

From the Department of Neurobiology, Care Sciences and Society,
Center for Family and Community Medicine,
Karolinska Institutet, Stockholm, Sweden

**EPIDEMIOLOGICAL AND CLINICAL
ASPECTS OF FERTILITY AND
DISEASES ASSOCIATED WITH
INFERTILITY AMONG SWEDISH-BORN
AND FOREIGN-BORN WOMEN**

Jan Eggert



**Karolinska
Institutet**

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Main supervisor: Kristina Sundquist

Supervisor: Aino Fianu-Jonasson

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ABSTRACT

Objective To examine the association between sociodemographic factors and first birth fertility trends in Sweden during the 90s (study 1). To examine the association between country of birth and hospitalization for pelvic inflammatory disease (PID), ectopic pregnancy (EP), endometriosis (EM) and infertility (study 2). To examine the long-term effects of alcohol consumption on female fertility (study 3). To describe the clinical symptoms and signs in women diagnosed with PID in a Swedish hospital setting in comparison with the diagnostic criteria from the CDC 2002 Guidelines (study 4).

Methods In study 1, the impact of socioeconomic factors and years in Sweden on first birth fertility was examined in 1991–92 (N = 452,000) and 1997–98 (N = 495,756) among Swedish-born and 19 subgroups of foreign-born women aged 20–41 years. Poisson regression was used in the analysis. Study 2 followed 2,170,177 women living in Sweden at some point between 1990 and 2004 for hospitalization for PID, EP, EM or infertility. In study 3, self-estimated alcohol consumption was obtained from postal questionnaires to 7,393 women in the age-range 18–28 years in 1969. Data on deliveries, miscarriages, legal abortions, EP, PID, EM and infertility examinations, in relation to the intake of alcohol, were analysed until 1987. Study 4 included 189 out-patients diagnosed as having PID at the obstetric and gynaecological emergency department of a Swedish university hospital in 2001. Data on symptoms, signs, pelvic examination and laboratory tests were extracted from the electronic medical records.

Results First birth rates decreased and mean age at first birth increased between the two periods among the Swedish-born and most foreign-born women. Non-employment and low income were associated with decreased first birth fertility, and low educational status was associated with slightly increased first birth fertility. Several groups of foreign-born women increased their first birth fertility even if they were non-employed or had a low income. Among foreign-born women fewer years in Sweden was significantly associated with increased first birth fertility (study 1). For PID and infertility, all groups of foreign-born women exhibited significantly increased risks compared to Swedish-born women whereas country of birth was associated with EM and EP to a smaller extent (study 2). High consumers of alcohol had an increased risk for infertility examinations, as compared with moderate consumers, relative risk ratio (RR) = 1.59 (95% confidence interval (CI): 1.09–2.31) and low consumers had a decreased risk (RR= 0.64; CI: 0.46–0.90). For both high and low consumers a significantly lower number of first and second partus were observed (study 3). Most symptoms associated with the PID diagnosis are mentioned in the CDC 2002 Guidelines. Detected rates of Chlamydia Trachomatis (CT) and Neisseria Gonorrhoeae (NG) were 5% and 0%, respectively, among the tested patients (CT = 52% and NG = 12%). The women presented clinical symptoms and signs that largely were in accordance with guidelines. Only half of the patients were tested for CT (study 4).

Conclusions Public health information should emphasize that postponement of first birth could lead to involuntary childlessness. Even in a country like Sweden, which offers publicly financed treatment for infertility, differences based on country of birth exist. Additionally, to limit alcohol intake may be of importance for women who intend to have children. The clinical basis for the diagnostics of PID was largely in accordance with the criteria in the CDC 2002. The testing rate for CT should be improved in clinical praxis.

To my family

LIST OF PUBLICATIONS

- 1 Jan Eggert, Kristina Sundquist. Socioeconomic factors, country of birth and years in Sweden are associated with first birth fertility trends during the 1990s: A national cohort study. *Scandinavian Journal of Public Health*, 2006;34(5):504–14.
- 2 Jan Eggert, Kristina Sundquist. Country of birth and hospitalization for pelvic inflammatory disease, ectopic pregnancy, endometriosis and infertility: a nationwide study of 2 million women in Sweden. Submitted to *Fertility and Sterility*.
- 3 Jan Eggert, Holger Theobald, Peter Engfeldt. Effects of alcohol consumption on female fertility during an 18 year period. *Fertility and Sterility*, 2004; Feb;81(2):379–83.
- 4 Jan Eggert, Kristina Sundquist, Caroline van Vuuren, Aino Fianu-Jonasson. The clinical diagnosis of pelvic inflammatory disease: reuse of electronic medical record data from 189 patients visiting a Swedish university hospital emergency department. *BMC Women's Health*, 2006;Oct 21;6:16.

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LIST OF ABBREVIATIONS

ART	Assisted Reproductive Technologies
CDC	Centers of Disease Control and Prevention
CI	Confidence Interval
CRP	C-reactive Protein
CT	Chlamydia Trachomatis
EM	Endometriosis
FBR	First Birth Rate
GP	General Practitioner
ICD	International Classification of Diseases
ICSI	Intra-Cytoplasmic Sperm Injection
IR	Incidence Rates
IRR	Incidence Rate Ratio
IUD	Intra Uterine Device
IVF	In Vitro Fertilization
n	Sample size
N	Population size
NG	Neisseria Gonorrhoea
OGED	Obstetric and Gynaecological Emergency Department
PID	Pelvic Inflammatory Disease
RR	Relative Risk
SES	Socioeconomic Status
sp	species
STI	Sexually Transmitted Infections
TFI	Tubal Factor Infertility
TFR	Total Fertility Rate
TVS	Trans Vaginal Sonography
UTI	Urinary Tract Infection
WHO	World Health Organization

CONTENTS

Introduction.....	7
Consequences of infertility and childlessness	7
Involuntary childlessness – a disease.....	8
Factors contributing to female infertility	9
Pelvic Inflammatory Disease (PID).....	9
Medical complications of PID	10
PID diagnosis.....	10
The role of laparoscopy, endometrial biopsy and TVS in the diagnosis of PID	11
Factors and mechanisms involved in the development of PID.....	12
Three main types of situations associated with the development of PID ..	13
PID after childbirth, abortion and uterine operations.....	13
Spontaneously occurring PID without sexually transmitted infections (STI).....	14
STI and PID associated with STI.....	14
STI and “silent” PID.....	15
Ectopic Pregnancy (EP).....	15
Endometriosis (EM)	16
Urinary Tract Infection (UTI)	16
Sociodemographic and global perspectives on fertility	16
Global population growth.....	17
Falling fertility rates in Europe and postponement of first birth.....	17
Socio-economic factors and attitudes related to childbearing.....	18
Assisted reproductive technologies (ART).....	19
Legal abortions in Sweden	19
Migration to Sweden	20
Lifestyle factors and female fertility	20
Aims	22
General aim.....	22
Specific aims.....	22
Methods.....	23
Study 1	23
Study 2	24
Study 3	26
Study 4	27
Results	29
Study 1	29
Study 2	35
Study 3	37
Study 4	39
Discussion	41
Main findings.....	41
Postponement of first birth and its consequences.....	41
Socioeconomic factors and fertility	42
Acculturation	43

Alcohol and fertility	44
Diagnosis of PID	44
Strengths and limitations	47
Conclusions	49
Summary in Swedish	50
Acknowledgements	53
References.....	54
Study 1	
Study 2	
Study 3	
Study 4	

INTRODUCTION

This thesis will address some factors and diseases that may affect female fertility, leading to infertility and involuntary childlessness: delayed childbearing, pelvic inflammatory disease (PID), endometriosis (EM), ectopic pregnancy (EP) and high consumption of alcohol.

Historically, the percentage of Swedish women that have remained childless has varied between 11% and 16% for each age cohort throughout the 20th century [1]. The corresponding percentages for men have varied between 16% and 22% [1]. A proportion of these eventually childless women and men have consisted of infertile couples who wish to have children. Others may not have wanted to have children or may not have found a partner.

Since the 1960s, there have been increasing possibilities to examine and treat couples who have sought medical help for infertility. Methods have included hormonal ovarian stimulation, surgical tubal reconstruction, and assisted reproductive technologies (ART), such as insemination and in vitro fertilization (IVF), with or without intracytoplasmic sperm injection (ICSI) and the use of donor eggs. Such treatments have been used particularly in the case of primary infertility (the woman does not become pregnant) and gradually also for secondary infertility, i.e. the woman has been pregnant at least once, after which hindering factors have emerged. In an infertile couple hindering factors may exist in the woman or in the man or they may both contribute with subfertile characteristics. The proportions of these subgroups account for approximately one-third each in Sweden [2]. Today in Sweden, after a complete infertility examination, the most common conclusions are infertility of unknown origin, impaired ovulation and tubal factor infertility (TFI) [2, 3]. The woman's age also has an impact in many cases of unexplained infertility. TFI is defined as an impaired function of the fallopian tubes, which causes between 20 and 50% of all female infertility globally [4–8]. The main cause of TFI is a bacterial infection of the upper female genital organs, i.e. PID.

CONSEQUENCES OF INFERTILITY AND CHILDLESSNESS

The wish to have children is fundamental and for most women and men related to the meaning of life [9–12]. This wish seems to be very strong in all cultures and is independent of ethnicity, religion and social class [13]. A marriage without children has historically been seen as a great misfortune.

It is possible that many couples of today would prefer a life without children. However, two recent Swedish studies from 2001 and 2006 have shown that more than 95% of women and men aged 23–25 years old were definitely interested in having children in the future [14] [15].

To be able to reproduce is normally taken for granted, “to have children if and when we want to”, and to be diagnosed with infertility is for many people emotionally shocking, leading to a psychological crisis. This crisis has been interpreted within the context of the “life-crisis theory” and the “biopsychosocial theory” [16] and include feelings of guilt, anger, depression and isolation [2, 17–19]. Not becoming a parent can also lead to feelings of being isolated from friends, neighbours and relatives because

childless people are not included in social networks associated with having children, such as day-care, school and children's activities in sports and culture [17].

Childlessness can also indirectly affect parents of a childless couple, both emotionally and in other ways. Having grandchildren is considered very natural and desired. Infertile couples may feel grief and dishonour for not continuing the family inheritance. Economically, childlessness can have severe consequences in societies where children are responsible for supporting their parents in old age [20]. Not only social implications occur with the inability to reproduce; psychological and sexual problems may also affect the couple [9, 10, 21]. For both men and women fertility is closely linked to self-respect, self-esteem, sexual function and sexual and social identity [22].

For women pregnancy and delivery have a unique significance from biological, intra-psychological and interpersonal points of view [2, 23]. When interviewed at fertility clinics, women have expressed stronger feeling of stress, anxiety, depression and loss of self-esteem than men [24] and to be fertile is more important for women's quality of life than for men [18, 25]. Men may, however, have different ways of reacting to infertility, i.e. suffering likewise but coping differently [26].

Most previous research has been performed among couples attending fertility clinics. However, little is known (in a published form) about how women or couples who do not seek medical help for their childlessness feel, and how their mental health and their life develop. Such knowledge, in the form of women's and men's individual narratives, is likely to have accumulated among professionals like general practitioners (GPs) [19], gynaecologists, psychiatrists, priests, and psychotherapists.

The woman has traditionally and even today been the one to blame in case of childlessness, which is paradoxical as male infertility or subfertility contribute to 20–40% of all infertility cases worldwide [27]. Globally, the role of male infertility is “vastly underestimated and even hidden in many societies” according to Inhorn et al. [28, 29]. European studies in recent years suggest that men's age (>40 years) is an important risk factor for infertility and miscarriage [30–32]. However, male factors contributing to infertility are not dealt with in the present study.

The societal effects of undesired childlessness in a woman or a couple will vary dramatically from acceptance (including adoption) to stigmatization and is grounds in some cultures for divorcing a woman against her will [33, 34]. According to one study stigmatization in Nigeria may include rejection, emotional abuse, partner's infidelity and even accusations of being evil or a witch [35].

INVOLUNTARY CHILDLESSNESS – A DISEASE

Involuntary childlessness has been classified as a disease since 1997 according to the World Health Organization (WHO). In industrialized countries, 10–15% of all couples are estimated to suffer from primary or secondary infertility [36, 37]. In some sub-Saharan African countries secondary infertility of up to 25% has been reported [38]. However, the “true” incidence of infertility and involuntary childlessness among couples remains unknown in most countries.

The percentage of couples with infertility problems that seek help has been estimated to be less than 50% in industrialized countries [37, 39, 40]. However, this percentage is probably increasing due to better medical possibilities for treatment of

infertility and widespread publicity on successful treatments. In less developed countries, however, the percentage of couples seeking help is probably lower. The propensity to seek help depends on cultural values and traditions and may for the woman include the permission of her husband [41]. Furthermore, it will depend on the economic possibilities for each couple and their families, and to what extent national or private health insurances cover the considerable costs of investigation and treatment of infertility. For example, treatment with IVF is economically far beyond the reach of large groups of inhabitants in most countries. In addition, the success rate in IVF is strongly dependent on the woman's age [7, 42].

FACTORS CONTRIBUTING TO FEMALE INFERTILITY

In women infertility or subfertility can be caused by a wide range of factors, some of which are listed below:

Abdominal operations with postoperative adhesions around the ovaries and fallopian tubes.

Age, i.e. decreasing fertility caused by increasing age, particularly after 32–35 years.

Chromosomal aberrations.

The Cervix factor including IgA antibodies to partner's sperm.

Congenital malformations of the vagina, uterus and ovaries.

Diseases of the ovaries, e.g. cysts and cancer.

Diseases of the uterus, e.g. myomas and cancer.

EP, resulting in TFI.

EM.

Hormonal dysfunction, affecting maturation of eggs, ovulation and implantation.

Lifestyle factors, such as obesity, alcohol, smoking, excessive physical activity and stress.

PID, resulting in TFI.

Traumatic lesions including female mutilation.

[2, 43–45]

PELVIC INFLAMMATORY DISEASE (PID)

From ancient China (about 2500 B.C.), Assyria and Greece there are written sources with descriptions of abnormal secretion from the vagina and the urethra. The Greek Galenos probably described and named gonorrhoea in the 2nd century AD, one well-known agent in PID [46, 47]. Theses and scientific articles on PID were published as early as the 1870s–1880s, e.g. in the USA and in Sweden [48, 49]. In 1898 it was hypothesized that PID with salpingitis was caused by lower genital tract micro-organisms spreading along the endometrium to the fallopian tubes [50]. This was later proved by experimental resection of the fallopian tubes during sterilization operations in the 1940 and onwards [51, 52].

Puerperal (childbed) fever after delivery was described in England and Scotland in the 17th and 18th centuries [53]. During the 19th century, strict preventive anti-septic measures were recommended during and after delivery in the US [54]. In the mid-19th

century, Dr Semmelweis struggled in Vienna, Austria, for improved hand hygiene among students and doctors assisting at childbirth [55]. Later on, increasing knowledge and awareness of sterile, aseptic techniques, resulted in a dramatically lowered incidence of puerperal fever [46], known since the 20th century as postpartum endometritis.

PID, including postpartum endometritis, is caused by ascending bacteria from the cervix to the uterus, the adnexa and adjacent pelvic structures [56]. PID contributes to about 2% of the yearly visits in general practise/health care centres in the UK [57, 58]. In the US, PID will affect 8–10% of all women at least once during their reproductive period [59]. The PID incidence in Sweden during the 1960s and 1970s was estimated to 18–20 per 1000 women and per year in the age group 15–24 years [60]. Since the 1980s an increasing number of women with PID have been treated as out-patients. Out-patients are not recorded in the Swedish national patient registers, and therefore the Swedish incidence of PID after the 1980s is difficult to estimate.

PID and its complications entail considerable medical, social and economic consequences and this is therefore an important disease that affects healthy fertile women worldwide [61]. For example, in the US PID causes some 1.2 million doctor's visits per year, and the yearly costs of PID, including its sequelae, were around 1.9 billion dollars in 1998. However, as increasing numbers of PID cases are treated as out-patients, costs are decreasing [62].

MEDICAL COMPLICATIONS OF PID

The risk of medical complications after PID is considerable and consists of infertility, EP, chronic pelvic pain and recurrent PID [43]. EP is 8–10 times more common after PID [63] and chronic pelvic pain has been reported among 12–24% of PID patients [64]. The statistical risk of infertility after one PID has been estimated to 10–20% [65], and the risk after having had three to four PID has been estimated to 40–60%. These figures refer to PID treated in hospital care [65].

PID DIAGNOSIS

The vast majority of all PID cases are diagnosed by clinical methods, i.e. by bimanual palpation (also called pelvic examination), along with blood tests and bacteriological tests for Chlamydia Trachomatis (CT) and Neisseria Gonorrhoea (NG). Most cases of PID are thus diagnosed without laparoscopy (see below). The clinical diagnosis of PID can be difficult as symptoms range from severe to mild. Symptoms can also be atypical. National guidelines providing criteria for the diagnosis of PID are published and updated regularly in the US, the UK, and the Netherlands [58, 66–69]. The US guidelines are published by the Centers for Disease Control and Prevention (CDC) [68]. There are no Swedish guidelines on PID, although there are recommendations for the diagnosis and treatment of PID in the textbook “Läkemedelsboken”, provided by the national pharmacies to all hospitals and health care centres in Sweden [70].

The CDC 2002 Guidelines [71] define PID as follows: “Pelvic inflammatory disease (PID) comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic

peritonitis.” This definition does not differ between spontaneously occurring PID and PID occurring after deliveries, abortions and intra-uterine operations.

Symptoms described in the CDC 2002 Guidelines as criteria for diagnosis are abdominal pain, abnormal vaginal discharge and fever, while abnormal bleedings and pain at intercourse are mentioned as possible, albeit non-specific PID symptoms. Additional diagnostic criteria in the CDC 2002 Guidelines include the presence of white blood cells on wet smear, elevated erythrocyte sedimentation rate, elevated C-reactive protein (CRP), a positive culture of CT or NG and a transvaginal sonography (TVS) that shows fluid-filled thickened tubes with or without pelvic fluid.

CDC 2002 Guidelines recommend antibiotic treatment of suspected PID if (1) cervical motion tenderness or (2) uterine or adnexal tenderness is present and no other cause is identified. In addition, national guidelines have gradually modified the diagnostic criteria for PID in order to cover milder forms, minimize missed diagnoses and reduce serious complications of PID. Clinicians are recommended to have a high grade of suspicion and a low threshold for treatment of suspected cases. It is expressed in guidelines that delayed diagnosis and treatment is likely to increase the risks of complications [58, 71]. For the health care provider, every potential case of suspected or confirmed PID can hypothetically lead to infertility and childlessness.

THE ROLE OF LAPAROSCOPY, ENDOMETRIAL BIOPSY AND TVS IN THE DIAGNOSIS OF PID

Laparoscopy has been the “gold standard” to diagnose PID [61]. Laparoscopy is associated with a general anaesthesia in order to perform a direct intraabdominal inspection of the inner female genitals. For practical, economic and medical reasons (including the potential medical risk), most cases of PID have been diagnosed without laparoscopy. Since the 1990s, laparoscopy as a gold standard has been under debate as laparoscopy does not detect milder forms of PID [71–73]. For example, the endometrium is not visualized and discrete inflammatory alterations of the fallopian tubes may be overlooked. Moreover, some studies have shown a limited observer agreement with laparoscopic diagnosis [71, 74, 75].

The endometrial biopsy was developed in the 1980s in order to find less invasive and also less expensive methods than laparoscopy. With local anaesthesia a catheter is introduced through the cervical channel into the uterus, where fragments of the endometrium are taken out for microscopy assessment. The method requires an interpretation by a pathologist, which causes some delay of the diagnosis. Although used in studies with good sensitivity and specificity rates [76], the method has not reached a broader clinical use.

TVS has been increasingly used since the 1990s in order to identify details of early pregnancies, EP, cysts, and in IVF. TVS is also useful in severe PID where fluid filled tubes and tubo-ovarian abscesses can be visualized [77–80]. However, in mild to moderate PID the clinical use of TVS is limited by poor sensitivity [56], and its routine use is not recommended in guidelines [58, 68]. Consequently, in case of mild to moderate PID, TVS can not confirm the diagnosis. In addition, a normal TVS may very well give the patient the impression that everything is normal unless the doctor informs the patient that PID can not be excluded.

FACTORS AND MECHANISMS INVOLVED IN THE DEVELOPMENT OF PID

Bacteria

A number of bacteria have been recovered from the uterus, the fallopian tubes and the abdomen in PID. Examples are CT and NG but also genital mycoplasmas and anaerobic or aerobic bacteria from the normal flora such as *Prevotella species (sp)* (formerly *Bacteroides sp*), *Peptostreptococcus sp*, *Gardnerella vaginalis*, *Escherichia Coli*, *Hemophilus Influenzae* and *Staphylococci* [56, 81, 82].

The mechanisms of the initiation of a PID at the immunological and cellular level are still incompletely understood. About 8–10% of all women in western countries will have PID at least once in their lifetime [83]. Why the remaining 90% do not contract PID, despite exposure to the same risk factors (including sexually transmitted infections, STIs) as women contracting PID, remains unknown, although possible factors include a weakened immunological barrier and a higher virulence of the normal bacterial flora.

Age

PID is most common among women between 16 to 25 years [56]. Early sexual debut, multiple partners and a higher prevalence of sexually transmitted infections (STI) have been explanations for the high incidence of PID in this age group.

Bacterial vaginosis is a shift of the normal vaginal flora of lactobacilli to a mix of anaerobe bacteria, e.g. *Gardnerella Vaginalis* and mycoplasmas. This shift occurs spontaneously in healthy women and may cause abnormal vaginal discharge or remain symptomless. Between 30% and 70% of the women with bacterial vaginosis have no specific symptoms [56, 84]. A number of studies have demonstrated the association between bacterial vaginosis and PID, and bacterial vaginosis seem to predispose for PID [85–91].

Menstruation

Menstruation seems to facilitate the initiation of PID in many cases. A physiological barrier is normally present in the cervix to prevent micro-organisms from ascending to the uterus. At menstruation the protective cervical mucous plug is absent. The cervical mucous plug contain antibodies and other components, and its properties are changed during the menstrual cycle and by hormonal contraceptives [56]. In addition, as many as 90% of healthy women have retrograde menstrual blood flow through the fallopian tubes into the abdomen. Blood mixed with endometrial cell debris may contribute to an ascending infection [92–96].

Previous PID

The recurrence rate after one acute PID is estimated at 25%. Mechanisms discussed include microscopic fallopian tube damage, sexual habits, untreated male partner and women's immunological properties including the virulence of the individual bacterial flora [43] [56].

Ectopy of the cervix seems to facilitate the adherence of CT and establish infection, possibly proportionally to the ectopy size [97, 98].

The uterine muscular contractions during coitus might facilitate the transport of microorganisms and cause an ascending infection. This mechanism, along with others, could partly explain that the large majority of PID cases are seen in sexually active women [99].

Sperms have been suggested to be vectors for bacteria in PID, according to in vitro experiments [100].

Contraceptive methods

Earlier studies in the 1970s and 1980s on intrauterine device (IUD) and PID found a considerably increased risk for PID among women with IUD, whereas more recent studies have found a moderately increased risk only within the first 3 weeks after insertion [43]. However, women who have never been pregnant (nulligravities) are normally advised against the use of IUD. Women >35 with IUD may have an increased risk for PID [101].

Barrier methods (condom, diaphragm and spermicides) lower the risk of acute PID. Oral contraceptives reduce the risk for overt acute PID by approximately 50% [102]. However, it has also been proposed that oral contraceptives could facilitate an infection with CT by modifying the cervical ectopy [56].

Vaginal douching

Some studies have found associations between vaginal douching, PID and EP [103–105].

THREE MAIN TYPES OF SITUATIONS ASSOCIATED WITH THE DEVELOPMENT OF PID

There are three main types of situations associated with the development of PID.

1. PID after childbirth, abortions and surgical procedures in the uterus, which causes an ascending infection of bacteria normally present in healthy women [56].
2. Spontaneously occurring PID with bacteria normally present in healthy women [56].
3. PID associated with STI, principally caused by CT and NG [56] or in combination with bacteria from the normal flora, i.e. a polymicrobial infection.

PID AFTER CHILDBIRTH, ABORTION AND UTERINE OPERATIONS

The most well-known and also most feared form of PID is the infection of the uterus after childbirth, i.e. puerperal (childbed) fever or post partum endometritis, which in many countries worldwide is still associated with considerable mortality. It is more likely for PID to follow deliveries in countries or regions with lower standards of medical care, an uneven distribution of health care resources and poverty. Puerperal fever is an ascending infection of normally non-pathogenic bacteria [56] from the

woman's lower genitalia and/or from the assistant personnel at delivery. It occurs in a situation when the membranes of the lower parts of the uterus are compromised by mechanical factors.

Another important and feared form of PID is related to illegal and other unsafe abortions, especially when performed under poor hygienic condition. According to estimations from the WHO, 20 million unsafe abortions take place every year [41]. Complications occur after 10–50% of such abortions [41], constituting a major cause of female mortality and infertility.

PID will also more easily occur when there are remnants of the placenta in the uterine cavity after delivery, miscarriages and induced abortions. Remnants of the placenta could promote bacterial growth, which has led to strict recommendations for attention and fast intervention by health care providers after deliveries and abortions. Patients are informed to be observant to abnormal secretion, fever or bleedings.

From a global perspective, severe and even mortal PID is common. Intra-uterine operations are also associated with an increased risk of PID by mechanical influence of the inner cervical and uterine membranes [56]. The medical and economic possibilities to treat PID after childbirth, abortion and intrauterine operations (and later appearing sequelae) vary considerably in a global perspective.

SPONTANEOUSLY OCCURRING PID WITHOUT SEXUALLY TRANSMITTED INFECTIONS (STI)

In spontaneously occurring PID there has been no previous pregnancy or surgical intervention. It mostly occurs in women with an ongoing or previous sexual relation, and is considered uncommon after the menopause. It is the most common form of PID and causative agents are the bacteria of the normal flora of the vagina and the skin. The role of these bacteria in PID has been increasingly studied during the last decades [85, 106]. PID can also be caused by a mix of several bacteria, i.e. more than one specie of normally non-pathogenic bacteria involved, i.e. a polymicrobial infection [56].

STI AND PID ASSOCIATED WITH STI

The sexually transmitted infection NG was discovered in 1879, whereas CT was discovered in 1965 as a pathogen in the eye disease *trachoma*. Globally, the prevalence of NG and CT is highest in African countries, and less common in Asia [107]. Since their discovery, they have been assigned and described to cause an important part of PID [108, 109]. Pioneering work in identifying CT as a causative agent in PID was done during the 1970s [110, 111]. The involvement of CT and NG in PID studies (referred to in textbooks) often ranges from 15% to 40% and 5–25%, respectively [56]. Another sexually transmitted bacteria suggested to be involved in PID is *Mycoplasma genitalium* [106, 112–114] and it has been shown to cause symptomatic urethritis in men and their female partners [115].

A considerable part of the studies on PID and STI are from the US and the UK. The studies have been performed among younger women in inner city settings and public hospitals (USA) and in genito-urinary clinics (UK), where high incidence rates of CT and NG have been found [116, 117]. However, these patients often differ significantly

in socioeconomic group and ethnicity from the average population in the country [118, 119].

In contrast, a hospital-based study from a medium-sized Swedish city (Örebro) on the relationship between PID and STI found that the prevalence of CT among the PID-patients decreased gradually from 28% in 1985, 8% in 1995, to 0% in 1997. For NG the prevalence among the PID-patients was 3% in 1985 and 0% from 1988 onwards [120–122]. In a Norwegian study of PID from 1990 and 2002, the prevalence of CT was 8% and 4%, respectively, and the prevalence of NG was 1% in hospitalized PID patients [123]. In study 4 (included in the present thesis) the prevalence of CT was 5% [124]. The prevalence of CT in the population is estimated at about 5% in the UK and in Belgium [117, 125]. In Stockholm, Sweden, 77,000 women were tested for CT in 2001 giving 4.6% positive CT cases (n= 3,526). [126]. In the US, approximately 20% of women with CT infections develop symptoms of urethritis, cervicitis and/or intermittent bleedings [56]. However, many women and men do not develop symptoms of the CT infection, which is a considerable public health problem as these persons could unintentionally pass on the infection to others.

STI AND “SILENT” PID

Some infected women (how many is unknown) will develop PID with few, mild, atypical or no symptoms at all. These infections are “silent” PID and are to a certain proportion due to STI and particularly CT. They are not identified or perceived by patients and often remain undetected by health care providers or misdiagnosed, because the symptoms of PID can be mixed up with symptoms associated with intestinal problems, bacterial vaginosis and urinary tract infection (UTI). These “silent” infections will heal without or with sequelae. The sequelae include damage of the fallopian tubes and pelvic adhesions that could be revealed later in life in the form of an ectopic pregnancy or at an infertility examination [71, 127]. These “silent” PID became a growing concern to gynaecologists during the 1970s and 1980s when there was a sharply increasing rate of ectopic pregnancies [56, 127]. Moreover, as many as 50% of the women that are investigated for infertility report that they have not had any PID [128]. Some women report previous doctors’ consultations for abdominal symptoms not recognized as PID [127].

ECTOPIC PREGNANCY (EP)

EP is an implantation occurring elsewhere than in the cavity of the uterus, mostly in the fallopian tube (>99%). EP was probably first described by Abulcassis in Cordoba during the 10th century [129]. In the 19th century, before the initiation of common surgery, mortality from EP was estimated to be 60%. The first successful operation on EP was performed in 1883 in England [43, 130]. Globally, EP is still responsible for 10% of maternal mortality [131]. Today, EP occurs in 1–2% of all pregnancies and is 6–10 times more common after PID [63, 132, 133]. EP increased 4-fold in the US and 2- to 3-fold in England between 1970 and 1989 [134, 135]. Increasing prevalence of CT infections has been suggested to be the main reason for the increase in EP, which

has also occurred in Sweden [136, 137]. After EP, subsequent infertility is reported in about 33–45% [138, 139].

ENDOMETRIOSIS (EM)

EM is the presence and growth of the glands and stroma of the endometrium (the inner lining of the uterus) in an aberrant location such as on the surface of the uterus, the fallopian tubes, the ovaries, the pelvic wall, the intestines, the bladder and other anatomic structures. The exact mechanism behind this spontaneously occurring, chronic and often progressive disease remains unknown. There are several theories to explain various aspects of EM [140]. One main theory involves retrograde menstruation into the abdomen and the subsequent immunological response with inflammation, bleeding, connective tissue formation and scarring. Symptoms of EM include dysmenorrhoea, cyclic pelvic pain, pain at intercourse and infertility. EM is often diagnosed in women aged 25–30 years [43]. Up to 30% of all cases of EM, occasionally seen during abdominal operations, have no symptoms. EM is present in 5–10% of fertile women and in 10–50% of those presenting with infertility in western countries [140].

URINARY TRACT INFECTION (UTI)

UTI in women has some similarities to spontaneously occurring PID as it represents an ascending infection to the urethra and the urinary bladder by normally non-pathogenic bacteria from the skin, the intestines and vagina. The causal mechanisms are incompletely understood. Sometimes it is caused after mechanical irritation of the urethra by catheterization, similar to intra-uterine operations causing PID. UTI is also related to intercourse and the frequency of intercourse, including a mechanical component of pressuring against the female urethra [56] [141, 142]. UTI typically presents symptoms of dysuria, i.e. burning, aching or frequent urinating and is mentioned as a differential diagnosis to PID in textbooks and guidelines. PID may be misdiagnosed as UTI.

SOCIODEMOGRAPHIC AND GLOBAL PERSPECTIVES ON FERTILITY

Female fertility can be studied at several levels, such as the global, country, population and individual level. A well-known method to study fertility at the country level is *the total fertility rate* (TFR) that serves as a predictor of the future population structure. The TFR describes the mean number of children that would be born to a woman during her lifetime if she were to pass through her fertile years conforming to the fertility rates of a given year. To maintain the population at the present level, i.e. the so called replacement level, the TFR is considered to be 2.1 in more developed countries [143].

However, the TFR and the replacement level are strongly related to maternal and infant mortality rates, which are considerably higher in developing countries than in industrialized countries. Maternal and infant mortality rates are in turn related to the physical environment and climate, conflicts and war, water supply, sufficient food, infectious diseases, the economic development in the country, education level, public health policies, and level of access for the majority of the population to good health care.

Improvements in agriculture, education and economic development in a country allow public health measures such as improved health care during pregnancy and delivery, which will lead to decreasing maternal and infant mortality rates. However, economic development also leads to decreasing fertility rates because more children survive their first years. Many interacting factors including urbanization, industrialization, women's increasing age at marriage, medical progress and introduction of family planning methods also result in fewer children per couple, however with great differences between regions, countries, and cultures.

GLOBAL POPULATION GROWTH

Rapid population growth has been of considerable concern particularly in countries in Asia and Africa. Examples of countries with historically high birth rates are India, China, Turkey, Tunisia, Nigeria and Kenya. Organizations such as the International Planned Parenthood Federation (IPPF) [144] have been active in supporting birth control and family planning in many countries worldwide. Family planning programmes have also been developed in many countries as a means to promote economic standards and women's and children's health, taking into account the often limited resources in housing, fuel, food, schools and health care. Governmental family planning programmes to control birth rates have since the early 1970s been most consequently practised in China.

Another demographic reality is the epidemic of AIDS that has caused excessive mortality among both men and women, particularly in the Sub-Saharan African countries. The epidemic has mainly struck people in the age span 20 to 45 years, which has caused a skewed demographic distribution in these countries and left countless children without their parents.

FALLING FERTILITY RATES IN EUROPE AND POSTPONEMENT OF FIRST BIRTH

In contrast to the other continents, the fertility patterns are quite different in many countries in Europe, including Sweden, with falling TFRs for many decades. Along with the TFR, fertility patterns can also be studied as *the mean age at first birth* and *first birth rates* (FBR), which is normally calculated as FBR per 1,000 childless women per year.

Another demographic variable is *the mean age of women at childbearing* [143].

Decreasing or low TFRs are a reality in many European countries such as England, Germany, Austria, Finland, Russia and in countries in Eastern and Southern Europe [145]. In these countries as many as 20% of women born in the 1960s and onwards will risk permanent childlessness [145]. TFRs are very low in, for example, Bulgaria, Germany, Italy, Poland, Russia and Spain (range 1.23–1.37) [143]. No European country has a TFR above 2.1, and the underlying factors have been under continuous debate [146–149].

Postponement of first birth could lead to primary and secondary infertility as female fertility starts to decrease at population level as early as from about 32 years of age [150–154]. Late onset of family making could also result in one-child families among

couples who initially had planned for more children, i.e., secondary infertility related to the woman's age. Data from the Netherlands have shown that postponement of first birth will eventually lead to increased rates of involuntary childlessness and to secondary infertility [155]. A study of monozygotic Danish twins showed that one-year delay in the first birth reduces completed fertility by 3%, with an even higher reduction in older cohorts [156].

Today, Sweden has a relatively low TRF of 1.75, similar to Finland (1.80), Denmark (1.78) and the UK (1.74) [143]. A main feature in Sweden has been the increase of the mean age at first birth among women from 23 years in 1970 to 29 years in 2002. The childbearing patterns of Swedish and foreign-born women between 1961 and 1999 have been described by Andersson and Hoem [157, 158]. Swedish women had a more rapid progression from a first to a second child than foreign-born women. Sweden had a "baby boom" from 1985 onwards during a period when fertility levels stagnated or declined in a number of European countries [143]. Between 1985 and 1990, the Swedish TFR increased from 1.68 to 2.14 although FBRs were affected only to a limited extent, whereas birth intervals were reduced particularly between the second and the third birth [157]. This was a period of economic prosperity, low unemployment rates, and parental allowances that favoured a second and a third child. After only 5–6 years, the economy was in recession and the Swedish "baby boom" was rapidly replaced by a "baby bust" with falling TFR rates to the historically low level of 1.50 in 1998 [159].

SOCIO-ECONOMIC FACTORS AND ATTITUDES RELATED TO CHILDBEARING

There are several conceivable factors that could have an impact on childbearing such as income, employment, education, age at marriage (or cohabiting under marriage-like conditions), urbanization processes, cultural norms, values (if children are regarded as an asset or a burden), social support, access to family planning methods including legal abortion, divorce rates, housing, child care and female labour force participation. Socioeconomic conditions seem to be of considerable importance for fertility decisions [157, 160]. Econometric literature has focused on incomes as the main explanatory variables for the timing and spacing of parenthood [161]. A general pattern is that women with higher educational status have fewer children [1]. However, previous research in Sweden on the association between socioeconomic factors that may be associated with fertility rates is inconsistent. One study showed that higher income was associated with higher fertility [157]. Other studies found associations between decreased first birth rates and local unemployment [158, 162] and a fall in GDP per capita [163]. In contrast, another Swedish study, based on a small sample, found no relation between unemployment and first birth intensities [164].

Study 1 included the entire population of childless women aged 20–41 in Sweden in order to examine the association between first birth fertility trends during the 1990s and demographic and socioeconomic factors among Swedish-born and 19 different subgroups of foreign-born women.

Further important factors for fertility decisions are governmental subsidies in order to promote childbearing, the possibility and right to return to one's previous job after

childbirth, women's liberation from paternalistic structures including increasing financial independence and a free choice of partner, profession and lifestyle.

It is possible that many women and couples of today deliberately choose and even prefer a life without children. Many men and women may find that children would restrain them from professional careers, leisure-time activities and travelling. Some couples may also hesitate about family making because of a child hostile environment in e.g. large cities. Statistics Sweden, the Swedish government-owned statistics bureau, has repeatedly interviewed samples of young people about their future plans in family making. A majority wished to have two children [1]. An interview study from 2001 (n=2,057) showed that about 95% of 23-year-old women and 25-year-old men in Sweden were definitely interested in having children, however with an emphasis on the future [14]. A study among 401 Swedish university students in 2004 revealed that more than 95% desired to have children, and more than 90% wanted to have at least two children [15]. Similar results were found in recent studies from Australia, Germany and Finland [165–168].

A specific aspect and a matter of investigation is whether the general population is unaware of the impact of age on female fertility. Several studies indicate that also highly educated groups underestimate the role of the woman's age in reproduction, for example when expressing that an ideal would be to have the first child around the age of 30, or even later [15, 167, 169–172].

ASSISTED REPRODUCTIVE TECHNOLOGIES (ART)

Modern technology methods, i.e. ART can only compensate to a smaller extent for age-related female infertility. For example, the results of IVF depend strongly on the quality of the woman's eggs, with a poorer success rate after 35–39 years of age. The IVF methods are also quite expensive and at least today out of reach for a majority of the population in many countries. Utilization rates of IVF are dependent on health insurance coverage and were 3–5 times higher per capita in some European countries than in the US in 1998 [8]. Taking into account all infertile couples that participate in at least one treatment cycle of IVF, the final "take-home baby rate" is 20–30%. Selected, motivated and younger couples in some clinics have higher success rates [42] [7]. It is possible that the public is unaware of these somewhat disappointing figures and that people may overestimate the possibilities of ART. Magazines often tell stories about women who have become mothers in high ages, some of them with the help of modern technology. The unawareness or even ignorance of the limitations of modern technology might be independent of educational level [15].

LEGAL ABORTIONS IN SWEDEN

The present law in Sweden was passed in 1975. It permits induced abortion on demand until the 18th week of pregnancy and until the 22nd week with special permission from the National Board of Health and Welfare. The costs are included in the Swedish national health insurance. During the period 1980 to 2004, the number of legal abortions per year has been closely correlated to the yearly number of live births. During the period 1980–1984, there were 162,552 legal abortions and 469,543 live

births; the ratio abortions/live births was 0.35. During the period 2000–2004 the corresponding numbers were 165,044 legal abortions and 477,807 live births; the ratio was the same as before, i.e. 0.35 [173]. Foreign-born women from Europe, Asia, Africa and Latin America had more legal abortions than Swedish-born women in a study performed in the year 2000. The reasons for having an induced abortion were similar between Swedish and foreign-born women, as were age, number of children, previous abortions and use of any contraceptive method [174].

MIGRATION TO SWEDEN

Since the end of the Second World War Sweden has been a country of continuous immigration. Today, the foreign-born inhabitants constitute about 12.4% of the whole population [175]. During the period from 1945 to 1967, there was a large labour immigration from Finland (300,000 individuals) and Southern Europe (35,000 individuals). In addition, refugees and labour immigrants came from Eastern Europe to Sweden between 1956 and 1989 (50,000 individuals). In the years 1973–91 Sweden received large numbers of non-European refugees and asylum-seekers from Latin America (Chile, Argentina and El Salvador; 60,000 individuals), Asia and Africa (Turkey, Syria, Lebanon, Iran, Iraq, Ethiopia, Eritrea, Somalia and other countries; 80,000 individuals).

Immigration in the 1990s has been dominated by refugees from the Balkan countries (mainly former Yugoslavia; 120,000 individuals) and Iraq (40,000 individuals) [175]. Moreover, there has been continuous immigration in lower numbers from the rest of the world. Family reunification has been an important part of immigration to Sweden with more than 95,000 individuals in the 1980s and more than 200,000 individuals in the 1990s. There have also been simultaneous movements out of Sweden; between 1991 and 1998 about 260,000 individuals emigrated from Sweden mostly to their country of birth.

About 17% of all newborn children in Sweden had foreign-born mothers in 1998–99 [175]. Many foreign-born people live under poorer socioeconomic conditions than the majority population.

LIFESTYLE FACTORS AND FEMALE FERTILITY

Previous studies suggest that several lifestyle factors, such as overweight/obesity, excessive alcohol consumption, smoking, psychological stress, and physical inactivity or excessive physical activity have a negative impact on female fertility. There is also some evidence that multiple negative lifestyle factors have a cumulative negative effect on fertility [44], particularly obesity, alcohol and smoking.

Obesity

One of the largest public health problems of today is a sedentary lifestyle with an excessive energy intake and too little physical activity, leading to overweight and obesity, which has several negative effects on public health, including a negative impact on female fertility. Studies have shown that weight reduction increases the chances of becoming pregnant. Hormonal mechanisms seem to play an important role in female

obesity (including the polycystic ovary syndrome) [176], which leads to impaired ovulation [45, 176–180].

Alcohol

Studies on alcohol and fertility indicate a dose-response relationship where higher consumption has a more adverse effect on fertility [181]. Higher alcohol consumption seems to decrease the time to conception in healthy women and may be a negative factor in women treated with IVF [182–185]. The negative effects of alcohol on female fertility may act through the hormonal regulation of the ovaries and the ovulation process, the ageing of the ovaries, the quality and maturation of the ovum before conception [186–189] and the phase of implantation and early embryonic growth [190] [191]. Increasing alcohol consumption has occurred among both Swedish men and women, which has become an increasing public health concern since the end of the 1990s. The last decade has shown a dramatic increase in per capita alcohol consumption and the per capita consumption today is as high as in the 19th century. In 2004, it was assessed at 10.4 litres per capita for all individuals aged 15 years old and above. Swedish national data are based on recorded purchases at the Swedish government-owned liquor stores as well as on estimated consumption of unrecorded alcohol beverages (e.g. home-produced and personally imported alcohol beverages) [192, 193]. A questionnaire study in 2001 found an increase among women of the prevalence of hazardous or harmful drinking from 11% in 1997 to 15% in 2001. The increase was especially pronounced among women aged 28–38 years [194]. In addition, self-rated consumption is known to underestimate the true consumption by about 50–60% in population surveys [192, 195]. In study 3, the long-term effect of high alcohol consumption on female fertility was examined.

Smoking

Studies in the general population indicate negative effects of smoking on fertility as regards time to pregnancy [45, 196–198] and in IVF studies [44, 199–202]. The proportion of smokers has gradually decreased in the Swedish population during the last few decades [203].

Physical activity

Excessive physical activity in female athletes may induce reduced ovulations through hormonal mechanisms leading to temporary infertility [204]. However, excessive physical activity is probably a minor public health problem as physical inactivity is much more common.

Stress

Psychological, environmental and psychosocial stress could possibly contribute to female infertility. Additionally, infertility in a couple could induce stress reactions. Later on, during treatment, psychological stress might influence the outcome of IVF [205–207]. Stress could act on biological/hormonal systems, mainly through the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-ovary axis, with negative effects on ovulation [206, 208]

AIMS

GENERAL AIM

The general aim was to investigate different aspects associated with fertility outcomes in women, such as age, country of birth, socioeconomic factors, diseases causing TFI and alcohol intake.

SPECIFIC AIMS

Study 1

The first aim was to examine whether first birth rates and mean age at first birth had changed between 1991–92 and 1997–98 among Swedish-born and 19 different sub-groups of foreign-born women. The second aim was to examine the impact of three socioeconomic factors (income, education, and employment), country of birth, and years in Sweden on first birth rates.

Study 2

The aim was to examine the association between country of birth and hospitalization for PID, EP, EM and infertility after accounting for age, time period and socioeconomic status, defined as income.

Study 3

The aim was to examine the long-term association between self-reported alcohol consumption in young women and the reproductive outcome. In addition, we also analysed the impact of alcohol consumption on diseases frequently resulting in TFI, i.e. PID and EM.

Study 4

The aim was to describe the clinical basis for the diagnostics of PID in a Swedish hospital setting and compare them with the diagnostic criteria of the CDC 2002 Guidelines. For this purpose we determined the frequency of reported symptoms and signs, and performed examinations among 189 out-patients who were clinically diagnosed with PID at the obstetric and gynaecological emergency department in a Swedish university hospital during 2001.

METHODS

STUDY 1

The study population consisted of two cohorts. Cohort 1 included on 1 January 1991 all childless women who were living in Sweden and were born 1948–1971. Cohort 2 included on 1 January 1997 all childless women who were living in Sweden and were born 1956–1977. The women in both cohort 1 and cohort 2 were aged 20–41 and had their first births in Sweden in 1991–92 (cohort 1) or 1997–98 (cohort 2). All women were followed until first birth, first emigration from Sweden, death or end of the study at December 31, 1992, or December 31, 1998.

Data were collected from the WomMed database at Center for Family and Community Medicine, Karolinska Institutet. WomMed is a research database that consists of 2.2 million women with residence permits in Sweden and was constructed by the linkage of several national registers, such as the Register of the Total Population and the Medical Birth Register. WomMed includes highly complete individual data, such as age, employment status, education, income, country of birth, year of immigration and emigration. A unique personal identification number was replaced by a serial number in order to provide anonymity in all registers. The serial number was used to link the national registers to WomMed.

Exclusion criteria and population size

Women with unknown employment status, educational status and country of birth were excluded (1.2% of all women in 1991–92 and 0.3% in 1997–98). Foreign-born women with registered first births outside Sweden (1.3% of the foreign-born women in 1991–92 and 0.4% in 97–98) and foreign-born women for whom information was lacking about years in Sweden (0.2% in 1991–92 and 0.5% in 1997–98) were also excluded. Women over 41 years and women under 20 years were excluded because their share of the total number of first births is less than 0.5% and less than 2%, respectively. This procedure yielded 452,000 women in cohort 1 and 495,756 women in cohort 2.

Outcome variables

First births constituted all live first births in cohort 1 and cohort 2.

Mean age at first birth was also calculated in cohort 1 and cohort 2.

Explanatory variables

Age was classified in the following groups: 20–24, 25–29, 30–34, 35–39, and 40–41 years.

Country of birth was categorized in 20 countries or groups of countries: Sweden, Norway, Denmark, Finland, Former Yugoslavia, Southern Europe (except Former Yugoslavia, Bosnia), OECD (except Sweden, Norway, Denmark, Finland, Eastern Europe and Southern Europe), Poland, Bosnia, Eastern Europe (except Poland), Turkey, Iran, Iraq, Arabic-speaking countries (except Iraq) including Northern Africa, Chile, Latin America (except Chile), Asia (except Turkey, Iran, Iraq), Somalia, Eritrea/Ethiopia and Africa (except Somalia, Eritrea and Ethiopia and Northern Africa).

Employment status comprised two groups: employed and non-employed.

Women who were salaried for at least one weekly hour and reported by the employer to the taxation authorities were counted as employed. Self-employed were also counted as employed. Women who were counted as non-employed included unemployed, housewives and students.

Educational status was divided into three categories:

1. Compulsory school or less (< ten years)
2. High school (11 to 12 years)
3. Two years at university level or more

Income was defined by the woman's yearly income for the years that preceded the two study periods, i.e. 1990 and 1996. The income variable was then divided into tertiles (low, middle and high), and included all kinds of registered income such as wages, subsidies, pensions, interest, etc.

Years in Sweden was divided into three groups for the 19 subgroups of foreign-born women: > 5, 2–5 and < 2 years.

We chose not to include marital status because many women in Sweden are cohabiting under marriage-like conditions without being formally married. Unmarried, cohabiting women without children are classified as being single in Swedish national data.

Statistical analysis

All statistical analyses were performed using the STATA Statistical Software: Release 8.0 [209]. Age-standardized first birth rates were calculated as the number of first births per 1,000 childless women per person-year. Relative risks of first birth were estimated by the use of Poisson regression analysis [210] with the Swedish-born women as reference. The results are shown as incidence rate ratios (IRR) with 95% confidence intervals (95% CI). Two models were included in the regression analysis: model 1 was adjusted for age and model 2 was adjusted for all the independent variables simultaneously. We tested for possible interactions between country of birth and the three socioeconomic variables.

We also performed a regression analysis of the 19 subgroups of foreign-born women where age and years in Sweden were included. In this analysis, Finnish-born women were used as reference because they are the largest group of foreign-born women in Sweden. They are also to a high extent similar to Swedish women as regards socioeconomic factors included in this study.

STUDY 2

Data were collected from the WomMed database (see above). The study population consisted of all women born between 1949 and 1984 and living in Sweden at some point between 1990 and 2004. The study population was divided into five cohorts, based on the following five 3-year periods: 1990–92, 1993–95, 1996–98, 1999–2001 and 2002–2004. For each 3-year period all women who were aged 20–41 years at the start of the period were included, i.e. in total 2,198,619 women. We excluded 27,546 women (1.2% of the study population) because they had been hospitalized for all four outcome variables (see below) before 1990. Another 591 women were excluded because of missing data on income and 305 women were excluded because they lacked

information about country of birth. Finally, 2,170,177 women remained in the study population.

Outcome Variable

The four outcome variables were defined according to the WHO International Classification of Diseases (ninth and tenth revisions, ICD-9 and ICD-10):

Pelvic Inflammatory Diseases (PID): ICD 9: 614, 615; ICD 10: N70, N71, N73

Ectopic pregnancy (EP): ICD 9: 633; ICD 10: O00

Endometriosis (EM): ICD 9: 617; ICD 10: N80

Infertility: ICD 9: 628; ICD 10: N97

The outcome variable infertility includes various infertility examinations, such as hysterosalpingography and/or laparoscopy and is referred to below only as infertility.

Explanatory Variables

The explanatory variables included age, country of birth, income and time period.

Age at diagnosis was categorized as 20–24, 25–29, 30–34, 35–39, and 40–41 years of age.

Country of birth was categorized in the following ten groups:

1. *Sweden*
2. *Finland*
3. *Western countries* included Austria, Belgium, Canada, Denmark, France, Germany, Great Britain, Iceland, Ireland, Liechtenstein, Luxemburg, The Netherlands, Norway, Switzerland, and USA.
4. *Southern Europe* included Andorra, Bosnia and Herzegovina, Croatia, Cyprus, Greece, Israel, Italy, Malta, Monaco, Portugal, San Marino, Spain, Vatican City, and Yugoslavia.
5. *The former Soviet bloc* included Albania, Armenia, Azerbaijan, Bulgaria, Byelorussia, Czechoslovakia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Kirgizstan, Latvia, Lithuania, Macedonia, Moldavia, Poland, Romania, Russia, Slovak Republic, Slovenia, Soviet Union, Tadzhikistan, Turkmenistan, Ukraine and Uzbekistan.
6. *Eritrea/Ethiopia/Somalia*
7. *Other African countries* included Morocco, North African countries and all other countries in Africa.
8. *Latin America* included Argentina, Bolivia, Brazil, the Caribbean Islands, Central America, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru, Surinam, Uruguay, and Venezuela.
9. *Middle Eastern countries* included Bahrain, Brunei, the Gaza Territory, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, South Yemen, Syria, Turkey, the United Arab Emirates and Yemen.
10. *Other Asian countries* included Afghanistan, Bangladesh, Bhutan, Cambodia, China, East Timor, Hong Kong, India, Indonesia, Japan, Laos, Malaysia, the Maldives, Mongolia, Myanmar, Nepal, North Chorea, “Oceania”, Pakistan, the Philippines, Singapore, South Chorea, Sri Lanka, Taiwan, Thailand, and Vietnam.

Income

Individual income was coded into three groups: low income (25% of the study population), middle income (50% of the study population) and high income (25% of the study population). The spouse's income was not included in the study. The income variable was defined as each woman's disposable annual income calculated as the average income between 1990 and 2004.

Time period was categorized as 1990–92, 1993–95, 1996–98, 1999–2001 and 2002–2004.

Statistical analysis

All women in the five cohorts were followed for first hospital admission during three years, each cohort from January 1 in 1990, 1993, 1996, 1999 or 2002, respectively. Foreign-born women who immigrated to Sweden within one time period were followed from date of immigration. The follow-up for each cohort, i.e. 3-year period, ended at first hospitalization during the study period, emigration, age >41 years, death, or at the end of the 3-year period. Each diagnosis was analysed separately. Person-years were calculated for each 3-year period. Age-adjusted rates were calculated by all the explanatory variables. Trends in the rates of PID, EP, EM, and infertility were evaluated by Poisson regression in order to quantify the effects of time while adjustment was made for age and time period. The relative risks (RR) were obtained from the exponentiated regression coefficients and are shown with 95% confidence interval (CI). Interaction tests were performed between country of birth and income; no specific interactions were found.

STUDY 3

During the years 1969–70, a stratified sample of approximately 30,000 individuals aged 18–64 was drawn from the population in Stockholm County which by then had about 445,000 inhabitants in this age-range. The sample was stratified by age; 50% of the study population was in the age-range 18–25 years, 33% were in the age-range 26–44 years and 17% in the age-range 45–64 years. The main intention was to study the need for health services [211]. All women aged 18–28 years from the sample were selected for this study, numbering 7,393 individuals. Women aged 18–25 years were 6,146 and those aged 26–28 years were 1,247. The vast majority of these women were native Swedes and approximately 12% were immigrants, mainly from Finland (8%). All 7,393 women had received a postal questionnaire with 30 questions concerning physical and social difficulties in daily life, health care needs and two questions about alcohol use. There were no questions about smoking habits or other lifestyle factors. The response rate was 87%. Non-responders did not differ from responders regarding fertility in our drop-out analysis.

The definition of high-consumption of alcohol was based on the Swedish National Food Administration's recommendations that the consumption of more than 140 g per week should be considered to have negative effects on health [212]. Low consumers were defined as drinking less than 50 g per week [213]. The amount of alcohol consumed was estimated from the answers to two questions in the postal questionnaire. Women answering "Never" to the question "Do you drink alcohol?" and "Never" to the

question “Do you drink at least half a bottle of spirits or a couple of bottles of wine per week?” were defined as low consumers. Women answering “Often” or “Sometimes” to the first question or “Often” or “Sometimes” to the second question were defined as high consumers. The rest were defined as moderate consumers.

All participants were followed up in the National In-patient Register from the study start in 1970 to the end of 1987. The finally childless part of our study population was estimated to be 13%. The first time that a patient was registered for any diagnosis during the study period, was labelled “First partus”, “First miscarriage” etc. This means that a certain number of first-ever reproductive events and diseases had occurred before the study start.

The National In-patient Register kept by the National Board of Welfare contains records of all hospital admissions in Sweden. The main diagnoses during the hospitalizations were recorded in accordance with the ICD, according to the recommendations from WHO.

Statistical analysis

Multivariate analysis was performed utilizing a Cox regression model [214]. The results are shown as relative risk ratios (RR) for the exposure variable, with 95% CI. Moderate consumers were chosen as the reference group. The RR's were adjusted for age, using the two age-groups 18–25 years and 26–28 years. The analyses were performed by the PHREG procedure in the SAS data package (SAS Institute Inc., Cary, NC, USA).

STUDY 4

This retrospective study was entirely based on information from the electronic medical records. There were 4,671 gynaecological patients treated at the obstetric and gynaecological emergency department (OGED) at the Karolinska University Hospital, site Huddinge, in 2001. We checked all their ICD-10 codes (International Classification of Diseases, tenth revision) in the electronic medical records. There were 381 patients with ICD-10 codes for PID (N70.0–N71.9; N73.0–N73.5). Women with an obvious cause for their PID were excluded, i.e. women with PID following partus, miscarriage, abortion, insertion of IUD and intra-uterine operations (n=175). Sixteen in-patients were also excluded. The inclusion criteria gave 189 out-patients with PID diagnosis for the study.

The medical history data were collected by the doctor on duty. A pelvic examination, i.e. a bimanual vaginal palpation, was performed in all cases followed by, in 82% of the cases, a TVS.

We extracted from all 189 patient's electronic medical records background data (age, parity, contraceptive method), length of history, symptoms and signs, pelvic examination, laboratory tests and medication. The length of history was determined by the symptom with the longest reported duration.

For each laboratory test, there were tested and non-tested patients. CRP was analysed via a capillary test. A urine specimen was requested from all patients before the pelvic examination, and 52% were able to produce it (n=98). The urine was analysed for leucocyturia, measured by a test stick. Urine culture was performed in 28 patients. CT was analysed with a polymerase chain reaction (PCR) method (Roche

COBOS Amplicor®). A swab was taken always from the endocervix and mostly from the urethra. NG was cultured via an endocervical swab.

Ethics

The studies in the present thesis were approved by the Ethics Committee at the Karolinska Institutet, Stockholm.

RESULTS

STUDY 1

Table 1 shows the proportions of childless women, proportions of first births, and age-standardized FBRs in 1991–92 and 1997–98. Among both Swedish-born and almost all foreign-born women FBRs decreased between the two periods. The proportions of first births by Swedish-born women decreased from 91.6% in 1991–92 to 89.4% in 1997–98. The proportions of non-employment more than doubled among the women between the two periods. Women with a high educational status increased approximately by 50%. In both periods there was a tendency for the proportions of first births to be higher among women with high socioeconomic status. The peak in FBRs was found in the ages 25–29 in 1991–92 and in the ages 30–34 in 1997–98.

In 1991–92 the highest proportions of women with low income were found among women born in Iran, Iraq, Arabic-speaking countries and Somalia. In 1997–98 a similar pattern was observed. In both periods the highest proportions of women with low educational status were found among women from Turkey, Arabic-speaking countries and Somalia. Some groups of foreign-born women had a higher proportion of women with high educational status than Swedish-born women, such as women from Southern Europe, OECD and Eastern Europe. For all women, employment rates decreased between the two periods. The decrease in employment was especially pronounced among some groups of foreign-born women (data not shown).

Figure 1 shows that the mean age at first birth increased among Swedish-born women and most foreign-born women between the two periods. For example, among Swedish-born women the mean age at first birth increased from 26.5 to 27.8 years. In contrast, women from Somalia showed an opposite trend: their mean age at first birth decreased between 1991–92 and 1997–98. Figure 2 shows an additional analysis for the period 2002–2003. Several subgroups had a further increase in the mean age at first birth compared to the years before.

Data on mean age at first birth are not fully available in European statistics. To have an idea of the fertility trends in European countries, we compared our results with the *mean age of women at childbearing* (available in Eurostat 2004) for the period 1991–2003. Many European countries clearly exhibited an increase in the mean age of women at childbearing [143]

Table 2 shows the models. Model 1 is adjusted for age and model 2 is adjusted for age, employment, education and income. IRRs are shown with 95% CI with Swedish-born women as reference. In 1991–92 the age-adjusted IRRs (model 1) for first birth were higher for women born in Turkey, Iraq, Arabic-speaking countries, Somalia and Eritrea/Ethiopia than for Swedish-born women and increased after the addition of employment, education and income in model 2. In 1997–98 the age-adjusted IRRs for first birth were higher for women born in Norway, Yugoslavia, Bosnia, Eastern Europe, Turkey, Iran, Iraq, Arabic-speaking countries, Chile, Asia, Somalia, Eritrea/Ethiopia and Africa than for Swedish-born women and increased after the addition of employment, education and income. For example, in model 2 the IRR for women born in Iraq and Arabic-speaking countries was 4.40 (CI = 3.97–4.86) and 3.38 (CI = 3.08–3.70), respectively. In both periods non-employment and low income were associated with

decreased first birth fertility. Low educational status was associated with slightly increased first birth fertility.

There were significant interactions by country of birth and employment status and country of birth and income for both periods. Similar results were found for educational status, although less pronounced (data not shown). The significant interactions between country of birth and the socioeconomic variables show that several foreign-born groups increased their first birth fertility even if they were non-employed or had a low income. The opposite pattern was observed among Swedish-born women, who decreased their first birth fertility when they were non-employed or had a low income (data not shown).

Table 3 shows the IRRs for first birth for the 19 groups of foreign-born women (Finland is used as reference). There was an apparent gradient where fewer years in Sweden were associated with increased first birth fertility. For example, in 1997–98 the IRR was 2.83 (2.66–3.02) for foreign-born women who had spent less than two years in Sweden.

Table 1. Distribution of childless women and first births (in percentages) and age-standardized first birth rates (per 1,000 childless women per year) by country of birth, age and the socioeconomic variables. Sweden, ages 20–41, 1991–92 and 1997–98.

	1991–92			1997–98		
	Women % N = 452,000	First births % N = 86,812	First birth Rates	Women % N = 495,756	First births % N = 66,195	First birth Rates
Country of birth						
Sweden	91.1	91.6	87	91.0	89.4	26
Norway	0.69	0.47	74	0.30	0.36	83
Denmark	0.42	0.33	87	0.23	0.25	71
Finland	2.50	2.2	95	1.3	1.1	60
Southern Europe	0.30	0.22	71	0.23	0.19	57
OECD	1.10	0.68	60	0.86	0.75	54
Poland	0.50	0.47	104	0.47	0.45	65
Yugoslavia	0.32	0.36	107	0.31	0.47	105
Bosnia	0.01	0.01	154	0.35	0.56	102
Eastern Europe	0.43	0.37	86	0.58	0.67	71
Turkey	0.21	0.40	159	0.26	0.48	113
Iran	0.47	0.50	86	0.62	0.75	74
Iraq	0.05	0.10	158	0.21	0.58	171
Arabic-speaking	0.20	0.43	170	0.30	0.70	142
Chile	0.27	0.30	100	0.36	0.37	70
Latin America	0.26	0.27	94	0.42	0.42	66
Asia	0.91	0.89	93	1.6	1.6	67
Somalia	0.01	0.03	173	0.08	0.16	126
Eritrea-Ethiopia	0.24	0.30	104	0.34	0.53	93
Africa	0.12	0.13	103	0.16	0.19	77
Age						
20–24	46.2	35.3	69	44.0	25.1	37
25–29	28.2	42.0	127	29.1	41.3	88
30–34	13.6	17.4	112	15.1	25.9	105
35–39	9.0	4.8	50	8.7	6.9	51
40–41	3.0	0.5	17	3.1	0.8	18
Employment						
Employed	80.8	91.5	98	59.0	76.5	76
Non-employed	19.2	8.5	43	41.0	23.5	41
Education						
High	21.6	26.1	92	30.2	33.8	58
Middle	65.9	62.0	85	59.6	56.2	64
Low	12.5	11.9	92	10.2	10.0	66
Income						
High	32.1	43.3	114	31.5	51.5	91
Middle	32.1	38.7	103	33.3	32.6	61
Low	35.8	18.0	50	35.2	15.9	36
Total	100	100	89	100	100	64

Figure 1. Mean age at first birth by country of birth, 1991–92 and 1997–98.

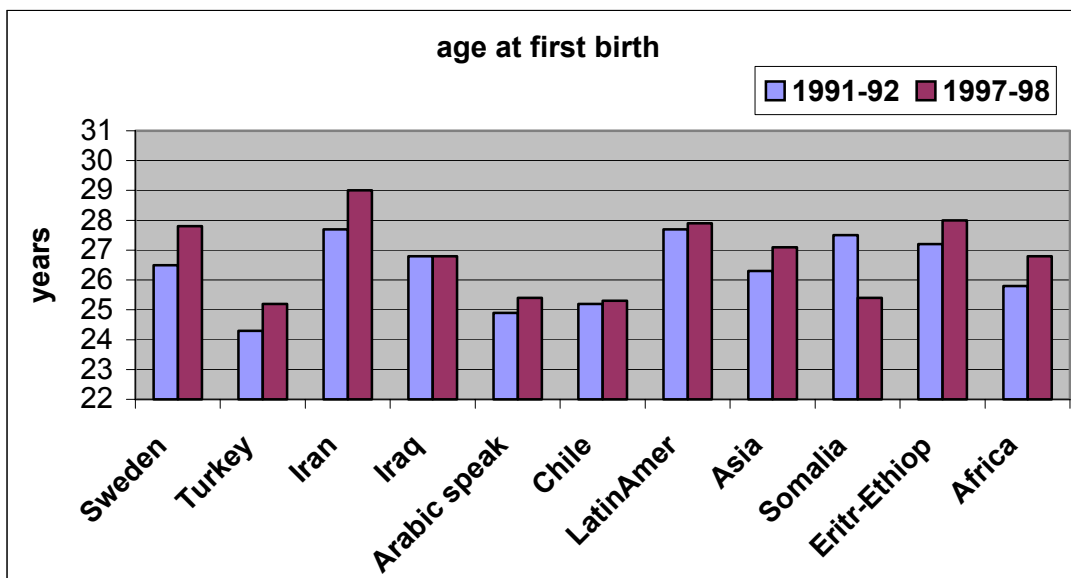
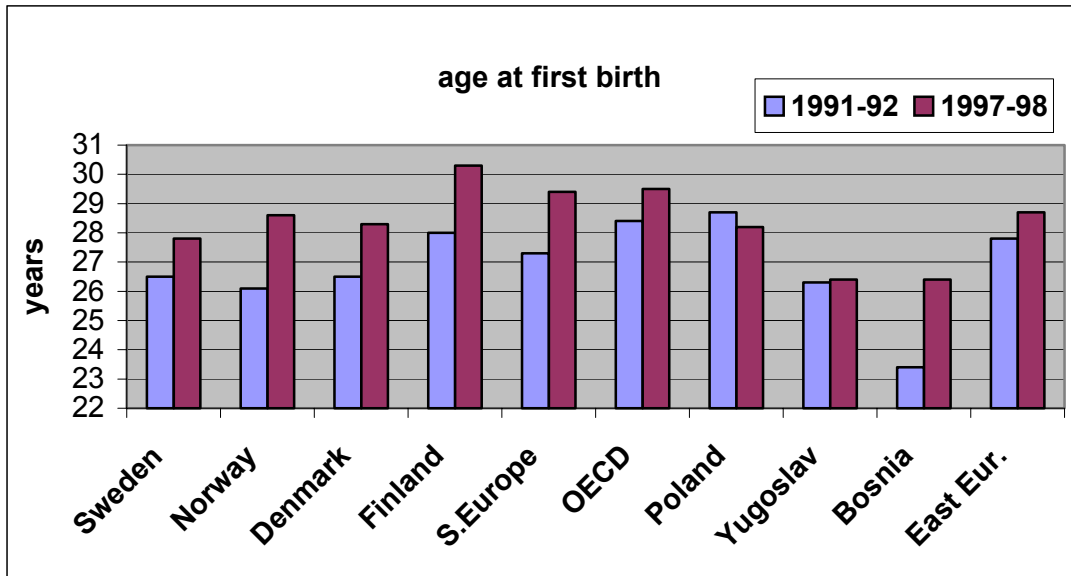


Figure 2. Mean age at first birth by country of birth, 2002 and 2003 added.

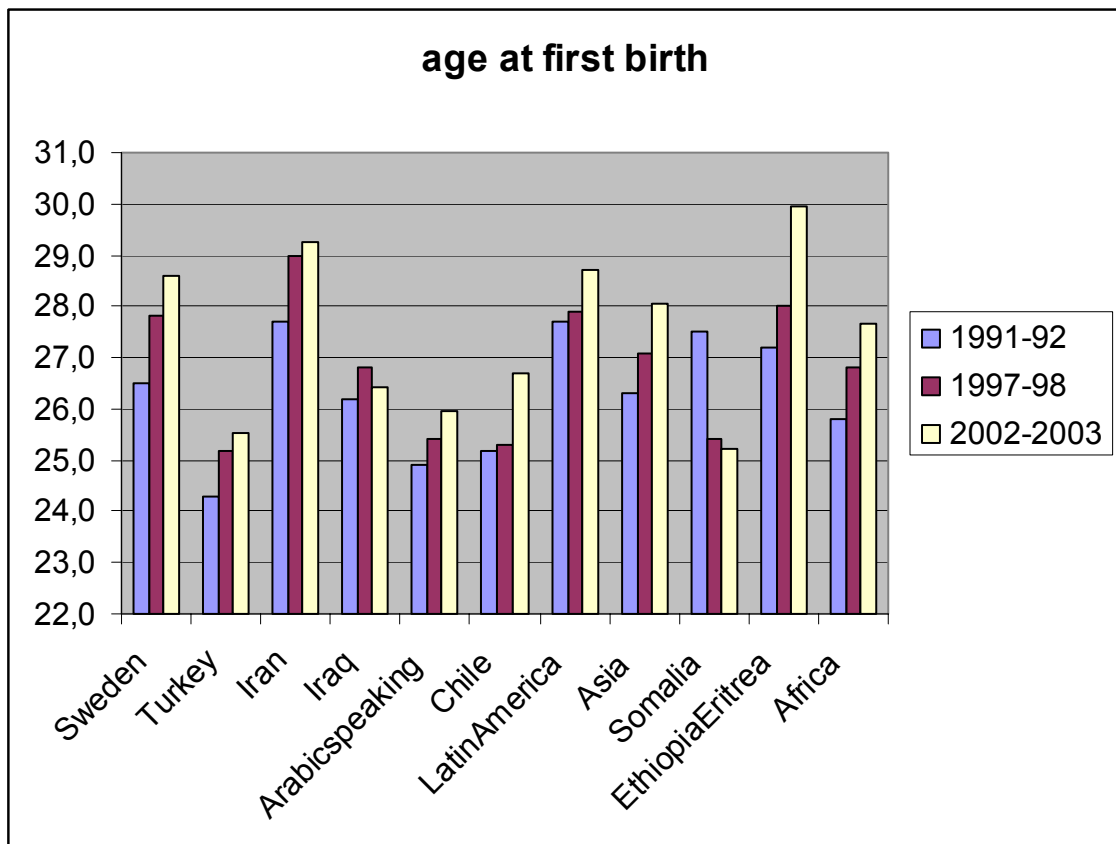
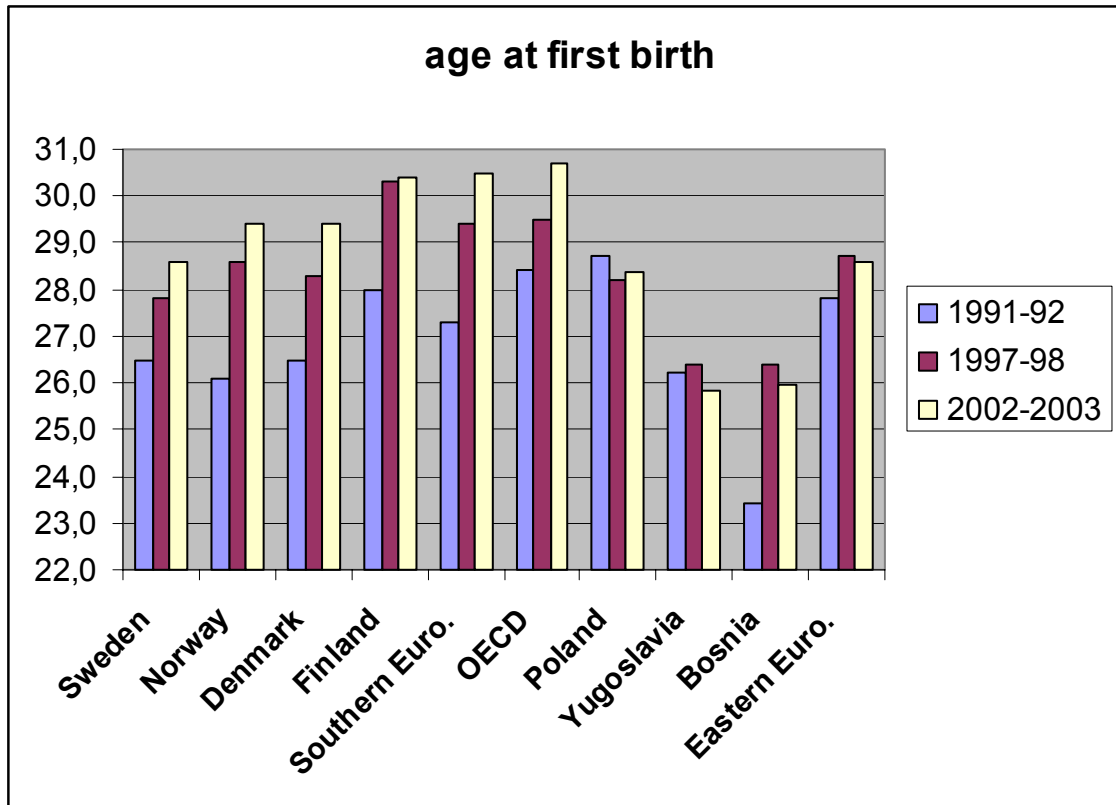


Table 2. Incidence Rate Ratio (IRR) with 95% confidence interval (CI) for first birth by country of birth, age, and the socioeconomic variables. Sweden, ages 20–41, 1991–92 and 1997–98. Poisson regression.

	1991–92		1997–98	
	Model 1* IRR(CI)	Model 2* IRR(CI)	Model 1* IRR(CI)	Model 2* IRR(CI)
Country of birth				
Sweden	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Norway	0.81 (0.73–0.89)	0.89 (0.81–0.99)	1.26 (1.11–1.43)	1.35 (1.19–1.53)
Denmark	0.93 (0.82–1.04)	1.01 (0.90–1.13)	1.07 (0.92–1.25)	1.15 (0.99–1.34)
Finland	0.96 (0.92–1.00)	0.97 (0.93–1.02)	0.87 (0.81–0.93)	0.89 (0.83–0.96)
Southern Europe	0.72 (0.62–0.83)	0.94 (0.82–1.09)	0.82 (0.69–0.98)	1.12 (0.94–1.33)
OECD	0.68 (0.63–0.74)	0.85 (0.78–0.92)	0.86 (0.79–0.94)	1.06 (0.97–1.16)
Poland	1.10 (1.00–1.21)	1.36 (1.23–1.50)	1.02 (0.91–1.14)	1.30 (1.16–1.46)
Yugoslavia	1.07 (0.96–1.20)	1.19 (1.06–1.33)	1.44 (1.28–1.61)	1.79 (1.60–2.00)
Bosnia	1.24 (0.59–2.61)	1.39 (0.66–2.91)	1.63 (1.47–1.80)	2.63 (2.37–2.91)
Eastern Europe	0.93 (0.83–1.03)	1.14 (1.02–1.27)	1.13 (1.03–1.24)	1.54 (1.41–1.70)
Turkey	1.88 (1.69–2.09)	2.23 (2.01–2.48)	1.93 (1.73–2.16)	2.40 (2.15–2.68)
Iran	0.98 (0.89–1.07)	1.52 (1.38–1.67)	1.20 (1.09–1.31)	1.71 (1.56–1.87)
Iraq	1.71 (1.38–2.11)	2.62 (2.12–3.24)	2.66 (2.40–2.94)	4.40 (3.97–4.86)
Arabic-speaking	1.95 (1.76–2.16)	2.72 (2.46–3.02)	2.43 (2.22–2.66)	3.38 (3.08–3.70)
Chile	1.12 (0.99–1.27)	1.33 (1.18–1.51)	1.21 (1.06–1.37)	1.44 (1.27–1.63)
Latin America	1.07 (0.94–1.22)	1.35 (1.18–1.53)	1.07 (0.95–1.20)	1.37 (1.22–1.54)
Asia	1.04 (0.97–1.12)	1.25 (1.16–1.34)	1.08 (1.01–1.14)	1.26 (1.19–1.34)
Somalia	2.02 (1.33–3.07)	2.94 (1.94–4.47)	2.17 (1.79–2.62)	3.27 (2.70–3.96)
Eritrea-Ethiopia	1.16 (1.03–1.32)	1.39 (1.23–1.58)	1.42 (1.28–1.57)	1.68 (1.51–1.86)
Africa	1.12 (0.93–1.34)	1.36 (1.13–1.64)	1.23 (1.03–1.46)	1.54 (1.29–1.84)
Age				
20–24	Ref	Ref	Ref	Ref
25–29	1.84 (1.81–1.87)	1.54 (1.51–1.56)	2.37 (2.33–2.42)	1.70 (1.66–1.73)
30–34	1.62 (1.59–1.65)	1.27 (1.25–1.30)	2.83 (2.77–2.89)	1.84 (1.80–1.89)
35–39	0.72 (0.70–0.75)	0.56 (0.54–0.58)	1.38 (1.34–1.43)	0.89 (0.86–0.92)
40–41	0.24 (0.22–0.27)	0.19 (0.18–0.21)	0.48 (0.44–0.53)	0.31 (0.28–0.34)
Employment				
Employed	Ref	Ref	Ref	Ref
Non-employed	0.44 (0.43–0.45)	0.65 (0.63–0.66)	0.54 (0.53–0.55)	0.73 (0.72–0.75)
Education				
High	Ref	Ref	Ref	Ref
Middle	0.86 (0.85–0.88)	0.88 (0.87–0.90)	1.03 (1.01–1.05)	1.02 (1.00–1.03)
Low	0.93 (0.90–0.95)	1.05 (1.02–1.07)	1.06 (1.03–1.09)	1.23 (1.19–1.26)
Income				
High	Ref	Ref	Ref	Ref
Middle	0.92 (0.91–0.93)	0.94 (0.93–0.96)	0.68 (0.67–0.69)	0.73 (0.72–0.74)
Low	0.43 (0.42–0.44)	0.50 (0.49–0.51)	0.38 (0.37–0.39)	0.43 (0.42–0.45)

*Model 1 adjusted for age

*Model 2 adjusted for age, country of birth, employment, education, and income.

Table 3. Incidence Rate Ratio (IRR) with 95% confidence interval (CI) for first birth for the foreign-born women by years in Sweden, adjusted for age and country of birth (Finland is used as reference). Ages 20–41, 1991–92 and 1997–98. Poisson regression.

Years in Sweden	1991–92	1997–98
	IRR (95% CI)	IRR (95% CI)
<2	1.38 (1.30–1.46)	2.83 (2.66–3.02)
2–5	1.18 (1.10–1.27)	1.65 (1.55–1.76)
>5	1 (ref)	1 (ref)

STUDY 2

Table 4 shows the RRs with 95% CI of first hospital admission for PID, EM, EP and infertility by country of birth. All risks mentioned below refer to risks of hospitalization. All models are adjusted for time period, age, and income. For PID, all groups of foreign-born women exhibited significantly increased risks compared to Swedish-born women. The highest risks of PID were found among women from Other African countries (RR = 2.11, CI = 1.73–2.58), Eritrea/Ethiopia/Somalia (RR = 1.69, CI = 1.36–2.09), and Southern Europe (RR = 1.67, CI = 1.49–1.88).

For EM, slightly increased risks were observed among women from Finland and Western countries compared with the Swedish-born women, whereas women from Eritrea/Ethiopia/Somalia exhibited decreased risks of EM. Women from the Middle East and Other Asian countries had the highest risks of EM of all groups. Their significant RRs were 1.50 and 1.53, respectively.

For EP, women from Finland, Southern Europe, Former Soviet Bloc, Latin America, and Other Asian countries exhibited increased risks compared with the Swedish-born women. Their significant RRs varied between 1.14 and 1.34.

For infertility, all groups of foreign-born women exhibited significantly increased risks compared to Swedish-born women. The highest RRs were found among women from Other African countries (RR = 2.93, CI = 2.39–3.60), Other Asian countries (RR = 2.42, CI = 2.15–2.73), and Middle Eastern countries (RR = 2.21, CI = 1.99–2.46). RRs for all four outcomes were attenuated with time. Lower income implied a lower risk of EM whereas income had practically no effect on PID and EP. In contrast, women with low and middle income had significantly lower risks of hospitalization for infertility. The RRs for infertility were 0.26 (CI = 0.25–0.28) and 0.52 (CI = 0.50–0.54) for low and middle income, respectively.

Table 4. Relative risk (RR) with 95% confidence interval (CI) of first hospital admissions for the four outcome variables by country of birth, adjusted for time period, age, and income. Women aged 20–41 years between 1 January 1990 and 31 December 2004, Sweden.

	Pelvic inflammatory disease			Endometriosis		
	RR	95% CI		RR	95% CI	
Country of birth						
Sweden	1	Reference		1	Reference	
Finland	1.12	1.01	1.24	1.16	1.03	1.30
Western countries	1.30	1.16	1.46	1.18	1.03	1.36
Southern Europe	1.67	1.49	1.88	1.03	0.88	1.22
Former Soviet Bloc	1.41	1.25	1.60	1.09	0.94	1.28
Eritrea/Ethiopia/Somalia	1.69	1.36	2.09	0.51	0.33	0.81
Other African countries	2.11	1.73	2.58	0.91	0.64	1.29
Latin America	1.41	1.20	1.66	1.15	0.93	1.42
Middle Eastern countries	1.58	1.43	1.74	1.50	1.33	1.69
Other Asian countries	1.43	1.26	1.64	1.53	1.32	1.78
Period						
1990–1992	3.38	3.13	3.66	1.77	1.64	1.91
1993–1995	1.79	1.65	1.94	1.17	1.09	1.27
1996–1998	1.33	1.22	1.44	1.20	1.11	1.29
1999–2001	1.05	0.96	1.15	1.05	0.96	1.14
2002–2004	1	Reference		1	Reference	
Age						
20–24	1	Reference		1	Reference	
25–29	0.89	0.83	0.96	1.32	1.19	1.46
30–34	0.92	0.86	0.98	1.41	1.28	1.56
35–39	0.85	0.79	0.91	1.56	1.41	1.72
40–41	0.80	0.74	0.87	1.77	1.60	1.97
Income						
Low	0.98	0.93	1.03	0.53	0.50	0.56
Middle	1.05	1.01	1.10	0.72	0.69	0.76
High	1	Reference		1	Reference	

Table 4. Continued.

	Extrauterine pregnancy			Infertility		
	RR	95% CI		RR	95% CI	
Country of birth						
Sweden	1	Reference		1	Reference	
Finland	1.24	1.13	1.35	1.13	1.02	1.26
Western countries	1.08	0.97	1.20	1.49	1.33	1.68
Southern Europe	1.14	1.02	1.27	1.58	1.38	1.82
Former Soviet Bloc	1.34	1.20	1.48	1.87	1.66	2.10
Eritrea/Ethiopia/Somalia	0.87	0.69	1.10	1.55	1.18	2.03
Other African countries	1.18	0.95	1.45	2.93	2.39	3.60
Latin America	1.34	1.17	1.54	1.92	1.64	2.25
Middle Eastern countries	1.08	0.99	1.19	2.21	1.99	2.46
Other Asian countries	1.24	1.10	1.39	2.42	2.15	2.73
Period						
1990–1992	1.98	1.86	2.10	11.36	10.06	12.82
1993–1995	1.24	1.17	1.32	4.90	4.33	5.54
1996–1998	1.09	1.02	1.16	2.54	2.24	2.89
1999–2001	0.97	0.91	1.04	1.41	1.22	1.62
2002–2004	1	Reference		1	Reference	
Age						
20–24	1	Reference		1	Reference	
25–29	1.84	1.70	1.99	3.10	2.84	3.39
30–34	2.34	2.17	2.53	4.06	3.72	4.43
35–39	1.77	1.64	1.92	2.37	2.17	2.59
40–41	0.91	0.83	1.00	0.61	0.53	0.69
Income						
Low	0.98	0.93	1.02	0.26	0.25	0.28
Middle	1.00	0.97	1.04	0.52	0.50	0.54
High	1	Reference		1	Reference	

STUDY 3

Of the 7,393 women, 7% were high consumers and 23% were low consumers of alcohol. The remaining 70% were defined as moderate consumers. We found that 252 women were admitted to hospital for fertility examinations during the study period. Women with high alcohol consumption had a significantly higher risk (RR = 1.58; CI: 1.07–2.34) of being subjected to infertility examinations, as compared with moderate consumers (Table 5). The risk run by low consumers was significantly lower (RR = 0.64; CI: 0.46–0.90).

Table 5. Age-adjusted relative risks (RR) with 95% confidence interval (CI) of hospitalization for indicated diagnoses in relation to self-reported alcohol consumption for women aged 18–28 in 1970 and followed until the end of 1987.

Diagnoses	Alcohol consumption						Total cases
	Low n= 1,676	Moderate n= 5,192	High n= 525	No. of cases	RR (CI)	No. of cases	
Partus no. 1	944	3,274	286	1.00 (reference)	0.87 (0.81–0.94)	286	4,504
Partus no. 2	456	1,633	125	1.00	0.86 (0.78–0.95)	125	2,214
Partus no. 3	152	410	33	1.00	1.17 (0.97–1.41)	33	595
Abortion no. 1	337	980	119	1.00	1.17 (0.97–1.41)	119	1,436
Abortion no. 2	86	251	29	1.00	1.07 (0.84–1.36)	29	366
Infertility examination no. 1	39	184	29	1.00	0.65 (0.46–0.92)	29	252
Miscarriage no. 1	150	468	48	1.00	0.96 (0.80–1.16)	48	666
Miscarriage no. 2	27	94	9	1.00	0.87 (0.57–1.34)	9	130
Extrauterine pregnancy no. 1	26	121	16	1.00	0.67 (0.44–1.02)	16	163
Pelvic inflammatory disease no. 1	58	227	29	1.00	0.79 (0.59–1.06)	29	314
Pelvic inflammatory disease no. 2	20	52	6	1.00	1.20 (0.71–2.00)	6	78
Endometriosis no. 1	86	196	20	1.00	1.36 (1.06–1.76)	20	302

Moreover, for both low and high consumers, we observed a significantly lower number of both first and second registered partus, compared with moderate alcohol consumers. High consumers, but not low consumers, had a larger number of first registered legal abortions (RR = 1.25; CI: 1.03- 1.51). As for the second and third abortions, no significant differences were observed. Regarding miscarriages, ectopic pregnancies and PID, there were no differences between the groups (Table 5).

STUDY 4

More than half of the 189 patients were 30 years old or younger and 36% were childless. Twenty-four percent had an IUD. More than 50% of the patients had a length of history up to one week, and around 20% more than one month. Thirty-nine patients had visited a doctor, mostly a GP, within days or weeks before they came to the OGED. Fifteen of those had been treated for suspected UTI and another 15 patients had visited a gynaecologist, without receiving PID treatment (data not shown).

Abdominal pain was reported by 98%, abnormal vaginal discharge by 45%, while feelings of sickness, dysuria, fever and/or chills, lower back pain, and abnormal bleedings were each reported by 24–30% of the patients. Pain at intercourse was reported by 5%. All 189 patients were tender at examination. Almost half of the patients had tenderness over the uterus and/or motion tenderness of cervix and both adnexa, 20% were tender over the uterus and/or cervix only, 19% over the uterus and one of the adnexa and 12% over the adnexa only (Table 6).

Table 6. Frequency (percentages) of the symptoms and signs and tenderness at examination among the 189 patients diagnosed with PID.

Symptoms	percentage
Abdominal pain	98
Abnormal vaginal discharge	45
Feelings of sickness	30
Dysuria	27
Fever and/or chills	25
Lower back pain	25
Abnormal bleedings	24
Pain at intercourse	5
Tenderness at examination	
Uterus and/or motion of cervix and both adnexa	49
Uterus and/or motion of cervix only	20
Uterus and/or motion of cervix and one adnexa	19
Both adnexa (uterus untender)	6
One adnexa (uterus untender)	6

CT was detected among 5% of the 98 tested patients, while no NG was detected among the 23 tested patients. The CRP was normal (<10) among more than 50% of the 110

tested patients. About 50% of the 98 patients who were able to produce a urine test had leucocyturia (Table 7).

Table 7. Results of the laboratory tests among the tested subgroups of the 189 patients diagnosed with PID.

		Percentage
C-reactive protein		
	n=110/189	
<10	(normal)	55
10–20	(slightly elevated)	19
≥ 20	(elevated)	26
Urine leucocytes		
	n=98/189	
Negative		54
Positive		46
Chlamydia Trachomati		
	n=98/189	
Positive		5
Neisseria Gonorrhoeae		
	n=23/189	
Positive		0

TVS was performed in 156 patients. Wet smear was performed among less than 20% of the patients. All 189 patients were given oral treatment with antibiotics (data not shown).

DISCUSSION

MAIN FINDINGS

FBRs decreased and mean age at first birth increased between 1991–92 and 1997–98 among Swedish-born and most foreign-born women. In both periods non-employment and low income were associated with decreased first birth fertility. However, in contrast to Swedish-born women, several groups of foreign-born women increased their first birth fertility even if they were non-employed or had a low income. Among foreign-born women fewer years in Sweden was significantly associated with increased first birth fertility (study 1). In an additional analysis for the period 2002–2003, several subgroups had a further increase in the mean age at first birth compared to the years before.

For PID and infertility, all groups of foreign-born women exhibited significantly increased risks compared to Swedish-born women. The highest risks of PID were found among women from Southern Europe, Eritrea/Ethiopia/Somalia and other African countries whereas the highest risks of infertility were found among women from Middle Eastern countries, other Asian countries and other African countries. Country of birth was not strongly associated with EM with the exception for women from Middle Eastern and other Asian countries. Some groups of foreign-born women exhibited slightly or moderately increased risks of EP. Women with low and middle income had significantly lower risks of hospitalization for infertility (study 2).

High alcohol consumption was associated with increased risks of infertility examinations and with lower number of first partus (study 3).

The clinical basis for the diagnostics of PID at the OGED was largely in accordance with the symptoms and signs mentioned in the CDC 2002 Guidelines. Only about half of the patients were tested for CT, giving a prevalence rate among the tested patients of 5%. In addition, feelings of sickness, dysuria, and lower back pain were all frequent symptoms among our patients, although not mentioned in the CDC 2002 Guidelines. Some women had a relatively long symptom history, which suggests that they might initially have presented mild or atypical symptoms of PID. The CRP was normal (<10) among more than half of the tested patients (study 4).

POSTPONEMENT OF FIRST BIRTH AND ITS CONSEQUENCES

Female fertility declines already from the age of around 30 and especially after the age of 35 [150, 153–155]. Even when sophisticated and expensive methods are available in the country, such as IVF [155, 215], the risk of primary and secondary infertility and involuntary childlessness will increase if first birth is postponed. Increasing age of the woman at delivery also implies an increased risk of several medical consequences, for example chromosome congenital abnormalities and particularly Down's syndrome [216], low birth weight [217], preterm delivery [217], late foetal deaths, small for gestational age infants [218, 219], caesarean section [217, 220], breast cancer [221, 222], and postpartum psychosis [223]. In addition, there is a significant risk of psychological distress among both infertile women and men. For example, distinctions exist

between fertile and infertile populations with respect to depression, anxiety and self-esteem [206]. Women also seem to suffer more than men if they are diagnosed with infertility. Infertile women scored lower on self-esteem and reported lower life satisfaction than infertile men. They also tended to blame themselves to a higher extent than men [206, 224].

SOCIOECONOMIC FACTORS AND FERTILITY

Previous research in Sweden on the association between socioeconomic factors and fertility is inconsistent [157, 162, 164]. Study 1 showed a strong association between both non-employment and low income and decreased first birth fertility. Our data also showed that between 1991–92 and 1997–98 the proportions of employed women decreased from 82.5% to 61.0%. During this period Swedish society experienced the loss of over 500,000 jobs. This caused an almost four-fold increase of the official unemployment rates among women, which were particularly high among women under the age of 25 [225]. These changes in employment opportunities affected both Swedish-born and foreign-born women, although there are important socioeconomic, cultural and religious differences between Swedish-born and many foreign-born women. It is possible that some groups of foreign-born women do not strive to have as high employment rates as do Swedish women. However, before the unemployment rates rose in Sweden during the 90s many foreign-born women were employed. It is therefore likely that many foreign-born women involuntarily faced unemployment. The interaction tests revealed interesting findings. When Swedish women were used as reference, many groups of foreign-born women had higher first birth fertility even if they were non-employed or had a low income.

The proportions of women with high educational status in our study population increased markedly between 1991–92 and 1997–98. It is possible that the increased mean age at first birth is related to prolonged study periods. Women from Turkey, Iraq, Arabic-speaking countries and Somalia had the highest proportions of women with low educational status and the highest FBRs. A recent longitudinal study from the UK showed that women with higher educational qualifications entered motherhood on average five years later than women without such qualifications [226].

According to the United Nations [227], becoming a parent in Europe is related to five conditions in the couple: (1) having employment with sufficient potential earnings, (2) having a place to live in that is suitable for a family with children, (3) having completed their professional education, (4) living in a stable relationship and (5) feeling secure in one's life, including the relationship to the couple's own parents, and having an overview of the future.

Some of these conditions have also been mentioned in a Swedish study on attitudes towards parenthood among university students [15]. The results of study 1 supported some of the above-mentioned conditions for becoming a parent.

An important condition for parenthood includes living in a stable relationship. According to European statistics the risk of separation is considerable [228], which partly could explain the decreasing fertility rates in many European countries. Another important factor that could lead to decreasing fertility rates is that well-functioning day care is absent in many countries worldwide. However, Swedish society has during the last decades offered working parents well-functioning day care with highly qualified

personnel. This social service is to a high extent financed by the tax payers and the fees are low and dependent on the parents' incomes. Finally, the Swedish rules for parental allowance and parental leave are probably one of the most generous in the world, giving the mother (or father) 80% of the salary (up to a certain income level) for 12 months. Swedish legislation also gives all parents the right to return to their permanent employment after parental leave.

ACCULTURATION

Acculturation is defined as the complex processes of integration and adaptation to a new country [229]. Examples of high level acculturation are having good language skills and being gainfully employed [230]. Acculturation occurs in the immigrant over time [231]. Proxy measures of acculturation have been developed and include age at migration and years lived in the new country [229].

Several hypotheses about the relation between migration and fertility have been presented. The socialization hypothesis implies that migrants exhibit the same fertility patterns as in their country of origin. The adaptation hypothesis implies that migrants exhibit the fertility patterns in the new country. The selection hypothesis argues that there is a selection of migrants by fertility patterns and the disruption hypothesis suggests that migrants have lower levels of fertility immediately after migration [232, 233]. The results of study 1 show that more years in Sweden among foreign-born women were significantly associated with decreased first birth fertility, which support that a higher level of acculturation, measured as more years lived in Sweden, is associated with an adaptation to the fertility patterns in the new country. These findings are in agreement with previous research. During the period 1961–1997 foreign-born women who had lived more than 5 years in Sweden and for those who arrived before the age of 15, FBRs differed very little from those of Swedish-born women [157, 158, 162], which also indicates that level of acculturation has an impact on fertility patterns.

The higher risks of PID in foreign-born women (study 2) is in agreement with previous studies from the US of African-American and Hispanic women compared to Caucasians [8] [234]. Additionally, previous studies of sexually transmitted infections show a considerable disparity among racial/ethnic groups, including large disparities in socioeconomic status [235, 236]. A study from California showed that the incidence rates of EP were highest among African American women and lowest among Hispanic women [237]. A few previous studies indicate that EM might be more common in Asian women [238, 239]. The finding that women from Eritrea/Ethiopia/Somalia had a lower risk than Swedish-born women (study 2) is in agreement with previous studies from the US. However, the lower prevalence of EM in African American women has been suggested to be explained by diagnostic bias in which symptoms of EM are incorrectly attributed to PID [240]. In addition, the diagnosis of EM seems to be related to socioeconomic factors [240, 241].

Around 50% of infertile couples in the US seek medical help [242] whereas in some European countries this percentage is higher [243]. The propensity to seek help for infertility seems to vary with race, culture, ethnicity and socioeconomic status [244]. Additionally, infertility is more common among African American women and Hispanic women than among non-Hispanic white women [245]. In study 2, all groups of foreign-born women had significantly higher risks of hospitalization for infertility,

which could be partly related to the Swedish national health insurance. The findings that all groups of foreign-born women seemed to seek medical help at least as much as the Swedish born women is in contrast to findings from the US [246, 247]. Arab-American women experienced disparities in access to infertility care, largely because of poverty [248], which contrasts to the findings of study 2 where women from Middle Eastern and other Asian countries had some of the highest risks of hospitalization for infertility. Despite the lower income levels among foreign-born women than Swedish-born women [124], they were more likely to be hospitalized for infertility, which could reflect their possibility to receive infertility treatment within the national health insurance, irrespective of income. When access to care was improved in the US, utilization of assisted reproductive technology increased among African-American women [249]. In addition, apparent differences due to race and ethnicity in the use of infertility services in the US disappeared after adjustment for women's income and private health insurance [250].

ALCOHOL AND FERTILITY

Previous studies of the association between alcohol and fertility have shown somewhat contradictory results. A retrospective study of 1,050 women with infertility problems found that moderate alcohol consumption was associated with a slightly increased risk of infertility [182]. In contrast, a study from Italy found no negative effects of moderate alcohol intake on the fertility [251], which was in agreement with a study by Zaadstra et al. that found that moderate drinking was associated with normal fertility [252]. Retrospective analyses of 2,607 births in a Canadian population showed normal fertility rates independent of alcohol intake [253]. In a short-term, prospective study [184], it was found that conception was delayed proportionally with increased alcohol intake when 430 healthy couples were followed for 6 menstruation cycles. In a similar study, a dose-related, negative effect of alcohol on fertility was found [185]. Olsen et al. [254] found in a prospective study that high, but not moderate, alcohol consumption was associated with decreased fecundity, which is in accordance with the results of study 3.

There are several alcohol-mediated mechanisms that may impair conception. For example, an alcohol-induced rise of oestrogen levels, observed in animal experiments and among healthy women [186], may reduce the secretion of FSH, which may suppress folliculogenesis and ovulation. Alcohol may also have direct negative effects on the maturation of the ovum [188], on ovulation, early blastocyst development and implantation [189–191].

DIAGNOSIS OF PID

Clinical symptoms mentioned in the CDC 2002 as criteria for diagnosis are abdominal pain, abnormal vaginal discharge and fever, while abnormal bleedings and pain at intercourse are mentioned as possible, albeit non-specific PID symptoms. These symptoms were present, in various proportions, among the patients treated at the OGED (study 4).

The low threshold for treatment is emphasized in the updated CDC 2002 Guidelines in order to avoid a delay in the clinical diagnosis and treatment of PID. The criteria for PID diagnosis give particular attention to the findings at the bimanual pelvic examin-

ation and recommend antibiotic treatment of suspected PID if (1) cervical motion tenderness or (2) uterine or adnexal tenderness is present. The doctors in study 4 performed a bimanual examination on all 189 patients, and found that all had cervical motion tenderness or were tender over the uterus and/or the adnexa. Nineteen percent of the patients in study 4 were tender over the uterus and the adnexa, and 20% had only uterine tenderness, which is in agreement with the CDC 2002 Guidelines and with some previous studies [255, 256].

A severity score of tenderness has been used in treatment evaluations, including the large-scale PEACH study [118] and a few other previous studies [257, 258]. However, the degree of tenderness is not mentioned for diagnostic purposes in the guidelines. This is understandable considering the subjective dimension of tenderness, although most of the doctors in study 4 used three degrees of assessed tenderness in the bimanual examination; light, moderate and pronounced.

Additional diagnostic criteria in the guidelines include the presence of white blood cells on wet smear, elevated erythrocyte sedimentation rate, elevated CRP, a TVS that shows fluid-filled thickened tubes (with or without pelvic fluid) and a positive culture of CT or NG. Wet smear was performed among less than 20% of the patients in study 4. Erythrocyte sedimentation rate was not used in the diagnostic procedure, possibly because it has largely been replaced by CRP in acute medical consultations in Sweden. In the CDC 2002 Guidelines an elevated CRP is an additional criterion supporting a PID diagnosis, while a normal CRP cannot exclude it [259–261]. Of the 110 tested patients in study 4, 55% had a normal CRP.

TVS was performed among a large proportion of the patients in study 4. None of the patients in study 4 had TVS-specific signs and it is therefore possible that TVS was overused, especially since TVS cannot exclude mild to moderate PID. However, studies from Finland and the US have shown that TVS is a useful instrument in the diagnosis of severe PID [79] [262]. Some of the main reasons for the routine use of TVS in an OGED is to diagnose and assess conditions such as ovarian cysts, myomas, normal and ectopic pregnancies, placental residue after delivery and abortions, excessive fluid in the abdomen and also to confirm normal anatomy in patients with obesity.

Only half of the patients in study 4 were tested for CT. The prevalence rate of CT in study was 5% whereas no NG was found. The relatively low detected rates of CT among the tested patients are in accordance with other Swedish studies of the prevalence of CT. In greater Stockholm (population 1,700,000), a total of 77,000 women were tested for CT in 2001, resulting in 4.6% positive CT cases (n=3,526). The CT prevalence among younger women is higher [126]. In a Swedish study, CT rates in PID patients in a hospital setting decreased from 17% in 1988 to <5% in 1997 [120, 121]. The NG rates were 0%. In a Norwegian study the CT rate in hospitalized cases was 4% in 2002 [123].

We examined possible age differences in study 4 between women that were tested for CT and women that were non-tested and found that tested women had a mean age of 27 years and non-tested of 35. It is likely that older women were considered less important to test as younger women have a higher prevalence rate of CT than older women [117].

The low testing rate for NG follows Swedish traditions, i.e. testing mainly patients with pronounced risk behaviour, at the patient's own request, when tracing contacts and after therapy failure in patients with PID. In a Swedish study, the rates of NG in PID

patients treated in hospital care were 0% in both 1988 and 1997 [120], which corresponds to the rate of NG in study 4. In a Norwegian study, the NG rate was 1% [123].

In contrast, a study from the UK found that the rates of PID caused by NG were increasing [119]. Additionally, in some settings in the US and in the UK, the rates of CT and NG are considerably higher than in our studies. Studies of PID patients have shown that the CT and NG rates are 15–30% and 10%, respectively, however, mainly in inner-city settings [263] [264]. Moreover, in the US the studied women are often non-white and with lower educational status [118, 119, 265, 266].

A systematic review from the UK found that healthcare settings had higher CT rates than population-based studies, where the overall prevalence was 5% [117]. In Antwerp, Belgium, the overall prevalence of CT among sexually active women was 5% [125]. These two studies are in accordance with the present studies.

It has been mandatory by law since 1988 to report positive CT cases to the Stockholm Regional Department of Communicable Diseases, Control and Prevention [126]. However, despite mandatory notification of CT cases, doctors did not test a sufficient proportion of the PID patients for CT, which could have resulted in inadequate treatment of partners and the subsequent reinfection of some women after antibiotic treatment. Summarized studies of the cost effectiveness of screening for CT have shown that it is cost-saving to over-test symptomatic women at a prevalence as low as 1.1% [267]. In addition, a study from 1996 found that screening for CT had reduced PID by 60% [268].

However, the low testing rate for CT at the OGED is in accordance with a retrospective chart review study that determined whether emergency department doctors at an urban teaching hospital in the US adhered to CDC Guidelines in the diagnosis and treatment of sexually transmitted diseases. A number of deficits in the adherence to recommended guidelines were found [269, 270]. The quality of the diagnosis and treatment of PID in general practice was assessed in a national study from England and Wales. A low disease awareness and sub-optimal management of PID was found. The authors concluded that this was a fundamental obstacle to effective disease intervention [271].

However, lack of doctors' adherence to recommended guidelines is not specific for PID. For example, five European countries were included to investigate the implementation of guidelines for prevention of cardiovascular disease. Some suggestions for improving implementation were more education for both doctors and patients and simplifying the guidelines [270, 272, 273].

Time aspects are not discussed in the CDC 2002. In this study, the majority had a short symptom history, which is in agreement with the PEACH study [118]. However, 20% of the women in study 4 had a length of history of more than one month. Many of these women had an even longer symptom history. It is possible that some of the PID cases in study 4 started with milder and/or atypical symptoms that later on developed into more intense and specific symptoms for PID. A recent study from Australia discusses chronic versus acute PID, with more chronic cases (32–46%) found in the age groups >25 years [274]. A Norwegian study found duration of symptoms up to 3 months [123].

Twenty-one percent of the women in study 4 had had at least one previous doctor's consultation for their on-going symptoms, without being diagnosed with PID, shortly before they came to the OGED. The doctors were of various specialties including gynaecologists. The large number of women examined by doctors before the PID

diagnosis could reflect the difficulties in diagnosing PID, or lack of awareness of the PID diagnosis among both patients and doctors. For example, these initially undiagnosed cases of PID may have included women with milder, atypical or intermittent symptoms including symptoms that resemble those of UTI.

Dysuria, a characteristic symptom of UTI, was present in 27% of the women in study 4, which may have contributed to the antibiotic treatment for UTI in some women. Dysuria is not mentioned as a symptom of PID in the CDC 2002 Guidelines. However, although not mentioned in the CDC 2002 Guidelines, dysuria is listed as a PID symptom in the CDC Pelvic Inflammatory Disease – CDC Fact Sheet for the public 2004 [275]. Other consumer health websites list “painful” or “frequent” urination, i.e. dysuria, as a main symptom of PID [276, 277]. We found only one previous study of PID that had mentioned the symptom dysuria [278].

Lower back pain was reported by 25% of the women in study 4, and is considered a main symptom in the “eMedicine/Consumer Health” website for the public [277], but is not included in the CDC 2002 Guidelines. In addition, tiredness and feelings of sickness were common among our patients. Although often unspecific, such symptoms could strengthen the suspicion of PID in some clinical situations.

STRENGTHS AND LIMITATIONS

There are several strengths with study 1. To the best of our knowledge, it is probably the largest study of the impact of three socioeconomic indicators and years in Sweden on first birth fertility among Swedish-born and 19 groups of foreign-born women. Our data consisted of the entire Swedish population of childless women, aged 20–41. In addition, the Swedish Population Register is highly complete with very few missing data and the use of a personal identification number (replaced by a serial number in order to provide anonymity) made it possible to follow the individuals in different registers, e.g. the migrant register, allowing calculation of exact risk-time and years in Sweden.

It is likely that some residual confounding was present due to the insufficient measurement of socioeconomic status. For example, it was not possible to include housing tenure and the socioeconomic status of the woman’s husband since these variables were not available to us. In addition, our database only had information on employment (yes/no), which implies that we were unable to differentiate between unemployed, i.e. those who are looking for work and those who have chosen not to work due to studies or other reasons. Finally, marital status was not included in study 1 since childless women that are cohabiting under marriage-like conditions are classified as being single in Swedish data.

The key strength of study 2 is that the nature of the data allowed inclusion of all women aged 20–41 years living in Sweden at some point between 1990 and 2004, i.e. totally more than 2 million women. Another strength is that study 2 was performed in a country that includes a national health insurance covering all individuals with a residence permit. In addition, Sweden offers publicly financed health care including advanced infertility treatment to all childless couples, irrespective of income. This means that socioeconomic factors are minor confounders in study 2, allowing us to investigate possible differences between population groups stemming from different countries.

The most important limitation of study 2 is that data on out-patient care were not available. For example, during the study period hospitalization rates decreased for all four outcome variables whereas out-patient treatment increased. This could constitute a bias if the propensity for hospitalization due to PID, EP, EM and infertility varies by country of birth. Other limitations are that we could not distinguish between primary and secondary infertility.

A definite strength of study 3 was that data on alcohol consumption were obtained before the start of the study, eliminating the recall bias, which is likely to occur in retrospective studies. Furthermore, the response rate to the postal questionnaire was high (87%) and the analysis of the non-responders showed that they did not differ from the responders as regards to the fertility outcomes included in the study. In addition, only a small percentage of the diagnoses obtained at hospitalization were missing (<5% before and < 2% after 1974). This indicates that the data are highly complete. There is no “gold standard” as regards the estimation of “true” alcohol intake and the use of a postal questionnaire is an accepted method for screening. There are also reports indicating that single questions about alcohol consumption, when placed in a questionnaire that focuses on health and life-style factors, may provide more accurate data than those collected by other methods [279]. For example, a subgroup of women included in study 3 tended to report a lower alcohol intake than in the previous questionnaire when interviewed.

One important limitation is that the amount of alcohol intake was estimated only once, i.e. in many cases several years before the fertility outcomes occurred. Alcohol intake may change over time. However, the relationship between high and low consumers is probably fairly constant over time as most individuals reduce their alcohol intake with age [280]. One point estimate of the alcohol intake should therefore give a fair picture of the “true” alcohol intake when comparing groups with different alcohol intake. This is also in agreement with the results of other studies reviewed by Fagrell et al. [280]. High alcohol consumption was associated with higher risks of infertility examinations, whereas low alcohol consumption was associated with lower risks.

However, it could not be ruled out that diverging attitudes among low and high consumers and their partners may affect the inclination to seek help in case of infertility, thus affecting our results. In addition, high consumers could have suffered more often from impaired ovulations. Successful out-clinic treatment with hormonal stimulation of such cases would then mask a possible negative role of alcohol, thus underestimating the risk of alcohol on fertility. Finally, we were unable to adjust our results for smoking as smoking was not asked for in the postal questionnaire. Smoking has in some studies been associated with negative effects on fertility [199–202], and it is likely that high-consumers of alcohol also are more likely to smoke than low-consumers.

The key strength of study 4 was that the retrospective design implied that the doctors’ diagnosis and treatment of the patients was unbiased by, for example, any intervention. This means that study 4 gave a representative and possibly “true” picture of the doctors’ actual management of the patients. Additional strengths are the sample size and the inclusion of relatively non-selected open-care patients, which improves the possibilities to generalize our findings. The use of electronic medical record data was also a strength as it allowed us to include all patients treated for PID at the OGED during 2001.

It is possible that the stressful emergency ward environment may have affected the quality of the case notes, and that not all information that the doctors used for their management of the patients was included in the records. Our data did not allow us to include missed cases of PID, because the extracted electronic medical records' patients only included diagnosed cases of PID that were based on the ICD codes. Additionally, as all patients were clinically diagnosed it is likely that some patients did not have PID. However, the aim was not to determine how many of the patients actually had PID; rather, the aim was to describe the clinical basis for diagnosis.

CONCLUSIONS

Study 1 showed that FBRs decreased and mean age at first birth increased during the 1990s. Public health information should more actively emphasize that postponement of first birth could lead to involuntary childlessness. Hospitalization for PID, EP, EM and infertility is associated with country of birth (study 2). Even in a country like Sweden that offers publicly financed treatment for infertility, differences based on country of birth exist. Other factors besides socioeconomic factors seem also to be present in the aetiology of female health problems related to infertility. In a large number of infertility examinations, the reason for infertility remains unknown. The findings in study 3 showed that a high alcohol intake implied an increased long-term risk of infertility examinations. Limiting alcohol intake seems to be important for women who intend to have children.

The clinical basis for the diagnostics of PID at the OGED (study 4) was largely in accordance with the criteria in the CDC 2002. Many women had a relatively long history and/or had made at least one previous consultation for their on-going symptoms without being diagnosed as PID, which suggests that the PID diagnosis is difficult and/or that the women might initially have presented mild or atypical symptoms of PID. Further studies could focus on symptoms and signs in mild or atypical forms of PID, and how the testing rate for CT can be improved in clinical praxis considering the fact that effective disease prevention includes widespread screening.

SUMMARY IN SWEDISH

Bakgrund

Omkring 10 % av alla par i västländerna lider av ofrivillig barnlöshet som i en stor andel av fallen förblir oförklarad även om kända faktorer ledande till barnlöshet inkluderar livmoder/äggledarinflammation, utomkvedshavandeskap samt endometrios. Det är möjligt att livsstilsfaktorer, såsom ett högt alkoholintag, kan ha en negativ effekt på fertiliteten. Vidare ses en utveckling mot sjunkande födelsetal och ett uppskjutande av första barnets födelse i många industrialiserade länder. Tidigare studier antyder att denna utveckling kan komma att öka den ofrivilliga barnlösheten i befolkningen. En stor andel av befolkningen i västländerna är invandrare och i Sverige föder utlandsfödda kvinnor en allt större andel av de nyfödda barnen. Det är därför viktigt att inkludera även utlandsfödda kvinnor i studier av kvinnlig fertilitet. Slutligen, livmoder/äggledarinflammation utgör en viktig orsak till kvinnlig barnlöshet. Många fall av livmoder/äggledarinflammation diagnostiseras inte. Det är därför viktigt att ta reda på vilka kliniska symtom och tecken som utgör grunden för läkares diagnos av livmoder/äggledarinflammation.

Syfte

Delarbete 1

Syftet var att undersöka sambandet mellan sociodemografiska faktorer samt fertilitets-trender i Sverige under 90-talet hos svenskfödda och utlandsfödda kvinnor.

Delarbete 2

Syftet var att undersöka sambandet mellan födelseland och sjukhusinläggning för livmoder/äggledarinflammation, utomkvedshavandeskap, endometrios och infertilitet.

Delarbete 3

Syftet var att undersöka den långsiktiga effekten av hög alkoholkonsumtion på kvinnlig fertilitet.

Delarbete 4

Syftet var att beskriva de kliniska symtom och tecken som fanns hos kvinnor som fått diagnosen livmoder/äggledarinflammation på ett svenskt universitetssjukhus jämfört med de kriterier för diagnos som finns beskrivna i de rekommenderade riktlinjerna från USA (CDC 2002 Guidelines).

Metod

Delarbete 1

Förändringar i födelsetal (avseende första barnet) och kvinnans ålder vid första barnets födelse jämfördes mellan 1991–92 (antal kvinnor = 452 000) och 1997–98 (antal kvinnor = 495 756). Sambandet mellan socioekonomiska faktorer och antal år i Sverige

och födelsetal analyserades hos svenskfödda kvinnor och 19 kategorier av utlandsfödda kvinnor i åldrarna 20–41 år. Poisson regression användes i den statistiska analysen.

Delarbete 2

Sammanlagt 2 170 177 kvinnor boende i Sverige någon gång mellan 1990 och 2004 följdes fram till sjukhusinläggning för livmoder/äggledarinflammation, utomkvedshavandeskap, endometriosis och infertilitet. Kvinnorna (åldrar 20–41 år) var indelade i 10 grupper utifrån födelseland.

Delarbete 3

Ett slumpmässigt urval av 7 393 kvinnor i åldrarna 18–28 år drogs från de 445 000 invånarna i Stockholms län 1969. Självrapporterat alkoholintag erhöles från post-enkäter. Födslar, missfall, legala aborter, utomkvedshavandeskap, livmoder/äggledarinflammation, endometriosis samt infertilitetsutredningar analyserades fram till 1987, i relation till alkoholintag.

Delarbete 4

Datajournalerna användes för att ta fram information om kliniska symtom och tecken hos de 189 polikliniska patienter som fått diagnosen livmoder/äggledarinflammation på ett svenskt universitetssjukhus gynekologiska akutmottagning under 2001.

Resultat

Delarbete 1

Födelsetalen (avseende första barnet) sjönk och åldern vid första barnets födelse ökade mellan de två tidsperioderna hos de svenskfödda kvinnorna och de flesta utlandsfödda kvinnorna. Låga födelsetal var vanligare hos kvinnor som inte var sysselsatta i lönearbete och hos kvinnor med låga inkomster medan kvinnor med låg utbildning hade något högre födelsetal.

Flera grupper av utlandsfödda kvinnor hade ökade födelsetal även om de inte var sysselsatta i lönearbete och hade låga inkomster. Hos utlandsfödda kvinnor hade färre år i Sverige ett positivt samband med ökade födelsetal.

Delarbete 2

Alla grupper av utlandsfödda kvinnor hade en högre risk för sjukhusinläggning för livmoder/äggledarinflammation samt infertilitet. Samband fanns även mellan födelseland, utomkvedshavandeskap och endometriosis om än mindre uttalat.

Delarbete 3

Högkonsumenter av alkohol hade en ökad risk för att genomgå infertilitetsutredning jämfört med måttliga konsumenter av alkohol medan låga konsumenter av alkohol hade en minskad risk jämfört med måttliga konsumenter. För både hög- och lågkonsumenter av alkohol sågs minskade födelsetal avseende första och andra barnet.

Delarbete 4

De flesta symtomen som kvinnorna med livmoder/äggledarinflammation hade finns beskrivna i CDC 2002 Guidelines. Prevalensen av klamydia hos de testade patienterna (52 % testades) var 5 %. Inga fall av gonorré diagnostiserades.

Slutsatser

Hälsoinformation till allmänheten bör ske för att informera om att ett uppskjutande av första barnets födelse kan leda till ofrivillig barnlöshet. Denna information kan även nämna att kvinnor som vill bli gravida troligen bör begränsa sitt alkoholintag. Sjukhusinläggning på livmoder/äggledarinflammation, utomkvedshavandeskap, endometriosis samt barnlöshet har samband med födelseland. Det kliniska underlaget i diagnostiken av livmoder/äggledarinflammation överensstämde väl med CDC 2002. Provtagningen för klamydia bör dock förbättras i klinisk praxis.

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