0.43</td>
<td>0.31</td>
<td>0.24-0.46</td>
</tr>
<tr>
<td>35-39</td>
<td>0.32</td>
<td>0.22-0.47</td>
<td>0.31</td>
<td>0.21-0.46</td>
</tr>
<tr>
<td>40+</td>
<td>0.21</td>
<td>0.10-0.48</td>
<td>0.20</td>
<td>0.09-0.45</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Method of abortion</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>1.07</td>
</tr>
<tr>
<td></td>
<td>0.99-1.16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social status</th>
<th>OR (univariate)</th>
<th>95% CI</th>
<th>OR (multivariate)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper white collar</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower white collar</td>
<td>1.30</td>
<td>0.99-1.72</td>
<td>0.99</td>
<td>0.75-1.32</td>
</tr>
<tr>
<td>Blue collar</td>
<td>1.84</td>
<td>1.39-2.43</td>
<td>1.20</td>
<td>0.89-1.60</td>
</tr>
<tr>
<td>Students</td>
<td>1.92</td>
<td>1.49-2.47</td>
<td>0.93</td>
<td>0.71-1.23</td>
</tr>
<tr>
<td>Others</td>
<td>1.94</td>
<td>1.49-2.52</td>
<td>1.12</td>
<td>0.85-1.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marital status</th>
<th>OR (univariate)</th>
<th>95% CI</th>
<th>OR (multivariate)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohabiting</td>
<td>1.36</td>
<td>1.01-1.83</td>
<td>1.02</td>
<td>0.76-1.38</td>
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<tr>
<td>Single</td>
<td>1.50</td>
<td>1.14-1.98</td>
<td>1.00</td>
<td>0.76-1.33</td>
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<table>
<thead>
<tr>
<th>Type or residence</th>
<th>OR (univariate)</th>
<th>95% CI</th>
<th>OR (multivariate)</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Urban</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Densely populated</td>
<td>0.98</td>
<td>0.87-1.12</td>
<td></td>
<td></td>
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<tr>
<td>Rural</td>
<td>0.91</td>
<td>0.81-1.03</td>
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<table>
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<tr>
<th>Gestational age</th>
<th>OR (univariate)</th>
<th>95% CI</th>
<th>OR (multivariate)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 or less</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1.01</td>
<td>0.89-1.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1.00</td>
<td>0.89-1.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1.07</td>
<td>0.95-1.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Planned contraception</th>
<th>OR (univariate)</th>
<th>95% CI</th>
<th>OR (multivariate)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNG-IUD</td>
<td>0.48</td>
<td>0.28-0.80</td>
<td>0.76</td>
<td>0.45-1.29</td>
</tr>
<tr>
<td>Cu-IUD</td>
<td>0.79</td>
<td>0.58-1.06</td>
<td>1.17</td>
<td>0.86-1.59</td>
</tr>
<tr>
<td>Condom</td>
<td>0.89</td>
<td>0.72-1.11</td>
<td>1.11</td>
<td>0.89-1.38</td>
</tr>
<tr>
<td>Sterilization</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Other</td>
<td>1.07</td>
<td>0.68-1.30</td>
<td>1.18</td>
<td>0.97-1.43</td>
</tr>
<tr>
<td>None</td>
<td>0.90</td>
<td>0.50-1.63</td>
<td>1.13</td>
<td>0.62-2.04</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.82</td>
<td>0.66-1.03</td>
<td>0.91</td>
<td>0.73-1.14</td>
</tr>
</tbody>
</table>
5.2 Immediate complications following induced abortions (Study II)

The total number of women in the cohort was 42,619. Of these, 22,368 had primary medical and 20,251 primary surgical termination of pregnancy. The characteristics of the women in the cohort are described in detail in Table I in the original article II. The women in the medical abortion cohort were somewhat younger, and were more often primigravid, nulliparous and single. The most notable difference between the groups was the shorter duration of gestation in the cohort undergoing medical abortion.

The incidences of various adverse events and complications are shown in Table 7. The most common adverse events were hemorrhage and incomplete abortions, which were both more common in the medical group. The incidence of infections did not differ between the groups. Injuries requiring operation were rare, but were more common in the surgical group. No differences between the two groups were observed in the incidences of thromboembolic disease, psychiatric morbidity or death, partly because the overall incidence of these events was low. None of the deaths were related to pregnancy, but were fortuitous: suicide (n = 3), homicide (n = 1), subarachnoid hemorrhage (n = 1) and traffic accident (n = 1).

When comparing the numbers of women with adverse events or complications, the difference between the two groups was notable – 20% of the women in the medical abortion group and 5.6% of those in the surgical abortion group had at least one type of adverse event. When looking at the number of complications per subject, there were fewer multiple complications after surgical abortion (Table 7).

We also analyzed the three most common complications in relation to the duration of gestation (Fig. 8). In the medical abortion cohort, the proportion of women with hemorrhage decreased with advancing duration of gestation, whereas after surgical abortion it increased, albeit not significantly. In both groups the incidence of infections and incomplete abortions increased with advanced duration of gestation.
Table 7. Incidence of Adverse Events in the two cohorts. The adjusted OR for the main adverse events are shown.

<table>
<thead>
<tr>
<th>Medical Abortion (n=22,368)</th>
<th>Surgical Abortion (n=20,251)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage 3,487 (15.6)</td>
<td>433 (2.1)</td>
<td>&lt;0.001</td>
<td>7.93 (7.15–8.81)</td>
</tr>
<tr>
<td>hemorrhage with surgical (re)evacuation 645 (2.9)</td>
<td>173 (0.9)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Infection 383 (1.7)</td>
<td>342 (1.7)</td>
<td>0.85</td>
<td>1.15 (0.98-1.34)</td>
</tr>
<tr>
<td>infection with surgical (re)evacuation 172 (0.8)</td>
<td>122 (0.6)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Incomplete abortion 1,495 (6.7)</td>
<td>323 (1.6)</td>
<td>&lt;.001</td>
<td>5.37 (4.49-6.28)</td>
</tr>
<tr>
<td>incomplete abortion with surgical (re)evacuation 1,320 (5.9)</td>
<td>77 (0.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Injury 6 (0.03)</td>
<td>122 (0.60)</td>
<td>&lt;.001</td>
<td>NA</td>
</tr>
<tr>
<td>Thromboembolic disease 18 (0.08)</td>
<td>17 (0.08)</td>
<td>0.90</td>
<td>NA</td>
</tr>
<tr>
<td>Psychiatric morbidity 2 (0.009)</td>
<td>1 (0.005)</td>
<td>0.62</td>
<td>NA</td>
</tr>
<tr>
<td>Death 2 (0.009)</td>
<td>4 (0.020)</td>
<td>0.35</td>
<td>NA</td>
</tr>
<tr>
<td>Women with adverse events 4,479 (20.0)</td>
<td>1,127 (5.6)</td>
<td>&lt;0.001</td>
<td>4.23 (3.94-4.54)</td>
</tr>
<tr>
<td>Surgical (re)evacuation 1,320 (5.9)</td>
<td>363 (1.8)</td>
<td>&lt;0.001</td>
<td>3.58 (3.18-4.03)</td>
</tr>
<tr>
<td>Number of adverse events per a woman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17,889 (80.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3,624 (16.2)</td>
<td>1,021 (5.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>796 (3.6)</td>
<td>97 (0.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>59 (0.26)</td>
<td>9 (0.04)</td>
<td></td>
</tr>
</tbody>
</table>

NA, not applicable

Uni- and multivariable analyses were performed concerning the risk factors of three major classes of complications (hemorrhage, infections and incomplete abortions) and surgical (re)evacuation, separately for the medical and surgical abortion cohorts (Table 3 in original publication I), and for the whole cohort combined (Fig. 8). In multivariable analysis the risk of hemorrhage following medical abortion was increased in the age group of 20–24 years, among parous women, among those of lower socioeconomic status and among those living in densely populated or rural areas. The risk decreased with advancing duration of gestation. Following surgical termination of pregnancy, an increased risk of hemorrhage was seen in the age groups of 20–24, 25–29, 30–34 and 35–39 years when compared with women younger than 20 years. A rural type of residence was associated with a decreased risk of hemorrhage.
Multivariable analysis revealed an increased risk of infection following medical abortion in the age group of 20–24 years and with advanced duration of gestation of 50–56 and 57–63 days. Following surgical abortion, an increased risk of infection was found in the age group of 20–24 years, with increasing duration of gestation as well as among women of lower socioeconomic class. A decreased risk of infection was associated with parity and with women living in densely populated or rural areas.

The risk factors associated with incomplete medical abortion were age of 20–24 years, parity, previous abortion, being single, living in a densely populated or rural area and advanced duration of gestation. The risk of experiencing incomplete surgical abortion was associated with previous abortion, cohabiting or being single, and with a duration of gestation of 57–63 days.

In multivariable analysis (Fig. 9), the risk of bleeding was 7.8-fold greater, the risk of incomplete abortion was 5.2-fold greater and the risk of surgical (re-
evacuation was 2.1-fold greater after medical than surgical termination. The risk of infection, as derived from univariate analysis, was not associated with the method of abortion.
Fig. 9. Risk factors for adverse events in the whole cohort (both groups combined).
5.3 Clinical miscarriage trial (Study III)

During the study period, 753 patients with first trimester miscarriage were treated in the Department of Obstetrics and Gynecology of Oulu University Hospital. Ninety-eight of these patients (13%) were volunteers and eligible to be randomly allocated to treatment (49 women in both arms of the study). The analyses were made by “intention-to-treat”. The flow chart is seen in Fig. 10. No patients were lost to follow-up.

The baseline characteristics of the study subjects are shown in the original publication III. The groups did not differ statistically by age, gestational age, number of previous pregnancies, deliveries, miscarriages or induced abortions.
Fig. 10. A flowchart for studies III and IV.
5.3.1 The efficacy of the treatment

The primary outcome was the efficacy of the treatment. The main results of the study are seen in Table 8. The treatment was successful in 90% vs. 100% in the medical and surgical group, respectively (NS). In the medical group, three patients were admitted to the ward for intensive pain during the treatment (one patient after mifepristone and two after misoprostol administration), while none in the surgical treatment group were admitted. The need for follow-up in the hospital for pain did not differ significantly between the two groups.

Eight patients were diagnosed with infection after treatment. The mean time between treatment and diagnosis of infection was 7 days (range 3–20 days). More infections were seen following surgical treatment (7 vs. 1).

Table 8. The main results of study III.

<table>
<thead>
<tr>
<th></th>
<th>Medical (%)</th>
<th>Surgical (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated with randomized treatment</td>
<td>n=48</td>
<td>n=47</td>
<td></td>
</tr>
<tr>
<td>Failures (curettage after primary treatment)</td>
<td>5</td>
<td>0</td>
<td>0.06</td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
<td>7</td>
<td>0.03</td>
</tr>
<tr>
<td>Inpatient treatment for pain</td>
<td>3</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>Moderate or intensive pain</td>
<td>29 (63)</td>
<td>17 (37)</td>
<td>0.02</td>
</tr>
<tr>
<td>Satisfied with the treatment</td>
<td>37 (88)</td>
<td>44 (100)</td>
<td>0.02</td>
</tr>
<tr>
<td>Would choose the same method again</td>
<td>32 (70)</td>
<td>42 (91)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

5.3.2 Patient satisfaction

Subjective patient satisfaction was the secondary outcome. Ninety-four per cent (n = 92; 46 and 46)) of the patients returned the questionnaire. Seventeen patients (37%) in the curettage group, compared to 29 (63%) in the medical treatment group, found the pain “moderate or intensive” during the whole procedure (p = 0.02, 95% CI 1.15–7.41). Satisfaction with treatment was classified as “satisfied” or “dissatisfied”. Those who were neither were excluded from the analysis (2 women in surgical and 4 in medical group). Surgically treated patients were more satisfied with the treatment (100% n = 46 /vs./ 88% n = 37, p = 0.02, 95% CI 1.01–999). The patients were asked whether they would choose the same method again. In the surgical treatment group 91% (n = 42) and in the medical treatment group 70% (n = 32) said they would choose the same method in the future (p = 0.02, 95% CI 1.26–20.7). Background characteristics (gestational age,
pregnancies, deliveries, miscarriages and induced abortions) were also analyzed in relation to experienced pain and satisfaction with the treatment. Only advanced gestational age had a positive correlation with experienced pain (p = 0.01, 95% CI -12.78 – -1.44) and previous pregnancies with satisfaction with the treatment (p = 0.004; 95% CI 0.03 – 0.17).

5.4 Economic evaluation of the miscarriage treatments (Study IV)

The background characteristics of the women are described in the original publication III. The costs in the study groups based on hospital prices are shown in Table 9. The price of the medical treatment was 356 euros (€) and of surgical treatment €436 in the outpatient clinic. The price for an inpatient day with conservative treatment (including medication) was €219 and with curettage €834 per day. The price of the outpatient visit was €128 (follow-up visit or conservative treatment), and €45 for just a laboratory test. For each participant in the study the number, type and length of the hospital visits were examined in the hospital files and the total costs were calculated by using these institutional prices. Of all the randomized patients, 46/49 had the allocated procedure in each group. The total primary costs for performing the medical procedure were €16,376. The corresponding figure for the surgical group was €20,056. The difference in total costs was €3,680. Secondary costs for unplanned events, such as treatment in the ward (conservative treatment or curettage) or in the outpatient clinic (conservative treatment, curettage after the primary treatment or laboratory tests) were €5,906 and €3,914 in the medical and surgical groups, respectively. Thus, the secondary costs were €1,992 higher in the medical group. Total costs including both primary and secondary costs were €22,282 and €23,970, respectively. The costs for a single patient were €455 and €489 in the medical or surgical group, respectively, with a difference of €34.
Table 9. Costs (€) in the two study groups based on hospital prices. Primary costs include the costs of the allocated procedure under the study protocol; secondary costs include the costs of treating complications and other unexpected events.

<table>
<thead>
<tr>
<th></th>
<th>Medical (€) /patient</th>
<th>Total</th>
<th>Surgical (€) / patient</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(46 patients in both groups)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>356</td>
<td>46 x 356</td>
<td>€16,376</td>
<td>436</td>
<td>46 x 436</td>
</tr>
<tr>
<td><strong>Secondary costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Conservative treatment in the ward (€219 / inpatient day)</td>
<td>6 x 219</td>
<td>€4,175</td>
<td>4 x 219</td>
<td>€856</td>
</tr>
<tr>
<td>2) Curettage in the ward (€834 / inpatient day)</td>
<td>4 x 834</td>
<td>€3,336</td>
<td>2 x 834</td>
<td>€1,668</td>
</tr>
<tr>
<td>3) Outpatient visit (€128 /visit)</td>
<td>3 x 128</td>
<td>€384</td>
<td>10 x 128</td>
<td>€1,280</td>
</tr>
<tr>
<td>4) Curettage in the outpatient clinic (€436/visit)</td>
<td>2 x 436</td>
<td>€872</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5) Laboratory test (€45/visit)</td>
<td>--</td>
<td>--</td>
<td>2 x 45</td>
<td>€90</td>
</tr>
<tr>
<td><strong>Total costs</strong></td>
<td>≈ 455</td>
<td>€22,282</td>
<td>≈ 489</td>
<td>€23,970</td>
</tr>
</tbody>
</table>

Ten patients in both groups had events classified as a complication. Treatment in the ward was more often needed in the medical group (10 vs. 6 days), whereas surgically treated patients had more additional visits to the outpatient clinic (10 vs. 5). In addition, the medical group had more sick leave days than the surgical group (113 vs. 96 days). However, none of these differences reached statistical significance. The distribution of sick leave days was similar between the groups. Sick leave data were missing for 4 patients in the medical group and 3 patients in the surgical group.

In the CEA, the effectiveness was measured by using the number of patients with pain and the number of satisfied patients (Table 10). The average and incremental costs and C/E are presented in Table 11. The surgical treatment group had 5 more successfully treated (no subsequent interventions) patients than the medical group (incremental effectiveness), the incremental cost being €1,688. So, by investing €1,688 more in surgical treatment, it is possible to gain an additional five successfully treated patients with a cost of €338 per patient. In theory, if all the patients were treated surgically, by investing an additional €1,688 it would be
possible to have 12 more patients with no pain (€141/patient) and 7 more patients satisfied with the treatment (€241/patient).

Table 10. Cost-effectiveness analysis for pain and patient satisfaction in the two study groups. The costs consist of the sum of all treatments in the groups.

<table>
<thead>
<tr>
<th></th>
<th>Cost (€)</th>
<th>Patients with pain (n)</th>
<th>Satisfied patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>22,282</td>
<td>29</td>
<td>37</td>
</tr>
<tr>
<td>Surgical</td>
<td>23,970</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>Incremental</td>
<td>1,688</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 11. Incremental cost-effectiveness ratio (C/E-ratio) for the method of the treatment. The costs consist of the sum of the all treatments in the groups. *

<table>
<thead>
<tr>
<th></th>
<th>Costs (€)</th>
<th>Effectiveness (Successful treatment)</th>
<th>C/E-ratio (Costs/successfully treated patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td>22,282</td>
<td>44</td>
<td>506</td>
</tr>
<tr>
<td>Surgical</td>
<td>23,970</td>
<td>49</td>
<td>489</td>
</tr>
<tr>
<td>Incremental</td>
<td>1,688</td>
<td>5</td>
<td>338</td>
</tr>
</tbody>
</table>

* Successful treatment = no subsequent interventions
6 Discussion

6.1 Repeat abortions (Study I)

The risk factors of repeat abortion had similarities following medical and surgical abortion (young age, previous induced abortion(s), LNG-IUS as a planned contraceptive method), but they did differ in some respects. Importantly, the risk of repeat abortion was not affected by the method of abortion. The risk factors for repeat abortion were similar to those described in previous studies: young age, parity and history of induced abortion(s) (Prager et al. 2007, Heikinheimo et al. 2008). Among primigravid women, advancing age was the only factor associated with a significantly altered risk of repeat abortion.

In a previous study, lower socioeconomic status, low level of education as well as relationship status correlated with an increased risk of repeat abortion (Fisher et al. 2005). Similarly, in the present study, being a blue-collar worker or classified in the group of low socioeconomic status (such as unemployed) was associated with an increased risk of repeat abortion. Being single or cohabiting also emerged as risk factors. The risk was diminished among subjects living in rural or densely populated areas when compared with women living in an urban environment.

The external validity of this study is estimated to be high. The strength of this study is the large cohort, covering practically all abortions performed in Finland during the study period. In registry-based studies, coverage and quality of the data is of utmost importance. The validity of the information in the Finnish Abortion Registry has been studied previously by comparing consecutive samples of information with the medical records in the hospitals. The completeness of the registry was found to be reliable; 95% of the information in the registry was identical to that in the medical records (Gissler et al. 1996). Moreover, it was recently shown that 99% of abortions are included in the registry (Heikinheimo et al. 2008).

In Finland, medical termination of pregnancy has become the dominant method of abortion, while the use of surgical methods diminished during the study period. The follow-up time was significantly shorter (3.0 vs. 4.3 years) for subjects who underwent medical abortion. Hence the proportion of women undergoing repeat abortion was calculated per thousand women per follow-up
year. The time of follow-up was also taken into account in the uni- and multivariate analyses.

The risk of repeat abortion is mainly explained by various sociodemographic characteristics. Young women, especially those with a low socioeconomic and/or an unstable relationship status, are an important target group as regards contraceptive counseling, as are women with a history of previous deliveries and/or induced abortions. However, the method of abortion is not associated with an altered risk of repeat abortion.

6.2 Immediate complications following induced abortions (Study II)

The incidences of the two most common adverse events (hemorrhage and incomplete abortion) were notably higher among women undergoing medical abortion, whereas complications requiring surgical treatment, although rare, were more common after surgical abortion. The rates of postabortal infection and serious morbidity (such as thromboembolic events) did not differ between the two groups. There were no pregnancy-related deaths in the present data. As medical abortion is increasingly being used in several countries, it is likely to result in an elevated incidence of overall morbidity related to termination of pregnancy.

The present study covers practically all the induced abortions performed in Finland in 2000–2006, and thus enables the evaluation of even uncommon adverse events. However, the reliability of diagnoses and interventions can vary, and under- or over-reporting by physicians cannot be ruled out. In addition, the Hospital Registry, which was used as a data source, contains the data concerning hospital care only. Adverse events dealt with outside the public hospital system, especially those treated in primary health care, will have been missed. Thus, this study reflects the incidence of serious complications, although part of minor complications (e.g. mild infections) might have been treated in primary health care.

The rate of consultations related to a diagnosis of hemorrhage was eight times more common following medical termination of pregnancy. As medical abortion is associated with uterine bleeding lasting approximately two weeks (Spitz et al. 1998), the high rate of consultations is not surprising. Uterine bleeding necessitating uterine evacuation probably reflects better the severity of bleeding after termination of pregnancy. Its rate was relatively low, but it was more common in the medical abortion group. In earlier studies an average of 10% of
women who underwent medical abortion complained of excessive bleeding (Sitruk-Ware 2006).

In line with uterine bleeding, the rate of incomplete abortion was higher in the cohort undergoing medical abortion. Incomplete abortion, necessitating surgical evacuation, was performed in approximately 6% of cases after medical termination of pregnancy. The highest rates of complete medical abortion, reported from centers with extensive experience of the technique, are up to 98% (Ashok et al. 1998, Ashok et al. 2002c). However, it is reassuring to note that a high rate of complete abortion, approaching those reported from centers with extensive experience, was reached in the present national cohort.

One of the key findings was that the rates of infectious morbidity were similar following medical and surgical abortion. Prophylactic antibiotics are not routinely used in induced abortions in Finland (Finnish Gynecological Association's task force 2001). In a previous survey the need of postabortal antibiotics for suspected endometritis was higher following surgical abortion (Cameron et al. 1996).

The most important risk factor as regards the two most common adverse events (hemorrhage and incomplete abortion) was the method of abortion. Other risk factors were mostly in line with those reported previously – advanced gestational age, parity and previous induced abortions (Bartley et al. 2000, Allen et al. 2001, Child et al. 2001, Ashok et al. 2002c). For an unknown reason, the risk of hemorrhage diminished with advancing duration of gestation after medical abortion. Tolerance of bleeding – an inevitable part of medical abortion – varies from one woman and physician to another and also depends on pre-abortion counseling.

In conclusion, termination of pregnancy by either medical or surgical method is associated with a low level of serious complications. However, significantly more morbidity is associated with medical abortion compared to surgical method. It appears that increasing use of medical abortion results in an increased incidence of adverse events. Detailed analysis with additional indicators is needed to assess the total impact of this phenomenon on the health care system.

### 6.3 Clinical miscarriage trial (Study III)

This study indicated that medical treatment of miscarriages with the combination of mifepristone and misoprostol is effective. The success rate in the medical
group was 90% among randomized miscarriage patients, which is well comparable with other studies using mifepristone and misoprostol (Table 4).

There are some limitations in this study regarding the analysis of patient preferences. The few questions, although focusing on the most important issues – pain and satisfaction – cannot elucidate these important questions profoundly. However, the response rate was good (94%) and the differences between the groups were significant. Surgical treatment was considered more convenient, and the medically treated patients were more likely to experience pain and dissatisfaction with the treatment. A significantly larger group of patients would choose the same method in the future in the surgical treatment group compared with the medical method (91% vs. 70%).

In a RCT comparing psychological impact and client satisfaction of surgical and medical treatment of spontaneous abortion, the two groups did not differ in psychological outcomes (Lee et al. 2001). However, patients with failed medical treatment and subsequent surgical evacuation were significantly less satisfied with the treatment. In a prospective comparative study of induced abortions, medically treated patients rated the procedure as being more stressful and experienced the treatment as more painful compared to surgical abortion (Slade et al. 1998), possibly due to the close contact with the fetus in recognizable form.

In the present study, all kinds of miscarriages, including incomplete spontaneous abortions, were included. The same medicinal combination has previously mostly been studied in missed abortions and anembryonic pregnancies (Table 4). Incomplete spontaneous abortion has a higher chance of resolution with both expectant and medical management compared with cases of missed miscarriage or anembryonic pregnancy (Bagratee et al. 2004). Classification of miscarriages can be obscure in clinical practice, and one single protocol for all kind of miscarriages (excluding complete spontaneous abortion) increases the usability of the medical method.

In the MIST trial the overall incidence of infections was rather low, 2–3% (Petrou et al. 2006), and there was no difference between patients treated with the expectant, medical or surgical methods. In the present study more infections were diagnosed following curettage. Invasive procedure, surgical evacuation of the uterus, may potentially expose a patient to a higher risk for endometritis. However, in most cases the signs of infections were mild and were treated with oral antibiotics without admission to the ward.

In a qualitative study, regardless of the type of miscarriage treatment, many women stated that they would have liked more time and information to make their
decision (Ogden & Maker 2004). The setting in the present study was randomized, and this may have affected the overall satisfaction with the treatment. The possibility to choose the method increases the satisfaction with care (Rorbye et al. 2005). On the other hand, the women who were volunteers to be randomized in the study may have had a more positive attitude towards the health care system than the other patients with a miscarriage.

The medical procedure was more painful and the patients were less satisfied with the treatment. Still, the majority of women accept the method. It is of the utmost importance to offer sufficient analgesia to medically treated patients and to inform patients well about the possible complications of the procedure. The individual possibility to choose the method following patient information and discussion will probably improve the satisfaction with the treatment.

6.4 Economic evaluation of the miscarriage treatments (Study IV)

The primary costs of the medical treatment of miscarriage were smaller than those of the surgical treatment. The difference in the total costs between the groups diminished significantly when the secondary costs were taken into account. In fact, these additional costs caused by complications and other unplanned events were almost €2,000 more in the medical group. When calculated for a single patient on the basis of intention-to-treat, the difference was €34. Furthermore, the incremental cost-effectiveness ratio shows that by investing €1,688 more in the surgical treatment it is possible to have an additional 12 pain-free patients, 7 patients satisfied with the treatment and 5 successfully treated patients without additional curettage, the corresponding costs per patient being €141, €241 and €338, respectively.

In the MIST trial, the medical and expectant groups had significantly more unplanned admissions and unplanned curettages (Petrou et al. 2006). The results of this study are congruent with the MIST trial (Petrou et al. 2006), even though in the present study only the direct hospital costs (clinical management pathway for producing the treatment containing lightning, rent, heat, cleaning and salaries) were calculated, and not the indirect costs (e.g. costs of lost production).

The overall incidence of complications was similar in both groups. However, in the medical group more patients were treated in the ward, whereas surgically treated patients had more additional visits to the outpatient clinic. The differences in the inpatient days were also notable, but the differences were not statistically significant. As described in study III, surgically treated patients were more
satisfied with the treatment and experienced less pain following the treatment. All these findings indicate that adverse events were more severe in the medically treated group. However, the majority of the medically treated patients were also satisfied and their recovery was uncomplicated.

The medical method offers a good alternative for surgical treatment, but the risk of incomplete expulsion of the retained products of conception and the experience of pain are greater than with surgical treatment. The type of miscarriage, which evidently affects the success of the treatment as well as the costs (Petrou et al. 2006), was not analyzed in the present study. However, offering only the medical method because of the lower primary costs for the provider is not ethically justified.
7 Summary and conclusions

1. Altogether 14.2% of women undergoing abortion between 2000 and 2005 registered a repeat procedure. The risk of repeat abortion was associated with various sociodemographic characteristics, such as young age, parity, previous abortions, lower socioeconomic status and being single or cohabiting. The method of abortion was not a risk factor of repeat termination of pregnancy.

2. In the present nationwide cohort, complete abortion rates were 94.1% and 99.6% in the medical and surgical cohorts, respectively. Medical termination of pregnancy was associated with a 4-fold incidence of adverse events. Hemorrhage and incomplete abortions were more common following medical abortion. The incidence of infections did not differ between the cohorts. The impact of these findings needs to be considered when assessing the overall efficacy and cost-benefit ratio of different methods of abortion.

3. Medical treatment of miscarriage was an effective alternative to surgical treatment and increases the choices available to women. Surgical treatment seems to be associated with more infections. The present study suggests medically treated patients to be more painful and dissatisfied with the care than those treated surgically, although the majority of both medically and surgically treated women were satisfied with the treatment.

4. The primary costs of surgical treatment of miscarriage were higher when using direct hospital costs (institutional prices). Adverse events were more common after medical treatment and increased the secondary costs. In theory, by investing €1,688 more by treating all the patients surgically, 12 patients with pain, 7 patients dissatisfied with the treatment and 5 patients with surgical re-evacuation would have been avoided according to ICER. When summarizing the primary and secondary costs of the treatment, neither of these two methods was economically superior. Based on the present study, the role of economical aspects in choosing treatment for miscarriage should be minimal, and the choice of treatment should be made on an individual basis by respecting patients’ preferences.
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