The Clinical Appearance of Pelvic Inflammatory Disease in Relation to Use of Intrauterine Device in Latvia

A Study with Special Emphasis on Factors Influencing the Clinical Course of PID in IUD Users

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Dissertation presented at Uppsala University to be publicly examined in Rosénstaden, Kvinno-och Barnkliniken, SE-751 85 Uppsala, Friday, March 31, 2006 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English.

Abstract

The objectives of this case-control study, investigating 51 in-patient women with acute pelvic inflammatory disease (PID) and 50 healthy women attending for routine gynecological check-up, were to investigate the background and reproductive history of women, who are considered at low risk of sexually transmitted infection presenting with PID, to examine whether intrauterine device (IUD) use per se and long use affects the microbiology and clinical course of the disease, to identify risk factors for PID and to examine whether IUD use is an independent risk factor for PID.

The most striking difference regarding the background and reproductive history between women with PID and healthy women over age 25 were related to socio-demographic factors and not to common risk factors for PID.

There was little difference between healthy women and women with current PID with regard to single microbes. The finding of combinations of several anaerobic or aerobic/anaerobic microbes appeared to be associated with PID, particularly in women over 35. The pathogenesis of non-sexually transmitted PID appears to be associated with a synergistic effect between several pathogens, possibly facilitated by the presence of an IUD.

IUD use per se was associated with an increased risk of PID in women 35 and older. There was an association between IUD use and complicated PID in women over 35, which was possibly influenced by long-term IUD use. Age over 35 and IUD use, independently of each other, were associated with an increased risk of failed conservative treatment, necessitating surgery in patients with PID.

An observational study showed that Latvian obstetrician-gynecologists participate actively in contraceptive counseling and are very experienced with regard to IUD use. Physicians' attitudes and perceptions towards IUD are generally positive and their clinical considerations are in good agreement with that of doctors in other countries. Antibiotics are widely used around IUD insertion by doctors, possibly driven by a liberal attitude towards IUD use in women with a potential risk of STI. The study could identify some possible gaps in the theoretical knowledge about the IUD and other methods.

Keywords: pelvic inflammatory disease, complicated pelvic inflammatory disease, contraception, intrauterine device, reproductive history, microbiology, anaerobes, surgery, gynecologist, practice

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ISSN 1651-6206
ISBN 91-554-6471-8
urn:nbn:se:uu:diva-6458 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-6458)
Scio me nihil scire ex Socrates
(I know that I know nothing)
List of publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


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Abbreviations

AM  adnexal mass
CDC  Centers for Disease Control and Prevention
CI   Confidence interval
COC  combined oral contraceptive
CRP  C–Reactive Protein
Cu-IUD  copper intrauterine device
DNA  Deoxyribonucleic Acid
EC   emergency contraception
ESR  Erythrocyte sedimentation rate
IUD  intrauterine device
LNG-IUD  levonorgestrel intrauterine device
NE   not estimated
n.s. not significant
OR   Odds ratio
PI   Pearl Index
PID  pelvic inflammatory disease
STI  sexually transmitted infections
spp. species
TOA  tuboovarian abscess
vs.  versus
WHO  World Health Organization
WHS  Women’s Health Study
Introduction

Pelvic inflammatory disease

Probably one of the earliest clear descriptions of pelvic inflammatory disease (PID) was presented by Mauriceau in 1683, who described puerperal infection with inflammatory resistances and abscesses on the sides of the uterus (Viberg 1964). One of the first descriptions of acute PID caused by gonococci, discovered by Neisser in 1879, was given by the Swedish gynecologist Westermark in 1886 (Westermark 1886). As PID has remained an important issue for women’s reproductive health, many studies relating to etiology and risk factors, pathogenesis and diagnosis, treatment and sequelae of this clinical condition have been carried out since then.

At first glance, the question ‘what is PID’ seems so easy to answer, particularly if you consult the text book. The question becomes more difficult and complicated for the practicing clinician as it is apparent that PID can have various clinical characteristics as well as different etiological background and there is no clear definition of the condition. In most cases, PID results from ascending spread of microorganisms from the vagina and endocervix to the upper genital sites. Because PID encompasses a wide variety of pathologic processes and many etiologic agents, it has a broad clinical spectrum that includes acute PID, silent PID, atypical PID, the PID residual syndrome or chronic PID, postpartum/postabortal PID. Individual cases of PID can also be more specifically defined by the site(s) of the disease (i.e. endometritis, salpingitis, salpingo-oophoritis), or the etiologic agent(s) involved (i.e. those that cause chlamydial endometritis, gonococcal salpingitis, non-chlamydial/non-gonococcal salpingo-oophoritis) (Centers for Disease Control and Prevention 1991).

Microbial etiology and pathogenesis of PID

Multiple microorganisms have been implicated as etiological agents for the development of the disease, and most cases are associated with more than one microbe (Eschenbach et al. 1975; Sweet et al. 1981; Mårdh 1984; Weström 1987; Kirshon et al. 1988; Dan et al. 1993; Heinonen and Miettinen 1994; Soper et al. 1994; Bevan et al. 1995; Weström and
Eschenbach 1999). It is now clearly established that existence of sexually transmitted microbes in the female genital tract is one of the main etiological factors for acquisition of PID (Mårdh 1984; Weström 1987; Hoosen et al. 1989; Soper et al. 1992; Heinonen and Miettinen 1994; Soper et al. 1994; Bevan et al. 1995; Weström and Eschenbach 1999). *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the most important causative organisms associated with PID, accounting for 60–80% of cases in women less than 25 years of age (Mårdh 1984; Weström 1987; Kirshon et al. 1988; Hoosen et al. 1989; Soper et al. 1992; Soper et al. 1994; Bevan et al. 1995; Weström and Eschenbach 1999). In different studies investigating the microbial etiology of PID, the proportion of women with PID who are reported to be infected with *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* is very variable, probably due to variations among the populations studied, differences in used methods of microbial investigation, variations in the severity of the disease, sampling technology and site of sampling. Additionally, a wide variety of anaerobic and aerobic (facultative) bacteria as *Bacteroides* spp., *Fusobacteria* spp., *Streptococcus* spp., *Peptostreptococcus* spp. and others are recognized as playing an etiologic role for PID, especially in severe PID cases, also in cases where the classical sexually transmitted infection (STI) agents were not detected or could not be proved in suspected cases (Eschenbach et al. 1975; Sweet et al. 1981; Creatsas et al. 1982; Mårdh 1984; Brook 1986; Weström 1987; Kirshon et al. 1988; Dan et al. 1993; Heinonen and Miettinen 1994; Soper et al. 1994; Bevan et al. 1995; Murdock 1998; Walker et al. 1999; Weström and Eschenbach 1999; Brook 2002). *Mycoplasmas* have also been recovered from the female genital tract in PID cases, but their role is still less clear and questionable (Stray-Pedersen et al. 1982; Chatwani et al. 1996; Taylor-Robinson and Furr 1997; Arya et al. 2001; Simms et al. 2003). Similarly, the role in PID etiology of *Actinomyces* remains enigmatic. *Actinomyces*, which normally reside in the female genital tract, are quite often found in severe PID cases with tuboovarian abscesses (TOAs), especially in women with long IUD use (Cleghorn and Wilkinson 1989; Evans 1993; Fiorino 1996; Lippes 1999). Isolates from patients with PID are mostly polymicrobial, however, in 20–30% of cases, no microorganisms are recovered (Weström and Eschenbach 1999).

Cervical infection is usually initiated by the invading microbial agents leading to an alteration of cervico-vaginal environment. This change is thought to facilitate the overgrowth of facultative vaginal microorganisms. The initial epithelial damage caused by the pathogens then allows the original pathogens and vaginal flora to ascend into the endometrium, fallopian tubes and peritoneal cavity, developing the inflammatory reaction in these anatomical structures, and as a consequence, the manifestation of disease (Keith et al. 1984; Keith et al. 1986; Weström 1987; Cates, W, Jr et
al. 1990; Rice and Schachter 1991; Weström and Eschenbach 1999). At the same time, the classic descriptive model of PID omits any direct statement that sexual intercourse, where spermatozoa may serve as vector of pelvic infection, leads to the development of lower genital or cervical infection which, as a consequence, may ultimately develop into PID. Acute PID is a rarity in women who are not sexually active. Non-canalicular spread of cervical infections has also been observed, possibly extending via parametrial lymphatics (Keith et al. 1986; Weström and Eschenbach 1999). At least four additional factors could contribute to the ascent of microbial pathogens and/or be associated with the pathogenesis of PID. First, any uterine instrumentation may facilitate upward spread of cervical and vaginal microflora, thereby explaining PID occurring, i.e. after IUD insertion (Farley et al. 1992) or as a post-abortion complication (Duthie et al. 1987; Cates, W, Jr et al. 1990; Penney 1997; Weström and Eschenbach 1999). Second, the hormonal changes during menses, as well as menstruation itself, leads to cervical alterations that result in a loss of mechanical preventing barrier, and also decreased bacteriostatic effect of the cervical mucus at the onset of menses (Keith et al. 1986; Sweet et al. 1986; Weström 1987; Cates, W, Jr et al. 1990; Weström and Eschenbach 1999). Third, retrograde menstruation may be a contributing factor to the ascent of bacteria to the tubes and to the peritoneum (Keith et al. 1986; Weström and Eschenbach 1999). Finally, individuals have different immune response (poor or strong) to invading microorganisms, which may affect the spread and manifestation of virulence factors of any microbial pathogen (Cantor 1982; Belec 2002; Relman 2002; Fairweather and Rose 2004).

There are some established demographic and social indicators of the risk for having PID. These factors are closely associated with the risk for acquisition of STI and, therefore, development of PID. Commonly reported risk factors for STI and PID are young age, unmarried status, multiple sexual partners and having a new partner, smoking, practicing vaginal douching, use of non-barrier contraceptive methods and having a history of a prior PID and/or STI (Newton and Keith 1985; Keith et al. 1986; Forrest et al. 1989; Cates, W, Jr, 1990; Cates, W, Jr et al. 1990; Marchbanks et al. 1990; Wölner-Hanssen et al. 1990; Aral et al. 1991; Lee et al. 1991; Aral et al. 1992; Scholes et al. 1992; Scholes et al. 1993; Jossens et al. 1996; Aral and Wasserheit 1998; Simms et al. 1999; Weström and Eschenbach 1999; Suss et al. 2000; Martino and Vermund 2002). Additionally, low education, unemployment, and low income as measures of socioeconomic status as well as urban residence have been associated with an increased risk of PID (Simms et al. 1999; Pelayo Vera et al. 2002; Olowokure et al. 2004). However, the extent of the relationship between PID and those risk factors is not very well known. Many women with an apparent increased risk of PID, because of presence of one or several of those risk factors, will never develop PID,
whereas others, who do not at all fit a typical risk profile, will have PID. Moreover, in gynecological practice as well as in study reports, very little is usually known about the male partner and his health and socio-demographic status and behavioral risk factors, which are all likely to affect the risk of STI and PID in the individual woman.

Epidemiological aspects

PID carries a large burden of morbidity, requiring surgery and serious treatment in the acute phase and resulting in severe treatment requiring sequelae, such as infertility problems, ectopic pregnancy and pelvic pain syndrome. The actual prevalence and incidence of PID is indeterminable due to the fact that the disease is not always apparent. Careful investigations of infertile women without a history of PID have reported that in 64% up to 84% of the cases occluded tubes have been discovered, implying that PID is not infrequently silent (Sellors et al. 1988; Cates, W, Jr et al. 1993; The ESHR Capri Workshop group 2002; Sharma et al. 2003; Hubacher et al. 2004). Many uncomplicated cases of PID are poorly diagnosed and patients with suspected PID are usually treated in outpatient settings. Estimates of the true PID prevalence are therefore based predominantly upon complicated cases associated with in-hospital treatment. Surveillance and correct reporting of PID cases depend how the reporting system is organized. Available figures are mostly derived from industrialized countries and from regional studies or national surveys, or based on prevalence of STI. It has been estimated that the annual incidence of PID in women aged 15–45 is 10–13/1000, peaking at 20/1000 in women aged 20–24 (Weström 1980; Simms et al. 1999; Simms and Stephenson 2000). In the United Kingdom, PID accounts for 1.7% of general practice attendances of women aged 16–46 years (Simms et al. 1999). PID comes with heavy costs for health services as well as social and psychological costs due to serious sequelae, such as pelvic mass, fertility problems, and chronic pelvic pain (Keith et al. 1986; Rein et al. 2000; Yeh et al. 2003).

Diagnostic tools for PID

The correct diagnosis of PID is one of the most difficult and mostly discussed topics among clinicians because of the wide variation in symptoms and signs among women with this condition. This variability of symptoms can relate to inflammation of extragenital organs in the pelvis such as peri-appendicitis, peri-sigmoiditis, urinary tract infection etc. Many women with PID may exhibit subtle, vague, or mild symptoms that are not readily recognized as PID at all. However, the provisional subjective symptom or
complaint of an acute PID patient is lower abdominal pain of less than three weeks duration.

The diagnosis of PID, based on clinical findings, is imprecise. No single historical, clinical or laboratory finding has both high sensitivity and specificity for the diagnosis of PID (Hadgu et al. 1986; Kahn et al. 1991; Munday 2000). Studies in which laparoscopic confirmation was used have shown that from 30% up to 93% of women meeting the clinical and laboratory criteria in fact did not have PID, but another pathologic process (Jacobson and Weström 1969; Chaparro et al. 1978; Jacobson 1980; Sweet et al. 1981; Hager et al. 1983; Hadgu et al. 1986; Kahn et al. 1991; Soper et al. 1992; Dan et al. 1993; Morcos et al. 1993; Soper et al. 1994; Bevan et al. 1995; Eschenbach et al. 1997; Peipert et al. 1997; Munday 2000; Cibula et al. 2001; Eckert et al. 2002; Gaitan et al. 2002). However, laparoscopy as a diagnostic tool is often neither readily available for acute cases due to high cost, associated risks and infrequent use of laparoscopy in certain clinical settings nor easily justified when symptoms and signs are mild and/or vague. Moreover, laparoscopy will not detect endometritis and may not identify mild intratubal inflammation (Peipert et al. 1997; Gaitan et al. 2002). Consequently, the diagnosis of PID is often based on combinations of diagnostic clinical and laboratory findings, supplemented with results of cultures or non-culture tests of samples obtained from the endocervix, which improve both sensitivity and specificity (Hadgu et al. 1986; Teisala and Heinonen 1990; Kahn et al. 1991; Miettinen et al. 1993; Peipert et al. 1996; Reljić and Gorišek 1998; Reljić and But 1999; Munday 2000; Hall et al. 2004). According to CDC (2005), minimum criteria for clinical diagnosis of PID in the absence of competing diagnoses (e.g., positive pregnancy test, acute appendicitis) are (Centers for Disease Control and Prevention 1991):

- lower abdominal tenderness,
- bilateral adnexal tenderness,
- cervical motion tenderness.

Among women with severe clinical signs, more elaborate diagnostic evaluation is warranted because incorrect diagnosis and management may cause unnecessary morbidity. Thus, additional criteria should be used to increase the specificity of the diagnosis. Routine criteria are those that are simple to assess; elaborate criteria are more definitive but are more expensive and often invasive. Criteria are presented in Table 1. Although not necessary to justify initial treatment decisions, bacteriologic diagnosis is helpful. It provides diagnostic confirmation (thereby improving management and reinforcing the need to treat sex partners) and serves as baseline for test-of-cure cultures. Tests recommended for all suspected cases of PID are (Centers for Disease Control and Prevention 1991):
• cervical cultures or non-culture test for *Neisseria gonorrhoeae*,
• cervical culture or non-culture test for *Chlamydia trachomatis*.

Table 1. Additional criteria useful in diagnosing PID

<table>
<thead>
<tr>
<th>Routine</th>
<th>Elaborate</th>
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<tbody>
<tr>
<td>• oral temperature &gt;38º C</td>
<td>• histopathologic evidence on endometrial biopsy</td>
</tr>
<tr>
<td>• abnormal cervical or vaginal discharge</td>
<td>• tubo-ovarian abscess on sonography</td>
</tr>
<tr>
<td>• elevated Erythrocyte sedimentation rate and/or C–Reactive Protein</td>
<td>• laparoscopy</td>
</tr>
<tr>
<td>• culture or non-culture evidence of cervical infection with <em>Neisseria gonorrhoeae</em> or <em>Chlamydia trachomatis</em></td>
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</tbody>
</table>

Recently, Almog et al (2005) reported enhanced erythrocyte aggregation in PID cases and recommended that this variable should be further evaluated as a diagnostic tool in the context of this frequent disease (Almog et al. 2005).

Most studies are too small to be used as an evidence base for the formulation of diagnostic criteria for PID. In a recent study (2003) Simms et al used the largest available data set of acute PID of Lund University, Sweden, collected between 1960 and 1984, and which, due to its large size, was considered to provide an evidence base. They evaluated the clinical and laboratory presentation in women with laparoscopically confirmed PID as well as in women without laparoscopic confirmation. The study showed that there was insufficient evidence to support clinical diagnostic criteria without laparoscopy, but, at the same time, discussed about the limitations of the Lund dataset for the formulation of diagnostic guidelines for PID. The authors concluded that a new evidence base is urgently needed but this will require either new investigations of the correlation between the clinical presentation and PID based on a laparoscopic ‘gold standard’, or the development of new diagnostic techniques or a laboratory tests as markers for PID (Simms et al. 2003).

**Intrauterine contraception**

It is well established that the intrauterine contraceptive device (IUD) is one of the most effective, reversible, safe and for long-term use contraceptive
methods, the prototype of which was already reported in 1909 (Mishell 1998; Rivera and Best 2000; Thiery 2000; Bilian 2002; FFPRHC Guidance 2004). The early modern IUDs were made of plastic and when intrauterine administration of copper was reported to dramatically reduce the number of implantation sites in rabbits, that discovery resulted in the development of IUDs medicated with copper (Zipper et al. 1969). Copper IUDs were a great improvement, because, not only were they more effective than inert plastic IUDs with significantly lower pregnancy rates, they also were smaller and, therefore, caused less bleeding and pain. Most early copper-bearing IUDs carried a copper surface area of around 200 mm\(^2\) copper. Further clinical research resulted in the development of copper IUDs with a higher load of copper, 300–380 mm\(^2\), which were significantly more effective in preventing pregnancies than early copper IUDs and also effective for longer periods (WHO 1997).

The use of IUD varies considerably between regions of the world as well as between the countries in the region or in the country itself. According to Family Planning Worldwide 2002 Data Sheet, 56.3% in Uzbekistan, 48.5% in North Korea, 43.5% in Cuba, 42% in Kazakhstan, 41.2% in Vietnam, 39% in Turkmenistan, 38.2% in Kyrgyzstan, 36.4% in China, 34.5% in Moldova and 33.1% in Russia were IUD users among currently married women using family planning in 1999–2001. The corresponding figures were in the USA only 0.7%, in Brazil 1.1%, in Australia 2%, in Canada 3%, in the Netherlands 3.6% and in the United Kingdom 5% (Family Planning Worldwide 2002 Data Sheet 2003). IUD use has many advantages as a contraceptive method in terms of effectiveness, ease of use, low cost, long duration and reversibility. Nevertheless, there are some possible complications associated with the use of IUDs that have made this effective contraceptive method unpopular in some countries.

One of the main concerns relating to IUD use is whether it is associated with the development of PID. Already during the 1920s, when the Gräfenberg ring IUD was introduced, and ever since, PID has been discussed in relation to IUD use, the main issue being whether the use of IUD increases a woman's risk of PID, independently of other risk factors for the disease. The severe cases of PID occurring in women with the Dalkon Shield type IUD in the 1970s in the USA and some other countries have created great concern about the increased risk of PID associated with the use of IUD (Westrom et al. 1976; Burkman 1980; Buchan et al. 1990). In the early 1990s, the World Health Organization (WHO) performed a meta-analysis of data from 13 multi-country clinical trials and concluded that the risk of PID was more than six times higher during the 20 days following IUD insertion than during later time (Farley et al. 1992). In 1991 Kronmal et al reanalyzed data from the large the Women’s Health Study (WHS), carried out in 1976–1978 in the
USA, which had reported that IUDs increase the risk of PID. In the reanalysis, however, Kronmal et al concluded that the WHS in fact showed the opposite, no increased risk (Kronmal et al. 1991). Shelton presented his calculations regarding the risk of clinical PID attributable to an IUD and showed that the absolute risk is very low, even below 1% in a high STI setting (Shelton 2001). The findings indicate that development of PID is most strongly related to the insertion process and to the background risk of STI but not to continued IUD use or to use in women at low risk of STI. However, discussions regarding this topic have not ceased among professionals (Pettiti 1992; Toivonen 1993; Beerthuizen 1996; Burkman 1996; Hicks 1998; Gareen et al. 2000; Grimes 2000; Cox 2003; Gareen 2003). Safety concerns and litigations regarding the Dalkon Shield IUD and PID, originating in the 1970s, continue to taint the reputation of all IUDs among doctors and women, even now, 30 years later, despite existing reassuring data about the safety of IUDs in women at low risk for STI.

A second issue is whether the IUD influences the manifestation and clinical course of PID when PID occurs in a woman with an IUD in situ. Few studies have addressed this issue and different conclusions can be drawn (Paavonen and Vesterinen 1980; Söderberg and Lindgren 1981; Stadel and Schlesselman 1984; Edelman et al. 1990; Jossens et al. 1994).

Thus, the issue whether there is an association between IUD and PID risk as well as the issue whether IUD use affects the clinical course of a PID are important not only for the individual woman, but also for the clinician, who diagnoses and treats cases of PID and also is in a position to promote or discourage wide spread use of IUD in the society.

PID and IUD use in Latvia

Severe acute PID is still a common diagnosis at Women's Hospitals in Latvia, a country with a population of around 2.3 millions and where IUDs are widely used. However, there are no reliable statistical data regarding the prevalence or incidence of PID in Latvia. This clinical diagnosis is not reported to the Health Statistics and Medical Technology State Agency of Latvia. The only official statistical source that could be indirectly related to PID is the Register of Sexually Transmitted Diseases. The female morbidity with Neisseria gonorrhoeae and Chlamydia trachomatis as reported to that agency is presented in Table 2. This register contains only aggregated data on Neisseria gonorrhoeae and Chlamydia trachomatis based on data collected on special cards and reported from both outpatient and inpatient health care institutions. The register contains no information about the clinical manifestation of the infection. Moreover, it is not known whether the
Table 2. Female morbidity with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* according to the Register of Sexually Transmitted Diseases of Latvia, 1998–2004

<table>
<thead>
<tr>
<th>Year</th>
<th><em>Neisseria gonorrhoeae</em></th>
<th></th>
<th></th>
<th><em>Chlamydia trachomatis</em></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute No.</td>
<td>per 1000 000 women</td>
<td></td>
<td>Absolute No.</td>
<td>per 1000 000 women</td>
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</tr>
<tr>
<td>1998</td>
<td>357</td>
<td>27.5</td>
<td></td>
<td>659</td>
<td>50.7</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>324</td>
<td>25.1</td>
<td></td>
<td>296</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>225</td>
<td>17.6</td>
<td></td>
<td>216</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>151</td>
<td>11.9</td>
<td></td>
<td>194</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>153</td>
<td>12.1</td>
<td></td>
<td>187</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>113</td>
<td>9.0</td>
<td></td>
<td>150</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>122</td>
<td>9.8</td>
<td></td>
<td>164</td>
<td>13.1</td>
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</table>

Reporting from physicians is correct and complete and, therefore, the credibility of data could be questioned. The system of reporting is currently under reorganization in Latvia.

The second source for obtaining data about morbidity related to PID is the Health Compulsory Insurance State Agency that is the institution for health care financing and payments. This agency provides funding to the state and municipal health care outpatient and inpatient institutions, according to reported diagnosis of treated cases. However, these data will exclude cases diagnosed and treated in the outpatient private health care sector whose expenses are covered by the patients themselves or private health insurance agencies. The outpatient private health care sector, especially in gynecology, has a tendency to become increasingly popular among women in Latvia. Furthermore, STI diagnosed patients, when privately funding their treatment, allegedly often ask doctors to not report on the infection in fear of inadequate confidentiality provision. Therefore, in-hospital based data (all Women’s Hospitals in Latvia are public) regarding PID appear the most reliable to use and those data are, since 2004, obtained from the computerized system for payments. The available data from 2004 are presented in Figure 1.

Some additional information regarding PID in Latvian women is available from two national surveys ‘Reproductive health of the population of Latvia’ carried out in 1997 and 2003, surveying randomly 2990 and 1251 women aged 15 to 45, respectively. In both surveys, questionnaires included questions regarding PID morbidity history. In 1997, 27.5% and, in 2003, 31% of respondents reported that they had had an episode of PID in their lives (UNDPA 1998; UNFPA 2004). In the survey in 2003, 13.8% of women admitted having had some STI in their lives, and 31% of them acknowledged having had *Chlamydia trachomatis* and 14% *Neisseria gonorrhoeae*.
Latvia lacks reliable and objective statistics on used contraceptive methods and their prevalence. Only the two surveys offer valuable information on the use of contraceptives. Contraceptive methods are used by 81–90% of sexually active and fertile women (UNFPA 2004). The most popular contraceptive methods are male condoms, hormonal contraceptive pills and intrauterine devices (UNFPA 1998; UNFPA 2004). According to the survey in 1997, 20.3% of women aged 15–45 were IUD users and 16% of men reported that their partners were IUD users (UNFPA 1998). Most IUDs used in Latvia are copper IUDs with a copper surface area of 375–380 mm².

Aim of the study

No study relating to PID and IUD use has been performed in Latvia and few data are available on practices around IUD use. Thus, there is a need for new information on the epidemiology of PID as well as data on IUD use, derived from this region, to provide a basis for advice for clinical practitioners. Based on a clinical impression that PID is more often detected and more severe in IUD users than in non-users, an impression that appears to be in conflict with data in the literature, the study was designed to investigate the current situation with regard to PID risk in women using IUD in Latvia.

Figure 1. Absolute numbers of treated acute PID cases (inpatient and outpatient) in Latvia according to the data from the Health Compulsory Insurance State Agency of Latvia, 2004
Objectives

- to investigate the background and reproductive history of women presenting with PID
- to examine whether IUD use *per se* affects the microbiology and/or the initial status and/or clinical course of the disease
- to identify risk factors for PID and to examine whether IUD use is an independent risk factor for PID
- to determine whether the clinical course of a PID is different in women using IUD as compared with non-users
- to investigate the professional activity and perceptions of intrauterine contraception among Latvian obstetrician-gynecologists
Material and Methods

The study design I

The study was designed as a case–control study. Cases were recruited among women admitted to hospital with a diagnosis of acute PID. Cases were selected according to the following inclusion criteria: women aged 25–45, admitted to hospital for acute PID with clinical criteria as described in Table 3. Women, who were healthy and attended outpatient clinics for routine gynecological check-ups without any complaints served as controls. Healthy controls within the same age range (25–45) were selected among consecutive healthy visitors to the clinics. Traditionally in Latvia, women are recommended to have a routine check-up by a gynecologist, including PAP-smear and smear for Gram-staining, annually. If the case or control woman was an IUD user, the IUD use had to exceed one month in order to avoid any insertion related complications. Exclusion criteria for both cases and controls were pregnancy within the previous three months, use of glucocorticoids and antidiabetic drugs, or current use of antibiotics. Between December, 1998, and January, 2001, all women admitted to Riga 1st Hospital, Dzelzcelnieku Hospital and Lags-Centrs Hospital (Riga, Latvia), who were diagnosed with acute PID according to the protocol criteria, were invited to participate in the study by a gynecologist on duty. The purpose of the study was presented orally to every eligible woman by the doctor, and, before admission to the study, she was asked to sign an informed consent form. In total, 54 cases were identified and approached initially. However, three women were subsequently excluded: one woman refused to participate, in two women the clinical diagnosis was changed after surgery to appendicitis and to ectopic pregnancy, respectively. Finally, 51 sick women,

Table 3. Diagnostic criteria for acute PID

|   | lower abdominal pain
|---|-abnormal discharge from cervix
| 3 | adnexal tenderness, cervical and uterine motion tenderness, palpable mass at gynecological examination
| 4 | at least one out of three of the following laboratory signs:
|   | • leukocyte count ≥8000/mm³
|   | • Erythrocyte sedimentation rate ≥12 mm/h
|   | • C–Reactive Protein ≥10 mg/l
diagnosed with PID were involved in this study as cases. During the same time period, among all healthy consecutive clinic visitors, 50 women, who met the inclusion and exclusion criteria at the outpatient clinic, were invited to participate as controls by the principal investigator of the study during her work hours. None of the invited women refused to participate.

A complicated PID case was defined upon the clinical findings at admission of a palpable adnexal tumor (bilateral or unilateral) and elevated body temperature and at least one of three of the following laboratory signs: leukocyte count ≥10 000 /mm³, Erythrocyte sedimentation rate (ESR) ≥15 mm/h or C–Reactive Protein (CRP) ≥20 mg/l and also defined as complicated if treatment subsequently required surgery (unilateral or bilateral salpingectomy or adnexectomy). The records of the 51 sick women were reviewed retrospectively, and, according to the above mentioned definition, we constituted two PID groups: an uncomplicated PID case group (n=24) and a complicated PID case group (n=27).

After hospital discharge, all records of the 51 patients were retrospectively reviewed, and we constituted two PID outcome groups: those requiring surgical treatment during hospital stay (n=17) and those treated conservatively with antibiotics (n=34).

All the participants were asked to complete a structured questionnaire containing 60 questions about their sexual behavior, contraceptive use, reproductive and gynecological and medical histories with given closed answers, either during the outpatient visit (controls) or during the hospital stay (patients). The language of the questionnaire was Latvian or Russian and the women were asked to select the most appropriate for them. The questionnaire was anonymous, only number-coded and collected by the principal investigator directly from the women in sealed envelopes. All the participants were informed orally and in a written consent form about anonymity and non-disclosure of their sensitive private information to any person.

At admission, all women, both cases and controls, underwent a gynecological examination, and endocervical specimens for microbiological investigation were obtained. Specimens were number-coded according to the case/control questionnaire, collected and transported by the principal investigator. For transportation of bacteriological material transport-media (‘Amies’) with charcoal was used. Transportation time did not exceed 12 hours. For identification of Deoxyribonucleic Acid (DNA) of *N.gonorrhoeae* and *C.trachomatis*, material was transported in the medium (‘Digene’). Material from endocervix was Gram-stained, cultured and DNA of *N.gonorrhoeae* and *C.trachomatis* was identified. Microbiological analysis
was performed at the Department of Microbiology of Riga Stradins University and Laboratory of Virology of State Agency ‘Public Health Agency’. Methods used for identification of microorganisms are summarized in Table 4.

All cases (patients) were treated in-clinic and the clinical response to treatment was evaluated as cure: disappearance or improvement of presenting signs and symptoms by the end of therapy and at follow-up. The study process did not influence the patient's clinical course in hospital. The doctor responsible for a case had to complete three additional questionnaires regarding the clinical history, status and findings of the woman at admission, about the clinical course of the disease, the antibiotic therapy given, and the woman's clinical status at discharge from hospital. The doctor's questionnaires were number-coded according to the patient's questionnaire number; they were handed out and collected by the principal investigator.

Table 4. Identification methods of microorganisms

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaerobic bacteria spp.</td>
<td>bacteriological method, bacteria were incubated in Schaedler agar with 5% sheep blood in &quot;Genbag anaer.&quot; with further identification of biochemical properties and antigenic structure</td>
</tr>
<tr>
<td>Mycoplasma hominis, Ureaplasma urealyticum</td>
<td>bacteriological method, Mycoplasma Lyo medium, Bio-Merieux</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>bacteriological method, Trichosel broth, BBL</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>bacteriological method, Columbia blood agar, Bio-Merieux and Slidex strepto for identification of groups</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>bacteriological method, Columbia blood agar, Chapman's agar, Bio-Merieux and Slidex staphylo for identification of S.aureus</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>bacteriological method, Sabouraud chloramphenicol agar and API 32C system for yeast identification</td>
</tr>
<tr>
<td>Actinomyces spp.</td>
<td>bacteriological method, Columbia blood agar, Bio-Merieux</td>
</tr>
<tr>
<td>Gardnerella vaginalis</td>
<td>smear, Gram-stained</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae, Chlamydia trachomatis</td>
<td>DNA Digene C, G test (Hybrid Capture II System), general primers GP5,6</td>
</tr>
</tbody>
</table>
Data analysis I
The calculation of sample size with the statistical power 80% was based on the percentage of IUD use in Latvia's female population and the assumption, based on the clinical observation in Latvia, that approximately half of PID case women above 25 years age use an IUD. All data were analyzed and compared between groups using the Epi-Info 2000 and SAS statistical packages. Frequency tables were analyzed using chi-square and t-tests and Fisher's Exact test. Odds ratios calculations and testing were done using Wald’s test where appropriate. A p-value <0.05 was considered statistically significant in all analyses.

The study design II
An observational study was done, using an anonymous and structured questionnaire distributed among 231 specialists during the annual meeting of the Latvian Association of Obstetricians and Gynecologists in September 2003, at which the attendance was known. During that time, there were 484 specialists in obstetrics and gynecology registered and certified for legal practice in Latvia.

The questionnaire contained 28 questions about personal information on age, sex, working place, years of practice, daily work activities regarding contraception, detailed information regarding professional experience, perceptions and attitudes towards IUD in different clinical situations. Some questions covered theoretical knowledge about efficacy and main mechanism of contraceptive action of some contraceptive methods, including IUD. The final questions related to personal experience with contraceptive methods and personal attitudes to IUDs from a user point of view.

Data analysis II
All 122 returned questionnaires were included for analysis. For further analysis we divided the study sample according to gender, age below and above 45 years, and according to number of practice years below and above 15 years. Statistical analysis was done with Epi-Info 2002 statistical package. Most of the questions had categorical answers; therefore chi-square test was used for analysis of comparison groups according to gender, age, practice years, and p-value <0.05 was considered significant.
Ethical issues
The Ethical Committee of the Ministry of Welfare of Latvia and Uppsala University approved the study protocols.
Findings

Characteristics of women at low risk of STI presenting with pelvic inflammatory disease (Paper I)

The purpose of the study was to investigate whether an increased risk of PID could be found among typical IUD users, who are generally considered at low risk of PID, i.e. women older than 25 in monogamous relationships and therefore often counseled to use IUD. Women with PID (cases) differed significantly from healthy controls in that they were older (p=0.003), had shorter education (p=0.000003) and were more often unemployed (p=0.008) and were more often smokers (p=0.0009), also reported longer time since last pregnancy (p=0.009) and longer use of current contraceptive method than healthy controls (p=0.011).

However, there were no significant differences between cases and controls with regard to typical risk factors for PID such as age at first intercourse, number of lifetime sex partners, duration of current sexual relationship, and number of previous pregnancies and previous episodes of PID. IUD use was common in both cases (55%) and controls (40%) and this difference was not statistically significant. The study could not demonstrate that IUD use contributes in the development of acute PID.

Microbiology profile in women with pelvic inflammatory disease in relation to IUD use (Paper II)

The purpose of this report was to present the microbiological findings. There were no significant differences between healthy and ill women, between uncomplicated and complicated PID cases, or between IUD users and non-users in the PID group with regard to all detected aerobic microbes. IUD users among women with PID had significantly more *Fusobacteria* spp. and *Peptostreptococcus* spp. than did non-users with PID. *Lactobacillus* spp. was significantly less frequently found in the PID group than in the control group.
In order to test the hypothesis whether there is a synergistic effect between several microbes in the pathogenesis of PID, the five most frequently detected microbes were included in the analysis of various combinations. Among aerobic microbes *Staphylococcus* spp. and *Streptococcus* spp. and among anaerobes *Bacterioides* spp., *Fusobacteria* spp. and *Peptostreptococcus* spp. were included in the analysis. The finding of at least two anaerobic microbes was associated with a PID diagnosis (OR=2.8), the finding of at least three aerobic or anaerobic microbes was associated with an increased risk of PID (OR=2.4). The finding of at least two anaerobic microbes was associated with an increased risk of PID to be complicated (OR=4.0). Stratifying for age, the association between the finding of at least two anaerobic microbes or at least three aerobic or anaerobic microbes and the risk of PID or the risk of PID to be complicated appeared stronger in women over 35, however, not statistically significant.

In order to assess the role of IUD, and the duration of use, on the risk of PID, IUD users were analyzed separately from non-users with regard to microbial findings. The finding of at least two anaerobic microbes (OR=9.0) or at least three aerobic or anaerobic microbes (OR=4.0) in an IUD user was statistically significantly associated with PID. No statistically significant association was found between any combination of aerobic or anaerobic microbes and the risk of having a complicated PID. Stratifying data by duration of usage of IUD (<5 years and ≥5 years) did not reveal an overall higher risk in women with long (≥5 years) usage of IUD. Long duration of IUD use together with the finding of at least two anaerobic microbe appeared to be associated with an increased, although not statistically significant, risk of complicated PID (OR=3.0).

When IUD non-users were analyzed separately with the same approach there was no statistically significant OR for PID with any combination of aerobic or anaerobic microbes in the endocervix.

Thus, the study supports the hypothesis that the pathogenesis of non-STI PID is associated with a synergistic effect between several pathogens, possibly facilitated by the presence of an IUD.

‘Older’ age is a risk factor for pelvic inflammatory disease in IUD users (Paper III)

The aim of the study was to assess the role of an IUD *per se* in the development of PID and to study whether IUD use is an independent risk factor for PID, and for a PID to be complicated, in women who are generally
considered at low risk of STI/PID, i.e. women older than 25 and therefore often counseled to use an IUD.

The whole study group (n=101) was analyzed for risk factors for PID, using a univariate analysis. IUD use *per se* was not associated with an increased risk of PID in general. In the stratified analysis by age groups, IUD use in women ≥35 was associated with a risk of PID (OR=4.2). When adjusting for smoking, educational level, employment and microbial findings, the association with age ≥35 was still apparent, but became statistically non-significant.

To study factors associated with complicated PID, only PID cases (n=51) were analyzed. The risk of a PID to be complicated was strongly associated with IUD use in the univariate analysis (OR=8.5) as well as in the age group over 35 (OR=31.7) in the univariate stratified analysis. When adjusting for smoking, educational level, employment and microbial findings, IUD use remained a very strong independent risk factor for complicated PID (OR=6.8), and, after stratifying for age, in women ≥35 (OR=33.9).

To study the influence of the duration of IUD use on the risk of PID, only IUD users among cases and controls (n=48) were included in the univariate analysis. IUD use for ≥5 years as well as age ≥35 was associated with an increased risk of PID (OR=5.4; OR=6.8). When adjusting age and IUD use duration for each other, age ≥35 remained a significant risk factor for PID in IUD users (OR=4.9) but the association with long duration became non-significant.

In IUD users with PID (n=28), age ≥35 years was also a strong risk factor for a PID to be complicated in both the unadjusted and adjusted analysis (OR=12.7; OR=12.1). Long duration of IUD use was not associated with a significantly increased risk for a PID to be complicated in neither analysis. When adjusting for duration of IUD use and significant endocervical microbial findings, long duration of IUD use (≥5 years) was associated with a risk of PID (OR=4.4), but was less strongly associated with complicated PID when adjusted for microbiology findings. When additionally adjusting for age, the effect of IUD use for ≥5 years appeared strong, but significance vanished, whereas age ≥35 remained significantly associated with both PID and complicated PID (OR=5.01; OR=36.03).

The study results demonstrated that IUD use *per se* was not associated with PID in low-risk women younger than 35, but, in women over 35, IUD use was associated with an increased risk of PID. The study also demonstrated an association between IUD use and complicated PID in women over 35 and this association was possibly influenced by long-term IUD use.
The impact of age and intrauterine contraception on the clinical course of pelvic inflammatory disease (Paper IV)

The aim of the study was to investigate the clinical course of PID and factors that could predict failed conservative treatment of PID. Additionally, the study aimed to examine the role of age and IUD use on the severity of PID. Women who subsequently underwent surgical treatment were significantly older (p=0.0001) and significantly more often current IUD users (p=0.00009). Stratifying all women in the study by age, we found that women younger than 35 were significantly more often represented in the non-operated group (p=0.0009). After stratification of IUD users by age and IUD use duration, age and IUD use duration did not differ significantly between operated and non-operated groups.

There was no significant difference with regard to other socio-demographic characteristics. Women who subsequently underwent surgery had significantly more often complaints of severe abdominal pain, elevated body temperature (p=0.002) and symptoms of peritoneal irritation and appearance of adnexal mass (p=0.036; p=0.00006).

Microbial endocervical investigations showed significantly more frequent findings of aerobic microbes as *Streptococcus* spp. and *Ureaplasma urealyticum* in the operated group (p=0.045; p=0.034). No differences were found between groups with regard to anaerobic microbiological findings, nor with regard to the finding of *Actinomyces*.

Significantly higher mean leukocyte count and mean ESR at admission were found in the operated group (p=0.009; p=0.0007), whereas no difference in mean CRP was found.

Mean hospital stay was significantly longer for the operated women (p=0.0001), but assessment upon discharge as completely or almost healthy did not differ between those who were and those who were not treated surgically.

IUD use (OR=12.1) and age ≥35 (OR=12.5) were found to be highly significant risk factors for surgery in patients with PID.

Age over 35 and IUD use, independently of each other, were factors strongly associated with an increased risk of surgery for PID as a result of failed conservative treatment. Long duration of IUD use was not found to be associated with risk of being operated.
Practices and perceptions on intrauterine contraception among Latvian obstetrician-gynecologists (Paper V)

The questionnaire was completed and returned by 122 doctors, resulting in a response rate of 52%, representing nearly 25% of all obstetrician-gynecologists in Latvia. The sample included 88.5% (108) female and 11.5% (14) male doctors, closely corresponding to the total female/male ratio among obstetrician-gynecologists in Latvia, which is 88%/12%. The age range and mean age corresponded to the actual age distribution of the whole population of obstetrician-gynecologists. The mean work experience in the sample was 18.8±10.99 years.

Nearly every day consultancy regarding contraception was reported by 91.8% of the doctors whereas 8.2% of the respondents reported that they seldom consulted on contraception. There was no difference between physicians with regard to age or duration of practice. Most doctors (74.6%) inserted 1–5 IUDs per month, 6–10 insertions were done by 5.7% and 11 or more insertions were reported by 2.5% of the respondents. Few doctors routinely prescribed antibiotics immediately before or after IUD insertion whereas many did so sometimes. However, antibiotics were never prescribed before fitting an IUD by 50.8% and 36.9% of the respondents never prescribed antibiotics after insertion. STI was excluded before IUD insertion by taking a Gram-stained vaginal/cervical specimen (90.2%) and a careful history (58.2%). Special microbiological methods for the detection of *Chlamydia trachomatis* and/or *Neisseria gonorrhea* were used by 46.7%.

Never fitting an IUD in a nulliparous woman was reported by 30.3% and never fitting an IUD during lactational amenorrhea was reported by 29.5% of respondents. IUD insertion for emergency contraception had never been done by 57% of the respondents. A potential IUD candidate, who was not in a stable relationship with one partner, was definitely excluded by 9.8% of the respondents, whereas 59.8% of the doctors, who would fit an IUD in such a case, would fully inform about the risk of STI before insertion. Among the respondents, 32% had never inserted an IUD in a woman with a previous history of an ectopic pregnancy and 30.3% had never inserted an IUD in a woman with a previous history of PID.

Menorrhagia as the reason for removal was graded as ‘often’ by 18.9% and PID as ‘very often’ by 19.7% and ‘often’ by 17.2%. Experience of post-insertion (within one month) PID was reported by 4.9% as ‘often’, 65.6% as ‘seldom’ and 27% had never observed post-insertion PID during their practice. When asked about the causal relationship between IUD and PID, 52.5% responded positively whereas 32.8% of the gynecologists did not believe that IUD caused PID and 13.9% answered that they did not know.
There were no great differences between female and male doctors, but older and more experienced doctors more often did not answer the questions regarding Pearl Index of different contraceptive methods (p<0.05).

Personal experience of contraception was reported by 90.2% of the respondents. Combined oral contraceptives (COCs) had been used significantly more often by younger physicians and female doctors than by male doctors’ partners (p<0.05). With regard to emergency contraception (EC), condom and spermicides, ever use was reported significantly more often by younger than by older doctors, and ever use of copper-IUD was reported significantly more often by more experienced doctors (p<0.05). Current use of COCs, condom and spermicides was statistically more often reported by younger and less experienced doctors (p<0.05). Current use of copper-IUD use was significantly more often reported by male doctors’ partners (p<0.05). Among current and former IUD users, 93.4% reported that they were satisfied with the IUD as a contraceptive method.
Discussion

PID diagnosis

In the present study, the diagnosis of PID was based on clinical findings, strictly adhering to diagnostic criteria agreed upon in international guidelines (Hager et al. 1983; Hadgu et al. 1986; Centers for Disease Control and Prevention 1991; Kahn et al. 1991; Munday 2000), as, in Latvia, confirmation of the clinical diagnosis with laparoscopy is not routinely done. The diagnosis of PID in the present study is believed to be as accurate as is possible when clinical criteria are used. The in-patient care system in Latvia is strongly controlled by the Health Compulsory Insurance State Agency system and, due to limited funding, hospitalization of PID patients is only allowed for severe acute PID cases, diagnosed by experienced doctors. All patients were carefully examined at admission by a gynecologist and, for differential diagnosis purposes, culdocentesis was done in all, except one, of the PID patients and in most cases visually purulent material was recorded and sent for microbial examination. The results could not, however, be used for further data analysis. All women also underwent transvaginal ultrasonography for adnexal mass confirmation.

As reported in the literature (Teisala and Heinonen 1990; Kahn et al. 1991; Miettinen et al. 1993; Peipert et al. 1996; Reljić and Gorišek 1998; Reljić and But 1999; Munday 2000; Hall et al. 2004), elevated leukocyte count or ESR or CRP could be used for improving diagnostic accuracy of PID. Although no individual blood test or combination of blood tests can reliably diagnose PID, the finding of negative test result has a high sensitivity to rule out PID (Kahn et al. 1991; Miettinen et al. 1993; Peipert et al. 1996; Munday 2000). Miettinen et al (1993) looked at the ability of ESR and CRP to differentiate between mild, moderate and severe PID in women undergoing laparoscopy (Miettinen et al. 1993). They concluded that combined use of ESR and CRP is useful in assessing the severity of PID and could augment the clinical decision making regarding treatment. Halperin et al (2003) reported that significantly higher ESR at admission was associated with failed response to conservative antibiotic therapy in PID women with TOA (Halperin et al. 2003). Serial CRP and ESR were used as assessment of clinical success of conservative treatment of PID with or without TOA as reported by Reljić et al (1998 and 1999) (Reljić and Gorišek 1998; Reljić
and But 1999). Peipert et al (1996) evaluating laboratory tests commonly used to diagnose PID, concluded that elevated leukocyte count was the most specific laboratory indicator for upper genital tract infection (Peipert et al. 1996).

The severity of the disease in the present study is demonstrated also by the fact that one third of the PID cases subsequently underwent surgery as a part of the treatment (IV). Surgery as a treatment for PID was the final decision if conservative treatment failed during the first 1–3 days of hospitalization.

Thus, despite the fact that laparoscopy could not be used in the present study, the correct diagnosis of PID appears highly likely when clinical symptoms and laboratory findings as well as the clinical course were taken into consideration.

Risk factors for PID – differences between cases and controls

Contrary to what might have been expected, the study showed that risk factors for PID in the study population did not correlate to commonly quoted factors such as an early start of sexual life, high number of life time partners, recent new partner, having a history of a prior PID and/or STI (Newton and Keith 1985; Keith et al. 1986; Forrest et al. 1989; Cates, W, Jr, 1990; Cates, W, Jr et al. 1990; Wölner-Hanssen et al. 1990; Aral et al. 1991; Lee et al. 1991; Aral et al. 1992; Scholes et al. 1993; Jossens et al. 1996; Aral and Wasserheit 1998; Weström and Eschenbach 1999; Munday 2000; Suss et al. 2000; Martino and Vermund 2002). Thus, the most striking difference between women with PID and healthy women was related to socio-economic factors, such as short education and unemployment (I). Similar findings were recently reported from Mexico and England, also showing that PID was associated with low socio-economic status rather than occurrence of typical risk factors for STI (Simms et al. 1999; Pelayo Vera et al. 2002; Olowokure et al. 2004).

Previous studies have reported a relationship between PID risk and young age with the highest PID and STI prevalence found in younger women, closely associated with risk factors for STI acquisition (Weström 1980; Newton and Keith 1985; Weström 1987; Cates, W, Jr et al. 1990; Aral et al. 1991; Lee et al. 1991; Soper et al. 1994; Jossens et al. 1996; Aral and Wasserheit 1998; Munday 2000; Simms and Stephenson 2000; Suss et al. 2000). The present study was designed to investigate the influence of IUD use on PID and, therefore, the study population was restricted to women over age 25, an age below which IUD use is uncommon. It can be assumed
that the influence of typical STI related risk factors would have been more prominent, had younger women been admitted to the study (I).

An apparent potential weakness in the study, as in most other studies on PID, is the choice of control group and a selection bias of the control women, who were selected on the assumption that they were likely to be similar to the women with PID in most respects. Healthy women suitable to serve as controls to women with PID are always difficult to identify, especially in the absence of a population base from which control women could be selected (Hicks 1998; Gareen et al. 2000). There is no suitable population base in Latvia where such controls could be found. To reduce the risk of selection bias, only the principal investigator did the recruiting of controls, strongly adhering to the study protocol. The control women represented healthy women in general who followed the common national recommendation to have a routine gynecological check-up. According to a national survey in 1997, as many as 80% of Latvian women confirmed that they in fact go for gynecological check-ups once a year, which corresponds to our finding among healthy controls, whereas a little more than half of women with PID would attend (UNDPA 1998). However, both groups were similar with regard to previous gynecological morbidity and attendance to a gynecologist during the last year (I). It could be assumed that our controls represented women with a certain degree of health awareness and women with poor economy and/or less health awareness were probably under-represented. It could be postulated that women with low education or other negative socio-economic factors are less likely to seek early medical care, which might have prevented further progress of the disease.

The controls were not matched for age, except for falling within the age range of typical IUD users, i.e. 25–45 years, resulting in the cases being slightly older than controls (I). However, it is unlikely that the difference in age should influence the results, since there was little difference between the groups with regard to reproductive parameters (I). The finding that women in the PID group had a higher number of induced abortions than did healthy women, and more often had their last pregnancy more than five years ago, could be explained by the age difference between the groups. Moreover, other studies have reported high numbers of induced abortions among women in lower socio-demographic strata (Jones et al. 2002; Rasch et al. 2002; Addor et al. 2003; Elam-Evans et al. 2003).

The results, showing also that women with PID often smoke (I), correspond with data presented by others (Marchbanks et al. 1990; Scholes et al. 1992). It has been postulated that there may be an influence of cigarette smoking on the cervical mucus, affecting a woman’s risk of having an ascending infection (Scholes et al. 1992). This finding also suggests that women in the PID group might have had a lower degree of health awareness in general,
which was also indicated by their less frequent visits to a dentist and a
gynecologist (I, IV). Another possible sign of difference in health awareness
could be the finding that women in the healthy group reported more frequent
episodes of diagnosed genital infections in the past (I). However, among the
cases there was a high rate of ‘no/don't know’ answers, which does not
completely exclude previous episodes of genital infections in that group.
Moreover, the used diagnostic tools for detection of STI in the past might
not have been completely reliable.

A previous history of STI, as well as of PID, normally would increase the
probability of a subsequent PID episode and ectopic pregnancy (Weström
1980; Weström 1987; Cates, W, Jr et al. 1990). Around one third of the
women in both groups answered that they had suffered from PID in the past
(I). This diagnosis was not further confirmed, and might, therefore, represent
the woman’s subjective view. Additionally, a history of ectopic pregnancy
was extremely rare in both groups (I). As generally reported in the literature,
the first episode of PID in the majority of cases and controls in the study
population occurred before age 24 (Weström 1980) (I). Also in the study,
pelvic pain was the most commonly reported symptom at first PID episode,
which usually is reported to be the key symptom for the provisional
diagnosis of PID (Jacobson and Weström 1969; Jacobson 1980; Sweet et al.

A possible difference between women with PID and healthy controls, that
this study was unable to investigate - like almost any study relating to PID -
was the sexual history of the male partner. Knowledge about the male
partner, which was considered virtually impossible to obtain, would have
been both desirable and essential for better understanding the causes of PID.
The majority of women in both the case and control groups reported long
current relationships, a fact that does not rule out that those male partners to
women with PID might have had a more risky sexual behavior. In the
literature, no study on the sexual behavior of the male partner to women
suffering from PID could be found and only studies related to microbial
aspects in sex partners of women with PID were identified. Eschenbach et al
(1975), studied microbial etiology in 204 women with acute PID. Subsequent
contact tracing led to examination of sex partners to women with
cervical gonococcal infection, and N. gonorrhoeae was isolated from 38% of
asymptomatic partners and from 75% of partners with symptoms
(Eschenbach et al. 1975). Additionally, they examined partners to women
with negative cervical cultures and N. gonorrhoeae was isolated in 25% of
men with symptoms of urethritis and in 3% of men without symptoms.
Kamwendo et al (1993) reported the clinical and bacteriological findings in
current male partners of women hospitalized and treated for acute PID
(Kamwendo et al. 1993). In acute PID women infected with N. gonorrhoeae
and/or C. trachomatis, only 43% of male partners could be diagnosed with
N. gonorrhoeae or C. trachomatis infection. Non-specific urethritis was diagnosed in 34% of male partners to women with STI agents and in partners to PID women without a positive STI finding, 38% had non-specific urethritis. In the study by Kamwendo et al, the mean age of the PID women was 24.1 years whereas in the present study women were older.

Endocervical microbiology of PID

The mechanism behind the ascension of endogenous bacteria to the upper genital tract, thereby causing infection leading to disease, is still poorly understood. Despite the rapid progress made in the technology of bacteriology, few routine laboratories identify clinical isolates to species level. The present study also presents only genus level (II, IV). Simple methods for quantification of these microbes are needed, but, unfortunately, not yet well developed for ordinary routine laboratory facilities.

The low rate of common STI pathogens in the present study is believed to reflect that the study population represented women at very low risk of STI (I, II). It is unlikely that the low rate of common STI agents was due to methodological imprecision, since the DNA method used for the analysis is highly sensitive and specific for the detection of those sexually transmitted microbes (Girdner et al. 1999).

The study did not reveal differences in endocervical microbial flora between healthy and ill women, except that Lactobacillus spp. were found more often in the control group (II). Lactobacillus spp. is the dominant microbe in the vaginal/endocervical ecosystem of healthy women and acts as a defense factor inhibiting endogenous aerobic and anaerobic microbe overgrowth and colonization (Aroutcheva et al. 2001). Lack of this dominance could promote virulence activity of facultative pathogens in the vagina/endocervix and the development of PID, explaining the difference found between healthy and ill women (II).

There is considerable debate whether anaerobes can act as primary pathogens or only as secondary invaders when the urogenital tract is already damaged by STI agents, or whether they express their pathogenicity via a synergistic interaction with facultative organisms or other anaerobes (Brook 1986; Murdoch 1998). The finding of only one case with N. gonorrhoeae and none with C. trachomatis in the PID patients in the study tends to support a polymicrobial synergistic mechanism in non-STI PID development (II).

The microbial findings in the present study are in agreement with other studies with respect to the range of microbes and lack of clear difference with regard to single microbes between healthy and sick women (Creatsas et al. 1982; Kirshon et al. 1988; Dan et al. 1993; Heinonen and Miettinen 1994;
Walker et al. 1999; Weström and Eschenbach 1999; Halperin et al. 2003). The finding of combinations of several anaerobic or aerobic/anaerobic microbes associated with PID and with complicated PID (II), confirms that synergism between microbes, several of which are normally found in the female genital tract, plays a main role in the development of PID. Similarly, in other studies of non-STI PID, anaerobic or mixed anaerobic/aerobic microorganisms, obtained at culdocentesis or from cul-de-sac or tubes or adnexal masses at laparoscopy, have often been reported (Hoosen et al. 1989; Soper et al. 1992; Dan et al. 1993; Bevan et al. 1995; Weström and Eschenbach 1999).

Although there were more aerobic microbes such as *Streptococcus* spp. and *Ureaplasma urealyticum* in women who subsequently were operated (IV), endocervical microbial findings could not be used for prediction of the need for surgery, as most microbes found were part of the normal flora of the lower genital tract. In the literature, severe PID cases with actinomycosis and tubo-ovarian abscesses consistently are reported to require surgical treatment (Cleghorn and Wilkinson 1989; Evans 1993; Fiorino 1996; Lippes 1999). Although there were more detected cases of *Actinomyces* in the women requiring operation (IV), the study was not large enough to establish whether the difference was significant and, thus, the endocervical finding of *Actinomyces* could not predict the need for surgery in this study.

### Impact of IUD use on PID clinical course

The decision to collect data on women with the age restriction ≥25 was made to investigate if and to what extent IUD use could account for microbiological differences in endocervix and contribute to the etiology of PID and clinical course of the disease (II, III, IV).

There are no clear data about the prevalence and activity of microbes in the vaginal/cervical ecosystem in IUD users. Few studies have investigated bacteriological cultures of removed IUDs from PID patients and from asymptomatic women (Elhag et al. 1988; Lewis 1998; Tsanadis et al. 2000). A diversity of detected microbes has been reported and researchers have come to different conclusions. Haukkamaa et al (1987) examined the cervical flora of 18 healthy women before and 3–5 months after insertion of IUD and after long-term IUD use (3–5.5 years) in another 9 women (Haukkamaa et al. 1987). They revealed significantly more anaerobes in healthy long-term IUD users as compared to non-users. This finding correlates to some extent with the findings of the present study with regard to the anaerobes *Fusobacteria* spp. and *Peptostreptococcus* spp. in PID women with IUD (II). Thus, it appears as if IUD use could promote the growth of anaerobes. To what extent these anaerobes may play a role in the
development of PID is, however, not clear. A more clear picture regarding the role of an IUD in the microbial etiology of PID appeared after testing the hypothesis of synergistic effect between several anaerobic/aerobic microbes in the pathogenesis of PID in IUD users. IUD use *per se* together with combinations of anaerobic/aerobic microbes appears to facilitate the development of PID in IUD users, regardless of the duration of use (II). Moreover, the impact of IUD use on the microbial etiology of PID is supported by the finding that, among IUD non-users, no microbial combination affected the risk of PID (II). Additionally, IUD use *per se* was found to be a significant factor for a PID case to be complicated or in need of surgical treatment regardless of the duration of use (III, IV).

Those findings could to some extent be supported by the findings of Eckert et al (2002), who evaluated histologically proven endometritis as a clinical syndrome distinguished from laparoscopically confirmed salpingitis (Eckert et al. 2002). They concluded that among women with suspected PID, a diagnosis of endometritis-only was associated with an IUD *in situ*. Although current IUD use was not common in this study, this finding was confirmed even after stratification for the presence or absence of current endocervical STI or bacterial vaginosis. The authors noted that, to date, the natural history of endometritis remains unclear, and, in particular, the frequency with which endometritis cleared with menses or persisted but remained limited to the uterus or progressed into salpingitis.

Most studies on long usage of IUDs concern contraceptive effectiveness or the finding of *Actinomyces* (Løvset 1990; WHO 1990; WHO 1997; Bonacho et al. 1999). *Actinomyces* are part of the normal vaginal flora, but complicated PID, associated with *Actinomyces*, has been reported in the literature, especially among IUD users (Cleghorn and Wilkinson 1989; Evans 1993; Fiorino 1996; Lippes 1999). Understanding of the pathogenesis of pelvic actinomycosis and why it correlates with IUD use is poor and controversial. In the present study, there were too few cases of *Actinomyces* to show a clear impact on the development of PID, although *Actinomyces* were found slightly more often in IUD users with PID (II).

Modern copper-IUDs provide very effective contraception, especially for women in the later reproductive period and are generally recommended for long-term use (Edelman et al. 1990; Løvset 1990; WHO 1990; Bergsjo 1992; WHO 1997; Bonacho et al. 1999; FFPRHC Guidance 2004). Some copper-IUDs have been approved for more than 10 years of continuous use(WHO 1997; FFPRHC Guidance 2004). Moreover, women in their later reproductive years are often recommended by clinicians and by guidelines to continue using their current IUD until menopause, regardless of IUD labeling.
The present study could not confirm that long duration of IUD use was a particular risk factor for PID in general (II), whereas long duration was associated with a high risk of having a complicated PID, suggesting that the duration of IUD use still may be important (III). A few studies have reported that long duration of IUD use appears to increase the risk of PID and to complicate its clinical course, but those studies did not further analyze the role of IUD. Stadel et al (1984) studied the impact of long duration of IUD use in relation to surgical treatment in PID and found that five or more years with the same IUD increased the relative risk of surgery for PID, but this study was later criticized due to insufficient number of IUD users in the population (Stadel and Schlesselman 1984). Edelman et al (1990) analyzed risks associated with long-term IUD use in a review article of older studies, and, with regard to the risk of severe PID, stated that some studies show that the risk of complicated PID was increased with long duration of IUD use (Edelman et al. 1990). Farley et al (1992) stated that it is not known whether regular exchange of an IUD would modify the risk, whereas they showed that exchange of an IUD per se will increase the risk of insertion related infection (Farley et al. 1992). Halperin et al (2003) reported that long duration of IUD use could be a factor associated with failed response to medical treatment and severity of the disease (Halperin et al. 2003). Sørbye et al (2005) reported significantly longer mean IUD use duration in women with TOA as compared to those with uncomplicated salpingitis (Sørbye et al. 2005). Thus, the present study together with previous reports provide some evidence that long duration of IUD use can contribute to the severity of PID.

The finding that IUD use is associated with more severe PID is poorly understood. Apart from the fact that the IUD acts as a foreign body, resulting in a number of local effects in the endometrium (Stanford and Mikolajczyk 2002), continuous copper ion release results in the presence of products of copper corrosion in the uterus (Kjær et al. 1993; Bastidas et al. 2000; Beltran-Garcia et al. 2000). Some of the corrosion products have been reported to have not only spermicidal and anti-fertilization effect, but also bactericidal effect, particularly at the beginning stages of the corrosion process (Amla et al. 1993; Pradhan et al. 1997; Anjalika et al. 1999). There are scarcely any data in the literature on corrosion deposit formation of IUDs in relation to possible bacterial infection. It has been suggested that the formation of calcified deposits and incrustments on the device, due to a gradual corrosion process, may have a clinical significance, especially if bacteria are settled on them (Patai et al. 1998; Chretien et al. 2002; Berthou et al. 2003), a suggestion that would be expected to result in an association between PID and long duration of IUD use, which the present study could not entirely exclude (II, III, IV).
Impact of age on PID clinical course

The present study indicates that IUD use per se is not associated with PID in women younger than 35, but the results suggest that the risk of PID in women over 35 is higher in the presence of an IUD. Moreover, the presence of an IUD highly contributes for a PID to be complicated in women over 35 (III, IV). Those results are in line with other recent studies, suggesting that ‘older’ age is one factor that predisposes a woman with PID to be complicated (Dan et al. 1993; Heinonen and Miettinen 1994; Reljič and Gorišek 1998; Reljič and But 1999; Jamieson et al. 2000; Halperin et al. 2003; Sørbye et al. 2005).

Halperin et al (2003) reported that the mean age (39.6) of patients responding to conservative therapy was significantly lower than the mean age (45.5) of patients who did not respond (Halperin et al. 2003). Their entire study population was above 30 years. They did not analyze the role of IUD use in their study, although 50% in both responders and non-responders to conservative treatment were IUD users. Jamieson et al (2000), investigating women with PID, reported an association between age ≥35 and complicated PID (Jamieson et al. 2000). Reljič et al (1998 and 1999) studied laboratory parameters in the management of in-patient cases with severe PID and reported that the average age of the sick women was above 35 and more than 50% of them were IUD users (Reljič and Gorišek 1998; Reljič and But 1999). In a recent epidemiological study on hospitalization due to PID in Norway, Sørbye et al (2005) reported that women hospitalized for TOA and operated were significantly older (mean age 42) compared to the mean age of those hospitalized with uncomplicated salpingitis. More than half of the women hospitalized for TOA were IUD users, which was significantly more common than among those hospitalized with salpingitis (Sørbye et al. 2005).

Although not concluded by the authors, those results might again imply IUD as a risk factor for severe PID. In a hospital-based laparoscopy-proven acute PID study, Dan et al (1993) reported older mean age (34.4) of PID patients than had been found in previous studies. Severe PID was found in 50% of patients, and, moreover, 52.5% of women with PID were IUD users (Dan et al. 1993). A similar observation related to older age and IUD use for severe PID cases was reported by Heinonen et al (1994) in a laparoscopic study on the microbiology and severity of acute PID (Heinonen and Miettinen 1994). Additionally, Olowokure et al (2004) examined the relationship between age, material deprivation and hospital admissions for PID, and identified an increased relative risk of hospital admission in women aged 25–44 years (Olowokure et al. 2004). Despite the outlined limitations of this study, it indicated the importance of age for severe PID.
Impact on recommendations for IUD use in relation to study findings

The response rate of 52% of the distributed questionnaire was lower than expected (V) but did not differ substantially from that of similar studies in other countries, using postal surveys, reporting response rates between 35% and 75% (Makkonen et al. 1994; Gupta and Miller 2000; Stanwood et al. 2002). However, the number of completed questionnaires represented 25% of all practicing obstetrician-gynecologists in Latvia and the responding doctors corresponded well demographically to the whole population of Latvian obstetrician-gynecologists, supporting that the study participants were representative of Latvian obstetrician-gynecologists.

The professional activity of doctors regarding contraceptive counseling in general was high. The insertion rate of IUDs by Latvian obstetrician-gynecologists appears to be similar to that in Finland (Makkonen et al. 1994), a country where IUDs are widely accepted, and considerably higher compared to the situation in the USA, Canada and the UK (Russell and Love 1991; Stanwood et al. 2002).

The attitude of Latvian doctors on IUD use for emergency contraception, in nulliparous women, in women with postpartum amenorrhea or in women with a history of ectopic pregnancy corresponds with data from surveys from the UK, Australia, Turkey, the Netherlands and Finland (Makkonen et al. 1994; Weisberg et al. 1994; Reuter 1999; Gupta and Miller 2000; Vos et al. 2004; Zeteroglu et al. 2004).

The majority of Latvian obstetrician-gynecologists agree to insert an IUD in a woman who is not in a stable monogamous relationship. This apparent violation of current recommendations is compensated by active screening for STI, active information about the STI risk and a high degree of use of antibiotics around the insertion procedure, even when not demanded by clinical findings. Grimes et al (1999), in their meta-analysis of randomized controlled trials, concluded that there is no evidence for routine use of prophylactic antibiotics, nor is this a recommendation in current guidelines (Walsh et al. 1998; Grimes and Schulz 1999). However, they did discuss whether prophylaxis may reduce the risk of sub-clinical endometritis, which could be a reason for pain and bleeding post-IUD insertion, and thereby reduce the number of unscheduled visits to the clinician (Grimes and Schulz 1999). Although literature data (Hicks 1998; Gareen et al. 2000; Grimes 2000; Shelton 2001; Bilian 2002; Mazza 2002; Gareen 2003; FFPRHC Guidance 2004) show very low risk for upper genital tract infection in IUD users, more than half of the Latvian doctors believed that IUD could cause PID, which is in concordance with surveys in countries such as the USA, Finland, Czech Republic, Slovakia and Russia, reporting a similar high
proportion of doctors who believed that IUDs cause PID (Visser, A P et al. 1993; Makkonen et al. 1994; Visser, A et al. 1994; Stanwood et al. 2002).

The majority of more experienced and older doctors did not respond at all to questions relating to efficacy and contraceptive mechanism of action of some contraceptive methods and it could only be assumed that the reason was lack of knowledge. This lack of theoretical knowledge could be explained by previous conservative training curricula and only slowly increasing access to modern literature in the Latvian medical society.

The reported contraceptive method use among doctors corresponds well to findings in the national surveys in 1997 and 2003 (UNDP 1998; UNFPA 2004), confirming that doctors do not differ in this respect from the rest of the society. A similar conclusion was done in a similar study in the USA (Zbella et al. 1986).

It is apparent that Latvian obstetrician-gynecologists participate actively in contraceptive counseling and are very experienced with regard to IUD use. Intrauterine contraception traditionally has been one of the most popular contraceptive methods in Latvia for decades. At the same time, Latvian physicians express concern about IUD, especially long-term use, as a cause for PID. This is explained by the fact that PID is still a common diagnosis in everyday practice in Latvian hospitals.

The present study was performed to obtain scientific evidence for future clinical management and contraceptive counseling and the results emphasizes that IUD *per se* is not associated with PID risk in low-risk women younger 35. The finding that IUD use is associated with an increased risk of complicated PID in women over 35 does not discard IUD as a contraceptive method in that age group. The IUD is a highly effective, long-term contraceptive method that normally could be used in women until menopause. Although contraceptive benefits by far outweigh the risk of PID, the study findings highlight the need for clinical awareness, when monitoring women with IUD in their later reproductive years. Such awareness needs to focus on early signs of PID as well as on very-long-term IUD use in women approaching menopause. Additionally, the present study findings could be useful for the clinician in the assessment of patients in the emergency room.

**Future studies**

Although the study results found an association between IUD use and PID, the results can not entirely explain the role of an IUD in the pathogenesis of PID. More detailed studies regarding to microbial and histological findings,
especially in long-term IUD users, matching controls and cases for duration of IUD use, could be suggested.

For better understanding of the microbial characteristics of various forms of PID, simple improved methods for quantification of microbes and adapted for ordinary routine laboratory facilities are needed.

Neither the present study nor other studies found in the literature can reasonably explain the relationship between older age, IUD use and the development of PID. The possible association between PID severity and older age in otherwise healthy, menstruating women is unclear and needs to be studied further, focusing on other possible factors, such as endocrine and immunological changes, that may occur with ageing.

In Latvia, long-term national surveillance of reproductive health indicators, such as the occurrence of PID, is desirable and more reliable data regarding PID incidence and prevalence in different age groups within national statistics are highly needed. In Latvia, more observational studies could possibly also be performed, considering that the prevalence and incidence of PID still appears high.

Finally, an in-depth study of male partners to women with PID, including personal and life-style characteristics, would be highly desirable.
Conclusions

- the most striking difference regarding the background and reproductive history between women with PID and healthy women over age 25 were related to socio-demographic factors and not to common risk factors for PID, as proposed in the literature

- more data regarding male partners to women with PID are needed

- there was little difference between healthy women and women with current PID with regard to single microbes

- the finding of combinations of several anaerobic or aerobic/anaerobic microbes appeared to be associated with PID, particularly in women over 35

- the pathogenesis of non-sexually transmitted PID appears to be associated with a synergistic effect between several pathogens, possibly facilitated by the presence of an IUD

- IUD use *per se* was not associated with PID in low-risk women younger than 35, but in women 35 and older, IUD use was associated with an increased risk of PID

- there was an association between IUD use and complicated PID in women over 35, which was possibly influenced by long-term IUD use

- age over 35 and IUD use, independently of each other, were associated with an increased risk of failed conservative treatment, necessitating surgery in patients with PID

- Latvian obstetrician-gynecologists participate actively in contraceptive counseling and are very experienced with regard to IUD use

- Latvian physicians’ attitude and perceptions towards IUD are generally positive and their clinical considerations are in good agreement with that of doctors in other countries
• antibiotics are widely used around IUD insertion by Latvian doctors, possibly driven by a liberal attitude towards IUD use in women with a potential risk of STI

• the study could identify some possible gaps in the theoretical knowledge about the IUD and other methods
Acknowledgements

I began this work and successfully finished it thanks to the people I happily met in my life. They are people who helped me to find confidence about possibility of such research. If I would not receive their help, support and advice, I would never be able to carry out and complete my study. Therefore, I would like to express my acknowledgements to:

Viveca Odlind, my main supervisor, an excellent and wise teacher who helped me to learn how to think and write scientifically, look at things logically, avoid haste and be critical. I express my gratitude to you for the enormous encouragement and support to me when I felt hopeless and lost. I have learned much from you not only for my scientific research and academic world, but also for my personality and attitude regarding life and things around me.

Gunta Lazdāne, I greatly appreciate your support encouraging me to start the scientific research on this topic in Latvia.

Marie-Louise Nordström, for giving me the right direction at the very beginning for the organization of my study data collection from the biostatistical point of view. It is invaluable to have somebody who can see the whole ultimate picture of the possible data use and analysis, and give you sound advice helping to avoid mistakes at the initial stage of work.

Gunilla Lindmark, for welcoming me to the IMCH unit and your research group where I enjoyed working in a friendly and inspiring atmosphere, and learned how to organize my work and manage things with so different people around.

Lars Berglund and Sylvia Olofsson, for guiding me through the sometimes frustrating world of biostatistics, cooperation and fruitful discussions on the obtained results.

Karin Törnblom, for your excellent administrative work, for being always friendly and supportive and calming me down when I felt lost in documents and papers and other thing. Thank you for your ‘magic fingers’ touching my
computer and understanding my needs in specific situations, as well as for finding solutions for the problems I encountered.

Kristine Eklund, for your kind help in my struggle with my computer, Cristina Niska Bachelet for your assistance with practical preparing of thesis, Vera Holmgren and all the staff at the Department of Women’s and Children’s Health, especially at IMCH, for your friendship, encouragement and support.

All my friends at IMCH and especially my room-mates Thuba Mathole, Iryna Mogilevkina, Gunilla Aneblom, Margareta Larsson, David Urasa, Maira Jansone, Dmitrijus Kirilovas, Giumin Wang I happily shared every-day life and many unforgettable moments and chats with you. It was really great time with you.

All my colleagues in Riga 1st Hospital, Dzelzcelnieku Hospital and Lags-Centrs Hospital, for assisting me in the collection of the clinical material for the study. Without you and your support and understanding I could not carry out this study at all.

Juta Kroča and all Microbiology department staff, for assistance and precise work with my ‘collected microbial material’, excellent explanations of microbial world and valuable contributions throughout the work.

Uldis Teibe, for the kind guidance and assistance in data analysis and interpretation.

Jana Žodžika and other residents of obstetrics and gynecology in Latvia, for your commitment and enthusiasm working with me and your responsible attitude towards my tasks. I wish you all good luck in your studies and believe that you will do scientific work in future. You always can count on me to share my experience and knowledge with you.

All colleagues of mine and staff of the Department of Obstetrics and Gynecology of Riga Stradins University, for moral support and friendship throughout these years.

My friends in Latvia and Lithuania who always cared and gave me moral support and wished me success to reach the final stage of my study. Special thanks go to Elita Kalniņa, Sandra Õihiheberga, Rita Jakobčyonite.

My mum, I thank you for all your support provided to my men – husband and son – during my absence and presence at home. Now, as you say, you could retire from the charity job for my family.
My very best in-the-world brother Ivars, for the moral and financial support to me and my family during my study trips.

To my beloved husband Agris and our son Mārcis, for patience and waiting me home. I know that these years have been difficult to you both. But I can not promise that I will not be ‘a little bit crazy’ in future, I have new plans! Nevertheless, you always will be my most important people in the world. You both and my brother are the three whales of my life and world.

FIGO Fellowship (Schering Foundation), Stiftelsen familjeplaneringsfonden i Uppsala, The Swedish Institute Visby Program and In-Develop Fund, Department of Women’s and Children’s Health, thank you for providing the financial support for this work. It considerably contributed to the successful result!
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Acta Universitatis Upsaliensis

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Editor: The Dean of the Faculty of Medicine

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