**The influence of infertility and in vitro fertilization
treatment on postpartum and long-term mental
health in women**

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Printed by LiU-Tryck, Linköping 2016.

ISBN - 978-91-7685-637-6

ISSN - 0345-0082

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To Björn and Karl

Abstract

Introduction: It is estimated that about 10-15% of couples suffer from infertility, i.e. the inability to achieve a clinical pregnancy after at least one year of regular, unprotected intercourse and that between 2-5% of births are a result of in vitro fertilization (IVF) treatment. Infertility and its treatment can have adverse effects on psychological well-being. While previous studies on postpartum depression (PPD) in IVF women suffer some methodological issues, there are no published studies on the risk of postpartum psychosis (PPP) after IVF pregnancies. Long-term, most women adjust well emotionally after IVF treatment but some, especially the childless, still suffer negative consequences. Meanwhile, few studies have extended beyond the first decade after treatment. Some studies have found that the childless elderly have social networks of less support potential but most show that psychological well-being is not affected by parental status. None of the studies have focused on the oldest old (≥ 85 years) and many have excluded those who live in institutional care, thus the frailest.

Objective: The overall aim of this thesis was to study postpartum mental health in women who have undergone IVF treatment, using psychiatric diagnoses as outcomes, while controlling for major PPD and PPP risk factors as well as to determine the influences of childlessness, infertility and IVF treatment on long-term mental health in women.

Materials and methods: Studies I-II are register-based, case control studies of 3532 (I) and 10,412 (II) primiparous women included in the Swedish IVF register. A control group of 8,553 (I) and 18,624 (II) primiparous women with spontaneous conceptions was selected from the Medical Birth Register. The main outcomes were PPD and PPP diagnoses the 1st year postpartum collected from the National Patient Register. Studies III-IV are cross-sectional. Study III included 470 women who had undergone IVF treatment 20-23 years previously. The Symptom Checklist-90 was used to investigate self-reported mental health. The results were

compared with those from a population-based study and by parental status group. Study IV included 496 85-year olds. Psychological well-being, living situation, demographics and social network was investigated through a questionnaire and an interview.

Results: Study I-II: There were no differences between the IVF and control group in the risk of receiving a PPD or PPP diagnosis. Having previously been diagnosed with any psychiatric, an affective or personality disorder increased the risk of PPD while any previous psychiatric, psychotic, bipolar, depressive, anxiety or personality disorder diagnosis increased the risk of PPP. None of the women had committed suicide. Study III: The IVF women reported symptoms of higher intensity and were at increased risk of symptoms of depression, obsessive-compulsion and somatisation compared with the reference group. Childless women, compared with parents, reported a higher level of mental health problems as well as symptoms of depression and phobic anxiety. Study IV: No differences in psychological well-being, living situation or having friends close by were found across parental status groups. The childless 85-year olds were less likely to have relatives close by and to receive help.

Discussion: This thesis indicates that the risk of receiving a PPD or PPP diagnosis from in- or outpatient psychiatric care or of committing suicide during the first year postpartum is not increased in women who have undergone IVF treatment. Any negative effects of infertility and its treatment might have been mitigated by the “healthy patient effect”; those who choose to enter treatment are generally psychologically robust. A history of mental illness is a major risk factor for PPD and PPP. The risk of some adverse symptoms of mental illness might be increased in women who have undergone IVF treatment twenty years previously, especially in those who have remained childless. The childless elderly appear to have social networks of less support potential but are not more likely to live in institutional care and do not experience more adverse effects on psychological well-being than the elderly who are parents.

Sammanfattning

Studier har visat att infertilitet och infertilitetsbehandling kan orsaka stress och ha en negativ inverkan på psykiskt välbefinnande inför och under tiden utredning och behandling fortgår. Dock har inga ökade risker för att utveckla kliniskt relevanta psykiatriska tillstånd kunnat påvisas. Medan ett negativt resultat efter infertilitetsbehandlingen kan försämra det psykiska måendet kan ett positivt resultat reparera de tidigare negativa emotionella konsekvenserna för många kvinnor. Dock har studier visat att vissa kvinnor som blivit gravida efter infertilitetsbehandling löper ökad risk för graviditetsspecifik ångest, riskerar att idealisera föräldraskapet och vara i större behov av stöd när barnet är fött.

Postpartum depression (PPD) och psykos (PPP) är allvarliga psykiska sjukdomar som kan ha stora negativa konsekvenser för både mor och barn såsom en ökad suicidrisk. Forskningen har visat en möjlig association mellan stress under graviditeten, vilket kan resultera i en påverkan på hypothalamus-hypofys-binjure-axeln under och efter graviditeten, och risk för PPD. Således skulle den stress infertilitetsbehandlingen orsakar teoretiskt kunna leda till ökad risk för PPD. Tidigare studier på risken för PPD har dock inte funnit några skillnader mellan kvinnor som fött barn efter infertilitetsbehandling och kvinnor som fött barn efter spontana graviditeter. Dock har dessa studier använt enkäter och symtomskattningsskalor snarare än psykiatriska diagnoser för att identifiera PPD-fall och många har inte kontrollerat för den största riskfaktorn för PPD; sedan tidigare känd psykisk sjukdom. Inga tidigare studier har fokuserat på risken för PPP eller suicid efter in vitro fertiliseringsbehandling (IVF). Då risken för många graviditets- och förlossningskomplikationer, som även tjänar som riskfaktorer för PPP, är ökad under IVF-graviditeter kan man spekulera om en ökad risk för PPP hos kvinnor som fött barn efter IVF behandling. Ett specifikt exempel är preeklampsi, ett autoimmunt tillstånd

för vilket studier funnit likheter med PPP, vilket har en ökad prevalens under IVF-graviditeter.

Majoriteten av studierna på långtidseffekter av infertilitet och dess behandling har visat att de flesta kvinnor anpassar sig väl emotionellt till den aktuella livssituationen efter infertilitetsbehandlingen vare sig behandlingen var lyckad eller ej. En andel av kvinnorna upplever dock kvarstående negativa emotionella konsekvenser. Risken för sådana är ökad hos de kvinnor som håller fast vid sin önskan om att få barn eller som inte har tillgång till adekvata copingstrategier, det vill säga de verktyg som krävs för att anpassa sig till livet som ofrivilligt barnlös. Medan de flesta undersökningar har fokuserat på de första åren efter infertilitetsbehandlingen har endast ett fåtal studerat effekterna av infertilitet och dess behandling på psykiskt välbefinnande senare än 10 år efter behandlingens genomförande. En svensk studie har dock visat att de negativa emotionella konsekvenserna kan återkomma när dessa barnlösa kvinnor närmar sig den fas i livet då andra i samma ålder blir mor- eller farföräldrar.

Studier har visat att barn fortfarande ses som det huvudsakliga stödet och källan till hjälp för sina åldrande föräldrar varför man befarar att barnlösa äldre män och kvinnor därmed riskerar att inte erbjudas samma nivå av hjälp och stöd. Detta skulle kunna resultera i att dessa individer i större grad kan komma att lida negativa psykiska konsekvenser av åldrandet än de som är föräldrar. Medan vissa studier har visat att barnlösa äldre har mindre sociala nätverk, är mindre benägna att erhålla hjälp från anhöriga och att de i större utsträckning bor på äldreboenden har majoriteten av studierna inte kunnat påvisa några negativa psykiska konsekvenser. Dock har majoriteten av studierna exkluderat de allra äldsta äldre (≥ 85 år) och

de som bor på äldreboenden och därmed de som sannolikt är i störst behov av stöd och hjälp från andra.

Syftet med denna avhandling var att undersöka risken för psykisk ohälsa under postpartumperioden hos kvinnor som fött barn efter IVF behandling, med psykiatriska diagnoser som utfallsvariabler, under kontroll av de största riskfaktorerna för PPD och PPP samt att studera långtidseffekter av barnlöshet, infertilitet och IVF behandling på psykiskt mående.

Studie I och II är stora, register-baserade, fall-kontroll studier på 3532 (Studie I) respektive 10412 (Studie II) förstföderskor som fött barn efter IVF-behandling och som inkluderats i det svenska IVF-registret. Dessa jämfördes med kontrollgrupper av förstföderskor som fött barn efter spontan graviditet och som inkluderats i det Medicinska Födelseregistret. De primära utfallsvariablerna var diagnoskoder (ICD-10) för PPD och PPP från det Nationella Patientregistret inhämtade under det första året efter att barnet fötts. Information om suicid hämtades även från detta register. Skillnader i risk för PPD och PPP mellan IVF-gruppen och kontrollgruppen utvärderades.

Studie III är en tvärsnittsstudie som omfattade 470 kvinnor som genomgått IVF behandling vid Reproduktionsmedicinskt Centrum i Linköping 20-23 år tidigare. Självskattad mental hälsa utvärderades genom Symptom Checklist-90 (SCL-90) vilken undersöker mental hälsa under den senaste veckan. Kvinnorna jämfördes med en kontrollgrupp av kvinnor från en populationsbaserad studie som använts för att validera SCL-90. Nivån på de självskattade symtomen jämfördes mellan de kvinnor som med hjälp av IVF hade fått egna barn, adopterat barn eller som fortfarande var barnlösa.

Studie IV är en del av Elderly in Linköping Screening Assessment (ELSA-85) för vilken alla 85-åringar boendes i Linköpings kommun blev tillfrågade om att delta. Populationen i denna tvärsnittsstudie omfattade 496 män och kvinnor som fyllde i en initial studiespecifik enkät. Av dessa deltog 377 personer i studiens nästa steg vilket var ett hembesök av en arbetsterapeut som ställde ytterligare frågor. De frågor som ställdes, och som var relevanta för denna studie, rörde sociodemografisk information, psykiskt välbefinnande, självskattad hälsa, socialt nätverk, erhållen hjälp från närstående samt boendesituation. Jämförelser gjordes mellan de som var barnlösa respektive föräldrar.

Studie I och II visade inte några skillnader mellan de som fött barn efter IVF-behandling respektive spontan graviditet avseende risk att diagnosticeras med PPD eller PPP i slutet eller öppen psykiatrisk vård. Ingen av kvinnorna hade suiciderat. De kvinnor som tidigare hade diagnosticerats med någon typ av psykisk sjukdom, specifikt en affektiv sjukdom eller personlighetssyndrom löpte den största risken för PPD. De största riskfaktorerna för PPP var en tidigare diagnosticerad psykisk sjukdom eller specifikt en psykossjukdom, bipolär sjukdom, depressionsepisod, ångestsyndrom eller personlighetssyndrom. Risken för ett flertal graviditets- och förlossningskomplikationer, inklusive preeklampsi, var ökad i IVF-gruppen.

Studie III visade att de kvinnor som genomgått IVF-behandling 20-23 år tidigare skattade högre på symtom på depression, tvångsmässigt beteende och somatisering samt upplevde starkare symtom i förhållande till referensgruppen. De som var barnlösa skattade högre på generell psykisk besvärnivå, depressiva symtom samt fobisk ångest än de som var föräldrar.

I Studie IV sågs inga skillnader i psykiskt välbefinnande, förekomst av vänner i närheten eller boendesituation mellan de äldre som var barnlösa och de som var föräldrar. De som var barnlösa hade i mindre utsträckning släktingar i närheten och erhöll mindre hjälp från närstående. Den hjälp de barnlösa erhöll kom från deras partner, syskon eller vänner medan barnen var den största källan till hjälp hos de som var föräldrar.

Således indikerar resultaten att kvinnor som får barn efter IVF-behandling inte löper högre risk att diagnosticeras med PPD eller PPP eller att begå självmord under det första året postpartum jämfört med de som fått barn efter spontan graviditet. Dessa resultat överensstämmer med tidigare studier som visat att risken för PPD inte är ökad bland kvinnor som genomgått IVF-behandling. Vad gäller PPP var risken för flera graviditets- och förlossningskomplikationer ökade i IVF gruppen men dessa ökade i sin tur inte risken för PPP. Man har i tidigare studier föreslagit att bristen på dessa skillnader, trots den stress dessa kvinnor är utsatta för inför, under och efter behandlingen, beror på att de kvinnor som väljer att genomgå infertilitetsbehandling är psykiskt mer robusta än allmänheten vilket därmed minskar deras risk att utveckla PPD och PPP. I denna avhandling sågs vissa tecken på denna effekt, såsom en lägre prevalens av diagnosticerad psykosjukdom bland kvinnorna som genomgått IVF-behandling.

Resultaten indikerar också att de flesta kvinnor som genomgått IVF-behandling ca 20 år tidigare är av god mental hälsa men att vissa hade en ökad risk för vissa symtom på psykiskt illabefinnande och att de som fortsatt var barnlösa löpte en ännu lite högre risk. Det är möjligt att dessa kvinnor upplevde starkare negativa effekter på den mentala hälsan och välbefinnandet just under denna tidsperiod då de närmade sig fasen i livet när vissa av deras jämnåriga sannolikt hade börjat att få barnbarn. Vad gäller effekterna av barnlöshet hos 85-

åringar löpte de som var barnlösa inte högre risker för känslor av ensamhet eller symtom på depression och var inte mindre lyckliga än de som var föräldrar trots att de var mindre benägna att ha släktingar i närheten och att få hjälp av närstående. Trots detta hade de inte heller kompenserat genom att ha vänner i närheten eller ha större kontakt med grannar än de som var föräldrar. Majoriteten av de 85-åringar som deltog i studien var dock av god hälsa och bodde i eget hus eller lägenhet snarare än på servicehus eller äldreboende varför det är möjligt att dessa äldre ännu inte ännu var så beroende av andra att de börjat uppleva konsekvenser av sin barnlöshet.

List of papers

Study I

Vikström J, Sydsjö G, Hammar M, Bladh M, Josefsson A. Risk of postnatal depression or suicide after in vitro fertilisation treatment: a nationwide case-control study. BJOG 2015; DOI:10.1111/1471-0528.13788.

Study II

Vikström J, Josefsson A, Hammar M, Bladh M, Sydsjö G. Risk of postpartum psychosis after IVF treatment: A nationwide case-control study. Accepted for publication in Human Reproduction.

Study III

Vikström J, Josefsson A, Bladh M, Sydsjö G. Mental health in women 20-23 years after IVF treatment: a Swedish cross-sectional study. BMJ Open 2015;5:e009426. Doi:10.1136/bmjopen-2015-009426.

Study IV

Vikström J, Bladh M, Hammar M, Marcusson J, Wressle E, Sydsjö G. The influences of childlessness on the psychological well-being and social network of the oldest old. BMC Geriatrics 2011;11:78. doi: 10.1186/1471-2318-11-78.

Abbreviations

ART	Assisted reproductive technologies
DSM	Diagnostic and Statistical Manual of Mental Disorders
CI	Confidence Interval
CRH	Corticotrophin-releasing hormone
GDS	Geriatric depression scale
GSI	Global severity index
HPA	Hypothalamic-pituitary-adrenal
ICD	International Classification of Diseases
IVF	In Vitro Fertilization
ICSI	Intracytoplasmatic sperm injection
LBW	Low Birth Weight
LGA	Large for Gestational Age
MDD	Major depressive disorder
MBR	Medical Birth Register
NPR	National Patient Register
OR	Odds Ratio
PHC	Population and Housing Census
PIN	Personal identification number
PSDI	Positive symptom distress index
PST	Positive symptom total
PPD	Postpartum depression
PPP	Postpartum psychosis
PPV	Positive predictive value
PTB	Preterm birth

SCL	Symptom check-list
SD	Standard Deviation
SGA	Small for Gestational Age
TPR	Total Population Register
VAS	Visual analogue scale
VLBW	Very Low Birth Weight
WHO	World Health Organization

Introduction to the thesis

General introduction

Studies have shown that more than 95% of the general population wish to have children at some point in their lives (1). Meanwhile, a study initiated by the World Health Organization (2) estimated that 1.9% of women aged 20-44 years who wanted to have a first child were unable to have a live birth. This corresponds to almost 20 million couples worldwide who are affected by primary infertility. In addition, 10.5% of women are unable to have a second live birth after the first, thus suffering from secondary infertility. When combining primary and secondary infertility, the total number of infertile couples worldwide adds up to almost 50 million (2).

There are many different definitions of infertility. In the above mentioned study (2), the WHO demographic definition was used; "Infertility is an inability to become pregnant with a live birth within five years of exposure based upon a consistent union status, lack of contraceptive use, non-lactating and maintaining a desire for a child" (2). In healthcare settings, clinical definitions are used to enable early detection and prevention. The WHO clinical definition of infertility is: "A disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse"(3).

Infertility can have anatomic, infectious, environmental, life style related, dietary and genetic causes (4). It can be caused by a female and/or a male factor but cannot in all cases be explained using current diagnostic methods. In vitro fertilization (IVF) treatment was initially designed to overcome the problem of blocked fallopian tubes caused by infectious diseases, which remains a major cause of infertility worldwide (2, 5). An increasing tendency to

postpone childbirth has also affected infertility prevalence because of accumulation of causes over time as well as a decrease in fertility rates with age (2).

Since the birth of the first IVF baby in 1978, the use of IVF treatment has become increasingly common (6). The WHO defines assisted reproductive technologies (ART) as "all treatments or procedures that include the in vitro handling of both human oocytes and sperm or of embryos for the purpose of establishing a pregnancy" (3). This includes a series of different treatments such as IVF which is "an ART procedure that involves extracorporeal fertilization" (3).

It is estimated that, in some western countries, as many as 2-5% of births are results of IVF treatment (7). While IVF treatment can solve the infertility problem, it comes with its own set of risks such as increased prevalence rates of multiple births, low birth weight (LBW) and preterm birth (PTB), which in turn can lead to postpartum morbidity and mortality (8-12). Also, IVF treatment increases the risk of pregnancy and delivery complications such as preeclampsia, bleedings during pregnancy and delivery by caesarean section (8, 10, 11, 13).

Apart from the potential complications related to physical health, there are social, political, psychological and ethical complications to infertility and its treatment (14). As improvements and new developments in medical care become available, new questions arise such as how to handle differences in accessibility to IVF treatment between individuals depending on nationality, marital status, sexuality, health status etc.

Presently in Linköping, Sweden, childless couples in which the woman is younger than 40 years, who are married or cohabiting and who have attempted conception for more than one year can be accepted for infertility investigation and treatment. When couples apply for

treatment, an initial assessment is performed and the couple's medical charts are surveyed. If necessary, they are requested to participate in further evaluations before the decision is made regarding acceptance into treatment. Hence, those who have a history of problems such as severe mental illness, drug- or alcohol dependence are in most cases not accepted into treatment. The choice of treatment varies depending on the outcome of the infertility investigation, but if the couples are accepted for IVF treatment, currently the first three cycles are tax-funded.

Some individuals or couples with an unfulfilled child-wish have yet to be diagnosed with infertility and can therefore not be described as infertile. Some have not been able to fulfil their parenthood goals due to other factors such as a lack of partner, financial difficulties or have yet to seek infertility investigation. In some cases, individuals with an unfulfilled child-wish are therefore best described as involuntarily childless.

Not being able to fulfil one's parenthood goals can have a negative effect on many aspects of life, which naturally also includes psychological well-being. The duration that, and extent to which, individuals suffer from the consequences of involuntary childlessness, infertility and its treatment remains to be determined. This thesis focuses on the influences of infertility and its treatment on psychological well-being and mental health in the short and long term in women suffering from primary infertility as well as the effects of childlessness in elderly men and women.

Involuntary childlessness, infertility and psychological well-being

It is generally reported that infertility has negative effects on psychological well-being in women and men (15-18). However, in a review article, Greil (18) concluded that studies using

different forms of psychopathology as outcomes have not been able to find differences between individuals diagnosed with infertility and fertile reference groups. In addition, Eugster et al. (19) found that couples entering infertility investigation and treatment are generally psychologically well-adjusted. However, Schmidt (16) stated in a commentary on this field of research that standardized measures of general psychological distress might not be able to capture the specific stress associated with infertility, but that this does not mean that infertile couples do not experience psychological distress. In line with this statement, it should be noted that Greil (18) also reported that differences between infertile individuals and others had been found for outcomes such as stress and self-esteem, that Eugster et al. (19) found that feelings of stress, depression and anxiety at levels above the norm were common in individuals undergoing infertility treatment and that another review by Verhaak et al. (20) showed that infertile women about to undergo infertility treatment were at increased risk of symptoms of anxiety (20).

As indicated above, studies assessing psychological well-being and psychopathology in involuntarily childless women and men have shown divergent results. Some studies have shown that involuntary childlessness and infertility increase levels of stress (19, 21-23), symptoms of depression (21, 24-32) or anxiety (24-27, 32-35) and have a negative effect on quality of life (33, 36), mental health (37) and sexual relations (25, 38). Others have found equal or lower levels of anxiety (22, 39, 40), depression (22, 39-41) and psychological distress (22, 42) and no differences in relationship quality (39, 43) or sexual satisfaction (39) in involuntarily childless or infertile individuals compared to reference groups. In regard to hospitalizations due to mental disorders, Yli-Kuha et al. (44) found no statistically significant differences between infertile women about to enter treatment and controls for most

psychiatric disorders. They did, however, find lower risks of hospitalization due to psychosis in the infertile women.

Most studies examining the effect of involuntary childlessness and infertility treatment on psychological well-being in men and women have concluded that women suffer greater emotional consequences than men (18, 21, 22, 31, 34, 36, 45-48). However, some studies have found men to be greatly affected by the consequences of infertility and its treatment, perhaps as much as women (49-51). While some have found that male factor infertility increases the psychological distress experienced by men (21, 49, 52), others have found that men are equally affected by infertility, no matter with whom the cause lies (50, 51, 53). Wischman et al. (49) concluded that the emotional impact of infertility may be nearly balanced between men and women but that men's experience of infertility has not been studied to the same extent as that of women's.

Since some studies have found an increased incidence of depressive symptoms in infertile women (21, 24-28, 30, 31), it has been hypothesized that the risk of suicidal thoughts and behavior might be increased in these women. While Shani et al. (54) found that 9.4% of women scheduled for a visit at an IVF clinic met the criteria for high suicidal risk, Venn et al. (55) found that suicide rates were lower in women who had previously undergone IVF treatment compared with the general population.

Infertility treatment

While infertility in itself can be stressful, infertility treatment can further add to this stress (16, 56). Greil et al. (56) found that infertile women who had sought infertility treatment scored significantly higher on fertility-specific distress measures than those who had not.

Studies have shown that levels of depressive symptoms are higher in women (32, 48) and men (48) who have experienced several infertility treatment cycles compared with those who are at the start of the first cycle. Results are conflicting regarding the increase or decrease in anxiety levels over consecutive treatment cycles (19, 34, 48). The within-cycle psychological burden appears to be highest at the time of oocyte retrieval (20, 31), pre and post embryo transfer (31) and pregnancy test (19, 20, 31). Williams et al. (30) argued that infertility medication might contribute to the development of mood disorders since hormonal fluctuations are associated with these disorders in some women.

Evidence that infertility treatment adds to the psychological burden can also be seen in studies showing psychological strain to be the main reason for discontinuation of infertility treatment (57-61). Meanwhile, Stewart et al. (62) found that IVF, compared to other forms of infertility treatment, was associated with a lower risk of hospital admission for psychiatric disorders in women for whom IVF treatment was unsuccessful. The authors hypothesized that this was due to a “healthy patient effect”, meaning that women who decide to undergo IVF treatment are healthier than those who choose not to (62).

Infertility treatment outcome and psychological well-being

Unsuccessful treatment

Unsuccessful infertility treatment can further increase symptoms of depression (39, 52, 63-66) and anxiety (52, 64, 65), the occurrence of feelings of anger and sadness (19, 50). It can also have a negative effect on psychological well-being (47, 51) and increased levels of distress (56, 66) compared with before treatment (39, 47, 64) or compared with those for whom treatment was successful (65). While most studies have focused on women, a few have

studied men and others have included couples. Holley et al. (29) found that, using a structured diagnostic interview, almost 40% of women met the criteria for major depressive disorder (MDD) at some point during 18 months of unsuccessful infertility treatment. However, Verhaak et al. (20) concluded that while a subgroup of women develop clinically relevant emotional problems, most tend to adjust well to unsuccessful infertility treatment.

There are some studies on the risk of clinically relevant mental illness after unsuccessful infertility treatment. Studies focusing on the first weeks after childbirth have found that the risk of unipolar depression (67) or any psychiatric disorder (68) was higher in those who had become mothers than in those for whom infertility treatment was unsuccessful but that these differences decreased over time. It is likely that these increased risks were due to the role of childbirth as a trigger for mental illness (67, 68). In addition, there are some population-based register studies on women who had previously entered infertility treatment comparing women with and without children in regard to risk of psychiatric hospitalization. Baldur-Feldskov et al. (69) found that the risk of hospitalization was increased for most mental health disorders except for affective disorders, which was higher in mothers, and that the risk of anxiety-, adjustment-, obsessive-compulsive and eating disorders was equal in those who had become mothers and those who remained childless. Contrary to these results, Yli-Kuha et al. (44) only found increased risks of hospitalization due to depressive, anxiety and substance abuse disorders in women for whom treatment was unsuccessful compared to mothers. In a Danish study, Agerbo et al. (70) found that the risk of any psychiatric illness was equal in women who remained childless after treatment and those who had become mothers. Hence, the results from these studies are conflicting.

Successful treatment

Most studies have shown that those who become pregnant as a result of infertility treatment do not experience more general symptoms of depression (71-76) or anxiety (71-74) and have equal levels of self-esteem (77) during pregnancy compared with those who conceive spontaneously. However, feelings of stress (19) and pregnancy-specific anxiety (71, 75) can be increased in these women. Compared to before treatment, emotional well-being (47), as well as symptoms of anxiety and depression (64), tend to improve. Thus, becoming pregnant after IVF treatment can even repair previous negative emotional responses to infertility and its treatment (20).

In regard to adjustment to parenthood after infertility treatment, results are inconclusive (71). Studies have shown that, during the first months postpartum, women and men who have become parents after IVF treatment have lower or equal levels of anxiety (74, 78, 79), depression (74, 79) and similar general mental health (78) as those who have conceived spontaneously. However, women who conceive using infertility treatment can feel that they do not have the right to express ambivalence or regret in regard to parenthood (72, 80) and might also have idealized parenthood beforehand (71, 72, 80). These women can experience decreased self-confidence (76, 79) and a deterioration in mood during the transition to parenthood (76) and can therefore be in increased need of support (79, 80). Other studies have not found any differences in couples' adaptability to parenthood (81), or in the quality of the parent-infant relationship (71), and some even that this relationship is of higher quality in mothers and children after IVF treatment compared to spontaneous conception (19).

Voluntary childlessness

The proportion of women in the general population who choose to remain childless differ between studies. Rostad et al. (82) studied Norwegian menopausal women and found that 4.1% characterized themselves as being voluntarily childless while Biringier et al. (40) found that as many as 18.4% of Norwegian women aged 19-45 years thought of themselves as voluntarily childfree. Studies have shown that voluntarily childless adults often perceive that they are viewed negatively by others and are asked to explain their choice not to have children (83). In regard to psychological well-being in this group, studies are scarce. Biringier et al. (40) showed that voluntarily childless women had lower levels of depressive symptoms compared with a control group of mothers who had not experienced infertility. Rostad et al. found that voluntarily childless women reported the most favorable physical and mental health outcomes compared with involuntarily childless women and mothers (84). In middle aged and older women, studies have shown higher levels of psychological well-being (83) and lower levels of loneliness and depression (85) in voluntarily, compared with involuntarily, childless women.

Infertility, IVF treatment and postpartum psychiatric disorders

Childbirth is a well-known trigger of affective mental health disorders (67, 68). There is a variety of psychiatric disorders associated with the postpartum period ranging from the milder “postpartum blues” to the more severe; postpartum depression (PPD) and postpartum psychosis (PPP) (86). Common PPD symptoms include dysphoria, confusion, guilt and suicidal ideation (87) but the range of patients and their symptoms diagnosed with PPD are heterogeneous (86). PPP is a disorder in the psychotic spectrum with a rapid onset of

symptoms that include delusions, hallucinations, mood swings, disorganized behavior, confusion and stupor (86, 88, 89).

In the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-V), there is not a distinct set of diagnostic criteria for PPD or PPP but a peripartum onset specifier defined as the onset of mood symptoms that occur during pregnancy or in the 4 weeks following delivery (90). Women with symptoms matching the criteria for a depressive, manic or hypomanic episode in MDD or bipolar disorder, or a brief psychotic episode, as well as for the peripartum onset specifier, can receive a PPD or PPP diagnosis. While the DSM-V has defined the length of the postpartum period as the first four weeks after childbirth (90), the International Classification of Diseases (10th revision) (ICD-10) has defined this period as the first six weeks after childbirth (91). Meanwhile, psychiatric disorders occurring during the first 12 months after childbirth are often described as having a postpartum onset (87, 92, 93).

It is generally reported that PPD occurs after about 13% of pregnancies (94, 95) and that PPP follows about 0.1-0.2% of births (96-99). Most studies have identified cases using self-report screening instruments. When only MDD is included, the PPD prevalence during the first year postpartum ranges from 1.0-5.9% (95). While PPP cases are almost always in need of hospitalization (100), one study found the number of PPD cases that requires psychiatric care to be 0.3%, hence significantly lower than the generally reported PPD prevalence (101). Savitz et al. (102) found that the prevalence of women who were hospitalized due to PPD ranged from 0.06 to 0.26% depending on the PPD definition.

In addition to the negative effects on the woman's health and well-being, postpartum psychiatric disorders can have a negative effect on mother-child interaction (103-105) and the

child's emotional, behavioral and cognitive development (104). It increases maternal mortality rates (106, 107) and can even lead to suicide (106, 107) and infanticide (108).

Risk factors for postpartum psychiatric disorders

Risk factors for PPD include previously diagnosed psychiatric disorders (93, 109-111), and specifically a previous depressive episode (110, 111), antenatal depression and anxiety (109-111), stressful or negative life events (93, 109-111) such as domestic violence (111), a negative attitude towards pregnancy (109), lack of social support (93, 109-111), a poor marital relationship (93, 109, 111) and migration status (111).

Risk factors for PPP include a pre-pregnancy bipolar disorder diagnosis (88, 97, 98, 112, 113) and previous PPP episodes (88, 97, 112-114), family history of PPP or bipolar disorder (88, 97, 115, 116) and primiparity (97, 112, 117, 118). Some studies have found evidence that a history of any psychiatric disorder (97), or specifically a psychotic disorder (98), high maternal age (99), PTB (119), preeclampsia (120), obstetric complications (118) and delivery by caesarean section (97, 119) also serve as PPP risk factors. One Swedish study found that maternal diabetes and a high birth weight decreased the risk of PPP (99).

Women with a pre-pregnancy bipolar disorder diagnosis suffer increased risks of PPP (113, 121, 122), especially when unmedicated (121, 123). The risk further increases in women with a bipolar disorder as well as a family history of PPP (115). However, while PPP can occur as the first episode of a bipolar disorder (124, 125), it can also consist of isolated episodes during the postpartum period (120, 125). It has been hypothesized that isolated PPP and PPP as a bipolar disorder episode are different entities with different pathophysiologies, relapse rates and severities (113, 120).

Theories on the pathogenesis of postpartum psychiatric disorders

It has been suggested that postpartum psychiatric disorders occur due to immunological (126-128) or endocrinological changes (127, 129-132) that are associated with pregnancy and childbirth. Studies have reported the occurrence of similarities between PPD and some autoimmune disorders; pregnancy and childbirth are known to cause recurrences, exacerbations are common in late pregnancy and the postpartum period and they share some common risk factors such as primiparity, familiarity and childbirth by caesarean section (128). In addition, some studies have found an association between preeclampsia, which is an immune-related disorder in pregnancy, and PPP (120, 133). These phenomena share some common risk factors, for example primiparity and previous episodes of the respective diseases (120, 133). For both PPD and PPP, studies have shown various disruptions in the immune systems of afflicted women. Groer et al. (127) found that the normal increase in Th1-cells postpartum was lower in depressed compared with non-depressed mothers resulting in a low Th1/Th2 ratio while Bergink et al. (126) found evidence of a disrupted neuroendocrine set point with lower levels of T-cells and increased levels of monocytes and macrophages in women with PPP than in non-affected women.

In regard to endocrine factors, disruptions in the hypothalamic-pituitary-adrenocortical (HPA)-axis have been implicated in the pathogenesis of PPD (127, 129, 134, 135) and PPP (131). The DSM-V recognizes two forms of clinical depressive syndromes; melancholic and atypical depression (129). The first has been associated with HPA-axis hyper activation, the second with hypo activation (136, 137). Corticotrophin releasing hormone (CRH) is released from the placenta during pregnancy and form, together with the glucocorticoids, a positive feed-back loop causing high levels of CRH and cortisol during pregnancy. Placental CRH causes a down-regulation of non-placental CRH production and receptors which renders a

large drop in cortisol levels postpartum (127) . Some studies have shown that higher levels of CRH during pregnancy may in some women result in lower levels of cortisol postpartum (127, 129). The postpartum hypocortisolism might indicate that stress responses are faulty in depressed mothers (127) and has been interpreted as an association between PPD and atypical depression (136, 137). Studies have shown an association between low cortisol levels after pregnancy and PPD (127) as well as associations between high levels of CRH during pregnancy and PPD (134, 135). Psychosocial factors such as a good social support can mediate the stress response that influences the HPA-axis and thus decrease the risk of PPD (135). In addition, Paykel et al. (131) found that cortisol levels after a dexametasone-suppression test was significantly higher in subjects with PPP compared with healthy controls postpartum (131).

Gonadal hormones have also been implicated in the pathogenesis of PPP (130) and PPD (132). Bloch et al. (132) attempted to mimic the hormonal changes of pregnancy and the postpartum period in non-pregnant women with and without a previous PPD experience. When levels of estradiol and progesterone decreased during the artificial postpartum period, women with a history of PPD experienced a significant increase in depressive symptoms suggesting a different response to the withdrawal of gonadal hormones compared to the control women (132). Thus, women predisposed for PPD might have abnormal responses to the physiological hormonal changes in the postpartum period. In regard to PPP, Meinhard et al. (130) found, in their review study on the role of estrogen in bipolar disorder, that low levels of estradiol were associated with PPP. However, before any conclusions can be drawn in regard to immunological or hormonal mechanisms and their role in the pathogenesis of PPD, more research is needed (111, 112).

Postpartum psychiatric disorders after infertility treatment

Infertility and IVF treatment as risk factors for PPD and PPP

Women who are part of an infertile couple and who choose to seek infertility treatment generally have fewer risk factors of PPD and PPP compared with women who conceive spontaneously (138). Yli-Kuha et al. (44) found that women undergoing infertility treatment had fewer previous hospitalizations for most psychiatric disorders compared to the general population but that the difference was only significant for psychotic disorders. In regard to other PPD and PPP risk factors, studies have shown lower prevalence rates of pre-pregnancy psychotic (139) and depressive (140) disorders in these women. Compared to women who have conceived spontaneously, studies have shown that women undergoing infertility treatment do not have more symptoms of depression or general anxiety during pregnancy (71, 73-75) and have not suffered more stressful life events (141-143). In addition, women who have undergone IVF treatment generally have a higher socio-economic status (26, 44, 72, 142, 144) and relationships of better qualities (71, 72, 81, 141) than reference groups. It also seems probable that a greater proportion of these women would have a positive attitude towards pregnancy, having sought infertility treatment.

However, due to infertility and its treatment, these women have higher prevalence rates of some risk factors for postpartum psychiatric disorders such as a high maternal age (71, 143, 145, 146), obstetric complications (8, 11, 13) such as delivery by caesarean section (8, 10, 11, 145) and PTB (8, 10, 11, 13) than women who conceive spontaneously. Pregnancy-specific anxiety might be increased (71, 75) and expectations of what having a child will bring might also be higher, resulting in increased risks of psychological distress postpartum (71, 72, 80). As infertility and its treatment can cause levels of stress to rise (19, 21-23), it could be hypothesized that HPA-axis responsiveness would increase in these women thus resulting in

increased risks of postpartum psychiatric disorders. One study on women undergoing IVF treatment found a positive association between stress and cortisol levels (147). Compared to women having unstimulated infertility treatment and women undergoing laparoscopic surgery, levels of stress and cortisol were higher in the women who were undergoing IVF treatment (147). In addition, since preeclampsia (8, 11, 13) is associated with IVF pregnancies as well as PPP, it could be hypothesized that IVF pregnancies and PPP are linked.

PPD risk after IVF pregnancy

Most studies have not found any significant differences in the risk of depressive symptoms or PPD when comparing women who have conceived using infertility treatment with those who have conceived spontaneously (71, 74, 76, 79, 138, 142, 143, 146). Monti et al. (148), however, found increased risks of PPD in women who had given birth after IVF treatment, compared with women who had conceived spontaneously, but they used lower cut-off scores on the Edinburgh Postnatal Depression Scale (EPDS) than what is generally recommended to detect PPD (148). These results are in line with what was found in the review study by Ross et al.; mean depression scores are higher among the women who give birth after IVF treatment compared with those who conceive spontaneously, but differences are not statistically significant and scores are lower than the cut-off values commonly used to detect clinically relevant depression (138). Hence, these women might be experiencing slightly higher levels of distress postpartum, which has been indicated in previous studies by an increased need of support (79, 80), but they do not suffer increased risks of PPD.

All studies included in the reviews by Ross et al. (138) and Hammarberg et al. (71), as well as the other studies referenced above have used questionnaires or symptom rating scales rather than psychiatric diagnoses to identify PPD cases. In addition, Ross et al. (138) concluded that

most studies on this topic have failed to control for known risk factors of PPD and that these factors tend to favour the group of women who enter infertility investigation and treatment. Therefore, studies controlling for these factors may find the risk of PPD to be increased in women who have undergone infertility treatment (138). No previous studies have examined the risk of PPP after pregnancies following infertility treatment. As an increasing number of couples use infertility treatment to conceive (5, 6), it is important to determine if this treatment increases the risk of postpartum psychiatric disorders, especially since they might have grave consequences for the health of both mother and child (104, 105).

Long-term psychological consequences of infertility treatment

Unsuccessful treatment

The first decade

Some studies have found that psychological well-being in both men and women continues to be negatively affected the first decade after unsuccessful infertility treatment when compared to those with a successful treatment outcome or spontaneous conception (20, 149-152). There is evidence of increased risks of symptoms of depression (149, 150) and anxiety (149) and that levels of self-esteem (153) and life satisfaction or quality (20, 149, 151, 152, 154) are lower after unsuccessful treatment. A Swedish study by Volgsten et al. (155) showed that some couples still experienced unresolved grief three years after unsuccessful treatment. Other studies have not found any differences in relationship quality (154, 156), life satisfaction (152, 153) or general emotional distress (154) between those who remained childless after infertility treatment and reference groups. Several studies have concluded that while unsuccessful treatment might negatively influence psychological well-being the first years after treatment, adverse symptoms tend to return to baseline levels over time (144, 157).

About 10 years after treatment, Sundby et al. (158) found that while some women still suffered psychological consequences from their infertility, most women viewed the time of infertility treatment as a difficult part of their lives but had since moved on.

The second decade

The few studies that have focused on the influences of infertility and its treatment on psychological well-being beyond the first decade after treatment have found conflicting results. Gameiro et al. (159) found that the risk of mental health problems was increased in women who had undergone infertility treatment 11-17 years previously but that a sustained child-wish was an even stronger negative predictor for mental health. A Swedish qualitative study (160) showed that, 20 years after treatment, some women still suffered negative effects of their infertility and that these effects had become greater as their peers were becoming grandparents. Sydsjö et al. (161) found that mental health was generally good in men twenty years after treatment but that those who had remained childless were at increased risk of symptoms of mental illness. In addition, a study on couples twenty years after IVF treatment found that relationship quality was generally good, irrespective of the couples' parental statuses (162).

Several studies have demonstrated the importance of coping for the long-term psychological consequences of unsuccessful treatment (150, 157-159, 163). Gameiro et al. (164) found that most women had adjusted well emotionally 2.5 years after treatment, but that 37% showed evidence of emotional maladjustment and that, 11-17 years after treatment, 1 in 10 women showed no evidence of recovery (164). Unsuccessful treatment was a predictor for negative emotional adjustment (164). Several studies have found that women who come to terms with their unfulfilled child-wish and focus on new life goals adapt better to their childlessness and

experience a positive effect on psychological well-being unlike those who still pursued a desire for pregnancy (157, 159). Leiblum et al. (152) concluded that the crisis of infertility is never really resolved but that most women adjust to treatment outcome.

Successful treatment

Studies have not found any differences in marital relationship satisfaction or quality of life in mothers who conceive using infertility treatment compared to those who conceive spontaneously (149, 151) and that women who give birth after treatment have lower levels of anxiety and depression 3-5 years after, compared with before, treatment (157). About 3-5,5 years after infertility treatment, satisfaction with life does not differ between biological mothers and women who had undergone infertility treatment but who had since adopted children or were living with stepchildren (144, 151, 152). In addition, a Swedish study (151) found that couples who had adopted children scored even higher on measures of life satisfaction than biological parents. Verhaak et al. (20) concluded that women who conceive using IVF treatment do not differ from women who conceive after spontaneous conception in psychological well-being.

Psychological well-being and social support in middle- and old age

Psychological well-being

Because of the general view of children as the major source of support to aging individuals, and a general belief that children will bring happiness and meaning in life as well as reduce loneliness, it is often assumed that childlessness will have negative effects on psychological well-being and social support when childless individuals reach old age (165, 166). However, most studies on voluntary and involuntary childlessness in middle-aged and elderly

individuals have found that being childless does not appear to increase the risk of loneliness (167-170), unhappiness (168) or symptoms of depression (167, 168, 170-172) and does not influence life satisfaction (168, 173) or general psychological well-being (174, 175). Graham et al. (176) found that while childlessness might have negative effects on psychological well-being among women in their child-bearing years, it can even be protective against poor physical and mental health in women as they grow old. However, it has been hypothesized that studies including the oldest old individuals would find that childlessness has negative effects on psychological well-being since this group is in declining health and function (170).

In support of this theory, a review study on loneliness in elderly individuals found that while loneliness is not a problem among the "younger elderly", it can become a problem in individuals over the age of 80 (177). However, another review study by Hansen (165) showed that the age-gradient in the influence of parental status on well-being is weak and that even though social support deficits in childless older individuals have been reported, there are no associations between parental status and happiness. The author concluded that the childless elderly appear to adapt well to their situation and find support and a sense of meaning in other ways than through children (165). In addition, while most studies have excluded those living in nursing homes, Chang et al. (171) studied disabled individuals aged 75 years or older and found no differences in psychological well-being between those who were childless and those who were parents.

While differences between the elderly who are parents and those who are childless are few, some aspects of parenthood and childlessness might influence psychological well-being. Studies have shown that the effect of parental status on psychological well-being is not dependent on whether the children are biological, adopted or stepchildren (172) but is, among

parents, dependent on the quality of the parent-child relationship and, among the childless, on whether the individuals has a positive or negative attitude towards their childlessness (83, 85). Jeffries et al. (83) found that voluntarily childless middle-aged women scored higher, while involuntarily childless women scored lower, on measures of psychological well-being than mothers. Parents that have a relationship of poor quality with their children suffer a negative effect on psychological well-being compared to those with a relationship of good quality (83, 85).

Marital status, gender and self-rated health

While parental status generally does not appear to have a major influence on psychological well-being in the elderly, marital status, gender and self-rated health does (167-169, 171, 172, 175, 178). Studies have shown that being divorced or widowed increases levels of depressive symptoms (168, 171, 172), loneliness (168, 169, 178) and life satisfaction (168) in the elderly. Most studies have found that never-married women are less affected than the previously married (170, 176). While Hank et al. (175) found that marital status only influences psychological well-being if the quality of the marital relationship is good, other studies have not found any differences in psychological well-being among the elderly depending on marital status (167, 173).

Some studies have shown that men are less likely than women to feel depressed and lonely (167) but that these advantages disappear in the absence of marriage and children (167, 169). Hence, marital and parental status appears to have a greater impact on psychological well-being in men than in women (167, 172, 179). While childless elderly women often have a high level of education and independence, which in turn is beneficiary for their health (174, 178), unmarried or widowed childless elderly men appear to be an especially vulnerable

group which to a greater degree is dependent on others (167, 172, 179). However, Hank et al. (175) did not find any differences in psychological well-being depending on gender. In addition, several studies have shown that low levels of self-rated health also serves as a risk factor for depressive symptoms, loneliness and decreased general psychological well-being (168, 171, 172, 178).

Social support

In regard to social network and support, some studies have shown that the childless elderly have smaller social networks, that they are less likely to interact with relatives and to receive informal support (173, 174, 180). Other have found few or no differences between these two groups of elderly individuals (169, 171, 175). Chang et al. (171) studied disabled elderly individuals and found that the strength of the social network and the likelihood of receiving informal care was not dependent on parental status or gender. Meanwhile, those who were not married or had lower levels of self-reported health were less likely to receive care from informal sources such as a relative or a friend (171).

While most studies show that childless elderly individuals tend to have fewer relatives the evidence is conflicting whether or not this lack of relations is replaced by a greater network of friends. Some studies have shown that the childless elderly are more likely to participate in social groups (174) and had greater abilities when negotiating alternative social ties during the life course (165). Others did not find that the childless elderly had a greater network of friends compared to parents (169, 180). In addition, replacing younger relatives with same-age peers increases the risk of having lost large parts of one's social network in advanced age. Studies from Sweden (181), Canada (182) and Australia (174) have shown that parents receive more informal support from people they know but that the childless receive more formal support

from health care services. Larsson et al. (181) concluded that while formal services do not appear to fully compensate for the support deficits among the childless, having children is not a guarantee of receiving support since the children of the oldest old are likely to be approaching old age themselves. Some studies from western countries have shown that older childless individuals are more likely than parents to live in institutional housing (179, 183, 184).

Rationale and aims of the thesis

While there is some research on the consequences of infertility and its treatment on mental health and well-being in the postpartum period, these studies have not found any evidence of differences in PPD risk between those who have conceived using infertility treatment and those who have conceived spontaneously. Meanwhile, all studies have used questionnaires or self-report symptom rating scales rather than psychiatric diagnoses to define cases and many have failed to control for major risk factors of postpartum psychiatric disorders such as a history of mental illness. It is likely that the prevalence of such disorders is lower in the group of women who undergo infertility treatment due to “the healthy patient effect” and that this might have influenced the results of these studies.

There are no previous studies on the risk of PPP in women after IVF treatment. However, the risk of pregnancy and delivery complications, which in turn serve as risk factors for PPP, is increased in IVF pregnancies. This includes preeclampsia, a disorder which is associated with both IVF pregnancies and PPP. In addition, the increased stress levels that women who undergo IVF treatment are exposed to pre-, ante- and sometimes postpartum could influence the HPA-axis and make these women more susceptible to the hormonal fluctuations and general stressors associated with the postpartum period. Hence, it could be hypothesized that the risk of postpartum psychiatric disorders is increased in women who have conceived using IVF treatment.

While there are some studies on the long-term psychological consequences of infertility and its treatment, few studies have extended beyond the first decade after treatment. In addition, a previous Swedish study has indicated that negative emotions might reappear as women reach the age when their peers are becoming grandparents. In regard to the effects of childlessness

on psychological well-being and support in old age, none of the previous studies have specifically targeted the oldest old (≥ 85 years), a population of elderly individuals who are likely to be more frail and less able to compensate for their childlessness by seeking out other relations or engaging in activities.

With regard to the above mentioned insufficiencies in this field of research, the aim of this thesis was to add to the knowledge of postpartum mental health in women who have undergone IVF treatment using psychiatric diagnoses as outcomes while controlling for major risk factors of PPD and PPP. The aim was also to determine the influences of childlessness, infertility and IVF treatment on long-term mental health in women.

Aims of the individual studies

The aim of Study I was to examine whether women who undergo IVF treatment are at greater risk of suicide postpartum or postpartum depression requiring psychiatric care, compared with women who conceive spontaneously.

The aim of Study II was to assess if there is a difference in PPP risk between women who give birth after IVF treatment and women who give birth after spontaneous conception.

The aim of Study III was, first, to assess self-perceived mental health in a group of women treated with IVF 20–23 years earlier and, second, to study possible differences in mental health between those who had given birth, those who had adopted a child, those who had given birth and adopted a child and those who had remained childless.

The first aim of Study IV was to investigate the influences of childlessness, no matter if it was voluntary or involuntary, on the general life satisfaction, sense of meaning in life, happiness, depression and loneliness in a population of 85-year old individuals, and to examine the possible interactions with marital status and gender. The second aim was to investigate how childlessness influences social support network and the probability of ending up in institutional care among the 85-year old men and women.

Material and methods

Study I-II

Population

All primiparous women born from January 1st 1973 to December 31st 1983 (Study I)/ December 31st 1991 (Study II) and who were included in the Swedish IVF register from January 1st 2003 to December 31st 2009 (Study I)/ January 1st 1988 to December 31st 2012 (Study II) were included in the study. For Study I this corresponded to 3,532 women and for Study II 10,412 women who were included in the “IVF group”. A control group of primiparous women who had given birth after spontaneous conception was, using the SPSS sample procedure, randomly selected from the Medical Birth Register (MBR). For Study I the control group consisted of 8,553 age-matched women. For Study II the corresponding number was 18,624 non age-matched women.

Data sources

All Swedish residents are given a unique personal identification number (PIN). The PINs of the women included in this study were used to link information from the different registers.

National registers

All registers used cover Sweden as a whole, are of good quality and have a high level of coverage (185-188).

The Swedish Medical Birth Register

The MBR includes 97-99% of pregnancies that have resulted in births in Sweden since 1973 (185, 189). As a result of reporting errors, 1-3% of deliveries are missing from the registers

each year. The MBR contains information about the pregnancy, delivery and antenatal health of the child. The register is validated and is based on the medical charts from maternal, obstetric as well as neonatal care (185, 189). It has previously been thoroughly described by Harlow et al. (98). Information about maternal age at childbirth as well as pregnancy and delivery variables was collected from the MBR.

The IVF register

The Swedish IVF register includes all women who have given birth after IVF treatment. This register was started in 1982, is held by the National Board of Health and Welfare and managed by all Swedish centres conducting IVF treatment (190, 191). Source data are automatically transferred from patient charts to the register. A file based on the woman's PIN is set up to include information on the laboratory conducting the treatment, the date, the type of treatment, etc (191). From this register the PINs of the women who had given birth after IVF treatment were collected.

The National Patient Register

The National Patient Register (NPR) contains information about all patients who have been discharged from hospital or treated in outpatient care (192). It is held by the National Board of Health and Welfare and has complete coverage for psychiatric care since 1973 (192). The register includes the dates of admission and discharge as well as the main discharge diagnosis. It has a coverage rate of 99% and validation of the register has concluded that the diagnoses are of good quality with positive predictive values of 85-95% (186). It has previously been thoroughly described elsewhere (98). Psychiatric diagnoses pre- and postpartum and information about suicides were collected from the NPR.

The Education Register and the Total Population Register

These registers are held by Statistics Sweden. The Total Population Register (TPR) was established in 1968 and includes continuously updated information on births, deaths, migrations, and marital status (187, 193). This information was collected through the Population and Housing Census prior to 1976 (193). The register is validated and of good quality but some over-coverage exists due to missing reports on deaths and migrations (187). The Education Register (ER) was established in 1985, is validated and contains information about the educational level of the population, which is collected continuously (188, 194). From these registers, information about marital status and highest level of education was collected.

Study design

Covariates

Pregnancy and obstetric variables

For both studies, the variable “group” consisted of two categories; the IVF group and the control group. Birth weight was categorised into extremely low birth weight (<1000 g, ELBW), very low birth weight (1000-1499 g, VLBW), LBW (1500–2499 g), and normal birth weight (>2500 g). Gestational age was divided into <28 weeks (extremely preterm), 28–31 weeks (very preterm), 32–36 weeks (preterm), 37–40 weeks (term) and >40 weeks (post-term). For the regression analyses, gestational age was further divided into preterm (<37 weeks) or term/post term (≥ 37 weeks) and birth weight into LBW (≤ 2500 g) and normal birth weight (>2500g). For both studies, plurality was divided into single/multiple. For Study I, mode of childbirth was divided into normal/instrumental/acute caesarean/elective caesarean and for Study II into normal/instrumental/caesarean.

For Study I, previous miscarriages, previous experience of delivering a stillborn child or death of a child during the first month was categorised into yes/no. These factors might constitute stressful life events and could have different distributions in the two groups, hence potentially serving as confounding factors. For Study II, information about the occurrence of preeclampsia (ICD-10 diagnostic codes O11, O140-149, O15), gestational diabetes (ICD-10 diagnostic codes O240-249) and complications of labour and delivery (ICD-10 diagnostic codes O60-75) was collected since previous studies have found that these factors influence PPP risk. These variables were categorised into yes/no. Information about all the above mentioned variables was collected from the MBR.

Sociodemographic variables

Information about marital status was gathered from the TPR and was divided into 1, married/cohabiting and 2, unmarried/divorced/widowed. From the ER, information about highest level of education was collected and divided into 1, Secondary School, 2, High School and 3, University for both studies. Information about maternal age at childbirth was collected from the MBR and divided into three groups. For Study I the groups were 20-24, 25-29 and 30-34 years while for Study II the groups were <25, 25-34 and ≥35 years.

Previous psychiatric diagnoses

The pre-pregnancy diagnoses retrieved from the NPR were limited to the five years prior to childbirth in order to include diagnoses that were relevant for the current mental health of the women. The diagnoses selected corresponded to ICD-10 diagnostic codes F20–F29 (schizophrenia, schizotypal, and delusional disorders), F30–F39 (affective disorders), F40 (phobic disorders), F41 (other anxiety disorders), F42 (obsessive-compulsive disorder), F43 (reactions to severe stress), and F60 (disorders of adult personality and behavior).

Principal outcome variables

The diagnoses included in the PPD definition corresponded to ICD-10 diagnostic codes F32–F39, while those included in the PPP definition were F20-29 (Schizophrenia, Schizotypal and Delusional disorders), F30-31 (Manic episode and bipolar disorder) and F531 (Severe mental and behavioural disorders associated with the puerperium). For Study II, ICD-10 diagnostic codes were translated into ICD-9 codes and from them into ICD-8 codes using WHO conversion tables (195). Diagnoses collected from 1983 to 1987 emanated from the ICD-8, from 1988 to 1996 from the ICD-9, in 1997 from both ICD-9 and ICD-10 and from 1998 and onwards from the ICD-10. The translation was performed by one of the co-authors, a statistician, and audited by another of the co-authors, a medical doctor. Due to the fact that diagnoses were collected from 1998 and onwards for Study I, only ICD-10 diagnostic codes were used. Psychiatric disorders occurring during the first year after childbirth are often defined as having a postpartum onset (87, 92, 93). Hence, in order to include all possible PPD and PPP cases, a time interval of one year was used in these studies.

Data analyses

The calculations were performed using SPSS 20.0 (Study I) and 22.0 (Study II) (IBM Inc., Armonk, USA). Chi-square analyses were performed to determine differences between the IVF group and the control group in the following groups of covariates: Demographics (marital status, highest level of education), factors of the current pregnancy (plurality, mode of delivery, birth weight, gestational length), psychiatric diagnoses the last five years before childbirth and postpartum psychiatric diagnoses. For Study I factors of previous pregnancies (previous miscarriages, experiences of stillborn child or death of child during the first month) were included. The covariates maternal age, gestational diabetes, preeclampsia and complications of labour and delivery were included for Study II. When there were less than

five frequencies in a cell, Fisher's exact test was used to test statistical significance between the two groups.

For both studies, multiple logistic regression analyses with the primary outcome PPD or PPP as the dependent variable were performed. The covariates chosen were known risk factors of PPD or PPP respectively as well as the "group" covariate. For Study I there was a statistically significant difference in the chi-square analyses between the groups for the variable previous miscarriages, hence this variable was included in the analyses. In Study I, the multiple logistic regression model was saturated when all covariates were added at the same time. Therefore, initial analyses were performed with one group of covariates added per model. In a second step, individual covariates that were significantly associated with the dependent outcome were added in an additional multiple regression model so that the covariates that were most associated with the outcome could be analysed together. Separate models were performed for the variables 'any psychiatric diagnosis and 'any affective disorder diagnosis', since multicollinearity between these variables was high.

In Study II the above mentioned covariates, including all five groups of previous psychiatric diagnoses, were added to the same multiple logistic regression analyses without saturating the model. The p-values, odds ratios (OR) and 95% confidence intervals (CIs) reported for the other covariates stem from this regression analyses. However, due to a high multicollinearity for the psychiatric diagnoses variables, these variables were added to the non-psychiatric diagnosis covariates in five separate multiple logistic regression models, one for each group of psychiatric diagnoses. The p-values, ORs and CIs reported for each group of psychiatric diagnoses stem from these regression analyses. For both studies, post-hoc power analyses were performed.

Study III

Population

All women (n=520) who had undergone IVF treatment between 1986 and 1989 at the Centre of Reproductive Medicine, Linköping University hospital were, in 2008-2009, sent a letter asking for their participation in the study. While six were deceased and ten women never received the letter, 504 (97%) women were available for follow-up. Out of these, ten declined participation and 24 women did not answer, leaving 470 (93%) participants. The women were divided into four subgroups according to parental status; 1, No children (20.2%; n=95), 2, Biological children (55.1%; n=259), 3, Adoptive children (19.4%; n=91), 4, Biological and Adoptive children (5.3%; n=25). Mean score values from a population-based study used to validate the Symptom Checklist-90 (SCL-90) were used as reference (196). This study was based on Swedish women from the general population who were aged 40 years and older (196).

Data sources

The SCL-90

The SCL-90 is a multidimensional psychological symptom inventory measuring self-perceived mental health during the past week (196, 197). It consists of 90 questions with answers that are rated on a five-point Likert scale ranging from 0 “not at all” to 4 “extremely”. The SCL-90 assesses nine primary dimensions: somatisation, obsessive-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. There are also three global subscales which are used as summary dimensions. The global severity index (GSI) measures the mean reported level of mental health problems across all 90 questions. The positive symptom distress index (PSDI) measures the depth of the perceived problems by the mean of non-zero answers and indicates

the response style of the individual. The positive symptom total (PST) measures the total number of non-zero answers thus representing the number of symptoms (196, 197).

The study-specific questionnaire

A study-specific questionnaire was used to gather information about demographic factors such as employment and marital status. There were questions regarding whether the women were with the same or a different partner compared to the time of IVF treatment as well as on the number of children (biological and/or adopted). Fixed choice questions were used for all factors except for employment status which the participants were asked to describe with their own words. The answers were dichotomized into “Employed” and “Unemployed”.

Study design

Principal outcome variables

The global subscales GSI, PSDI and PST as well as the nine primary dimensions were measured. The cut-off score for each primary dimension was, in accordance with some previous studies (198), set at the 95th centile of self-reported symptoms in the study population in order to indicate a severe level of symptoms.

Sociodemographic variables

Marital status was divided into: 1 married/cohabiting and 2 divorced/separated/other. The question on whether the women were still with the same partner compared to at the time of the IVF treatment as well as employment status were dichotomous variables. Age at follow-up was a continuous variable.

Data analyses

The statistical analyses were performed using IBM SPSS 19 (IBM Corporation, Armonk, New York, USA). Chi-square tests were used to analyze differences between the parental status subgroups in sociodemographic factors and self-perceived mental health measured by the nine primary dimensions. Differences in the three global dimensions across parental status groups were calculated using one-way ANOVA analyses. Due to that multiple subgroup analyses were performed in order to draw one conclusion, Bonferroni corrections of the significance level were performed. Two-sided students t-test were used to compare mean scores between all women who had received IVF treatment to those of the reference group on the nine primary dimensions as well as the global dimensions. Using Cohen's distance, effect sizes were calculated in order to evaluate the magnitude of these differences. A value ≥ 0.2 was designated as small, ≥ 0.5 medium and ≥ 0.8 large. The significance level was set at $p < .05$.

Study IV

Population

The analyses are based on data from the "Elderly in Linköping Screening Assessment", ELSA 85, a population-based study of 85-year old men and women living in Linköping Municipality, Sweden (199). The names and addresses of all individuals born in 1922 and who were living in Linköping municipality in 2007 ($n=650$) were collected from the Swedish TPR. A postal questionnaire was sent to these individuals asking for their participation in the study. If the 85-year old was physically unable to answer the questionnaire by him- or herself, a relative or caretaker was allowed to assist.

Out of the 650 85-year olds, written consent was received from 76% (n=496), all of whom had filled out the questionnaire. Those who did not consent were 52 individuals who could not be reached, 12 who had died and 90 who declined participation. In the second part of the study, an occupational therapist contacted all participants to schedule an interview in their homes. While 110 individuals declined further participation, another nine 85-year olds had died leaving 377 (76%) participants.

Data sources

The ELSA-85 questionnaire

This non-validated questionnaire was specifically designed for the ELSA-85 study. There were questions on sociodemographic factors, social network, living situation as well as two of the questions used to measure psychological well-being; frequency and strength of feelings of loneliness. All questions included in the present study were fixed-choice. In addition, the ELSA-85 questionnaire included many other questions and measures which were not utilized in the present study, a description of which can be found in a study by Nägga et al. (199).

Interview

During the visit by the occupational therapist, using a structured interview protocol, the remaining questions measuring psychological well-being were posed; degree of happiness, sense of meaning in life and general life satisfaction. Depression was screened for using the Geriatric Depression Scale -20 (GDS-20), which is a questionnaire with 20 questions (200). Five of the questions were excluded to form GDS-15, which is considered a valid and reliable scale for screening for depression in the elderly (201). During the visit by the occupational therapist there were many other questions posed and evaluations performed, the results of which were not included in the present study.

Study design

Principal outcome variables

Psychological well-being

The question in the ELSA-85 questionnaire measuring loneliness had response alternatives 1 “Yes, often”, 2 “Yes, sometimes”, 3 “No, rarely”, 4 “No, never” and 5 “No, I wished that I had more time to myself”. For the logistic regression analyses the response alternatives were dichotomized into “Lonely” (1-3) and “Not lonely” (4-5). Those who answered 1 or 2 were asked to specify the strength of their feelings of loneliness. The response alternatives ranged from 1 “Very strong” to 5 “Very weak”. Information about depressed mood was gathered from the GDS-15. The cut-off value was set at ≥ 5 (range 0-15), which has a good sensitivity and specificity when screening for depression among the elderly (202). The response alternatives for the question on general life satisfaction ranged from 1 “Very good” to 5 “Very bad”, for sense of meaning in life from 1 “To the highest degree meaningful” to 5 “Without meaning”, for happiness from 1 “To the highest degree happy” to 5 “Very unhappy”. For the logistic regression analyses the response alternatives were dichotomized into “Happy” (1-3) and “Unhappy” (4-5). The participants were also asked to respond to the question “In general, would you say that your health is” with response alternatives ranging from 1 “Excellent” to 5 “Bad”. Three major dependent variables were selected for the logistic regression analyses; Loneliness, Happiness and Depression.

Social network

In the ELSA-85 questionnaire there were three response alternatives for the variable “Social network, relatives”: 1 “I have got relatives close by”, 2 “I only have relatives at a different location”, 3 “I do not have any relatives”. There were two response alternatives for “Social network, friends”: 1 “I have friends close by”, 2 “I do not have friends close by”. There were

three response alternatives for the question “Are you in contact with your neighbours?”: 1 “I am in close contact with my neighbours”, 2 “I am in some contact with my neighbours”, 3 “I do not have any contact with my neighbours”. The strength of the social networks was examined by the question “Do you receive help from family or friends?” with response alternatives: 1 “No”, 2 “Yes, from my husband/wife/cohabiter”, 3 “Yes, from a sibling”, 4 “Yes, from children/grandchildren” and 5 “Yes, from a friend/friends”.

Sociodemographic variables

In the ELSA-85 questionnaire, the response alternatives for “Number of children” ranged from 0 “No children” to 4 “Four or more children”. Response alternatives were dichotomized into 1 “No children (0)” and 2 “Children” (1-4). The response alternatives for “Marital status” was 1 “Married/cohabiting”, 2 “Unmarried” and 3 “Widowed”. The response alternatives for “Highest level of education” were 1 “Elementary school”, 2 “Secondary grammar school” and 3 “College/University”. The response alternatives for “Living situation” were 1 “Housing in the community”, 2 “Residential care” and 3 “Nursing home”.

Data analysis

Statistical analyses were performed using SPSS 16.0 (SPSS, Chicago, USA). Chi square analyses were performed to determine statistically significant differences between participants and non-participants for the two variables that were available for the non-participants; gender and living situation. The same statistical test was used to find statistically significant differences across the parental status groups in sociodemographic, psychological well-being, self-rated health and social network variables. Additional chi-square analyses were performed to find differences in loneliness, depression and self-rated health across the two parental status groups subdivided by living situation (1 “Living out in the community” or 2 “Nursing

home/residential care”). When there were less than five frequencies in a cell, Fisher’s exact tests were performed to test statistical significance between the two groups.

Multiple logistic regression analyses were performed to investigate parental status as a predictor for depression, loneliness and happiness while controlling for possible confounding factors; gender, marital status, living situation and self-rated health. For these analyses, the depression, loneliness and happiness variables were recoded as binary and modelled separately as dependent variables. Follow-up logistic regression analyses, including parental status and one control variable each time, were performed as well as a correlation analyses.

Results

Study I

Sociodemographic variables

Mean maternal age at the time of childbirth birth was 29.2 years. The women in the control group were more likely (12.4%; n=367) than the women in the IVF group (4.0%; n=120) to be single ($p<.001$). As their highest level of education, the women in the IVF group were more likely to have either completed nine years of school (7.8%; n=236) or to have continued to university (43.2%; n=1300) compared with those in the control group (6.5%; n=192 vs 40.8%; n=1206) ($p=.007$).

Characteristics of previous pregnancies

Those in the IVF group (15.4%; n=543) were more likely than those in the control group (12.7%; n=1089) to have previously experienced a miscarriage ($p<.001$). There were no differences between the groups for previous stillborn child/death of a child during the first month ($p=.114$).

Characteristics of the current pregnancy

As shown below in Table 1, all subcategories of PTB and LBW were more common in the IVF group than in the control group while those in the control group were more likely than those in the IVF group to have a post-term birth. While there were no differences between the groups in regard to plurality, the women in the control group were more likely than those in the IVF group to have an instrumental delivery (Table 1).

Table 1. Study I; Characteristics of the current pregnancy: Prevalence and chi-square tests							
	IVF		Control		Total		
	n	%	n	%	n	%	p
	3532	33.3	8553	66.6%	12085	100	
Gestational age							<.001*
Extremely preterm (<28)	36	1.0	37	0.4	73	0.6	
Very preterm (28-32)	88	2.5	60	0.7	148	1.2	
Preterm (32-36)	416	11.8	498	5.8	914	7.6	
Term (37-40)	2212	62.9	5520	64.6	7732	64.1	
Post term (>40)	762	21.7	2436	28.5	3198	26.5	
Birth weight							<.001*
ELBW (<1000g)	48	1.4	34	0.4	82	0.7	
VLBW (<1500g)	89	2.5	51	0.6	140	1.2	
LBW (1500-2500g)	368	10.5	324	3.8	692	5.7	
Normal (>2500g)	3014	85.6	8126	95.2	11140	92.4	
Mode of delivery							<.001*
Vaginal, spontaneous	2532	72.5	5950	69.6	8522	70.5	
Vaginal, instrumental	364	10.4	1219	14.3	1583	13.1	
Elective section	192	5.5	419	4.9	611	5.1	
Acute section	404	11.6	965	11.3	1369	11.3	
Plurality							.877
Yes	46	1.6	136	1.6	193	1.6	
No	2825	98.4	8417	98.4	11837	98.4	
Tests of significance using chi-square							
*Significant at .05 level							

Previous psychiatric diagnoses

In total, 2.5% of the IVF women and 4.2% of the control women had previously been diagnosed with any psychiatric disorder requiring in- or outpatient psychiatric care (Table 2). There were no differences between the IVF group and the control group regarding a history of the diagnoses schizophrenia or other psychotic disorders, obsessive compulsive disorder or reactions to severe stress. The women in the control group were more likely than those in the IVF group to have previously been diagnosed with bipolar disorder or mania, depression, any anxiety disorder, or specifically a phobic disorder or other anxiety disorder, and also to have previously received a personality disorder diagnosis (Table 2).

Table 2. Study 1; Psychiatric diagnoses 5 years prior to birth of child							
	IVF		Control		Total		p
	n	%	n	%	n	%	
	3532	100	8553	100	12085	100	
Diagnosis (≥1)							
Any psychiatric (F20-43, F60)	87	2.5	355	4.2	442	3.7	<.001*
Any affective (F30-39)	39	1.1	170	2.0	209	1.7	.001*
Manic or bipolar (F30-31)	0	0.0	14	0.2	14	0.1	.015*
Depression (F32-39)	39	1.1	159	1.9	198	1.6	.003*
Schizophrenic or psychosis (F20-29)	1	0.02	6	0.1	7	0.1	.681
Schizophrenic (F20-22, F24-25)	0	0.0	3	0.04	3	0.02	.556
Other psychosis (F23, F28, F29)	1	0.02	5	0.1	6	0.05	.678
Anxiety disorder (F40-43)	62	1.8	240	2.8	302	2.5	.001*
Phobic disorder (F40)	4	0.1	37	0.4	41	0.3	.008*
Other anxiety disorder (F41)	34	1.0	148	1.7	182	1.5	.002*
Obsessive compulsive disorder (F42)	1	0.02	9	0.1	10	0.1	.299
Reactions to severe stress (F43)	31	0.9	88	1.0	119	1.0	.477
Personality disorder (F60)	7	0.2	44	0.5	51	0.4	.016*
Significance testing using Chi2-tests							
*Significant at the p<.05 level							

Postpartum depression

The chi-square analyses showed an increased risk of receiving a PPD diagnosis among women in the control group (0.8%; n=66) compared with the women in the IVF group (0.4%; n=15) (p=.040). These results were repeated in the initial multiple logistic regression analyses (p=.037; OR 1.8; 95% CI=1.0-3.2) but disappeared when other covariates with a significant association to the outcome were controlled for in the additional multiple logistic regression analyses. When only women without previous psychiatric diagnoses were included in the chi-square analyses, there were no significant differences in the prevalence of PPD diagnoses between the two groups. None of the women in either group had committed suicide during the first year after childbirth.

The initial multiple logistic regression analyses also showed that being single (p=.006; OR=3.310; 95% CI=1.411-7.766), having any previous psychiatric diagnosis (p<.001; OR=8.355; 95% CI=3.100-22.520) or specifically an affective (p<.001; OR=5.416; 95% CI=2.347-12.497) or personality disorder diagnosis (p<.008; OR=2.971; 95% CI=1.330-6.636)

were risk factors of PPD. These variables with a significant relationship to the outcome were added to the multiple regression analyses along with the “group” variable but due to the high correlation between “any previous psychiatric diagnosis” and “any previous affective disorder diagnosis”, separate models were performed for these two variables. The significant results remained for any previous psychiatric diagnosis ($p<.001$; OR=25.5; 95% CI=11.7-55.5) and a personality disorder diagnosis ($p=.028$; OR=3.8; 95% CI=1.2-12.7) in the first multiple regression model and for any previous affective disorder diagnosis ($p<.001$; OR=26.0; 95% CI=10.5-64) and a personality disorder diagnosis ($p=.005$; OR=7.5; 95% CI=1.8-30.8) in the second multiple regression model.

Study II

Sociodemographic variables

The women in the IVF group were more likely to be aged ≥ 35 years (17.3%; $n=1797$) than the women in the control group (5.0%; $n=930$) while the women in the control group were more likely to be aged ≤ 24 years (25.0%; $n=4653$) than the women in the IVF group (3.0%; $n=309$) ($p<.001$). Those in the IVF group were more likely to be married or cohabiting (98.3%; $n=9793$) than were those in the control group (92.6%; $n=16337$) ($p<.001$). As their highest level of education, the women in the IVF group (61.2%; $n=6365$) were more likely than the women in the control group (47.7%; $n=8854$) to have completed an education at university ($p<.001$).

Characteristics of the current pregnancy

Gestational diabetes, preeclampsia, caesarean birth or instrumental delivery, multiple births, complications of labour and delivery and all LBW and PTB subcategories were more

common in the IVF than in the control group (Table 3). When only those with singleton births were included in the analyses, the statistically significant differences for all above mentioned pregnancy and delivery complications remained.

Table 3. Study II; Pregnancy and delivery factors: Prevalence and chi-square tests							
	IVF		Control		Total		
	n	%	n	%	n	%	p
	10412	35.9	18624	64.1	29036	100	
Gestational diabetes	90	0.9	109	0.6	199	0.7	.007*
Preeclampsia	607	5.8	822	4.4	1429	4.9	<.001*
Gestational length	10410	100	18607	100	29017	100	
Extremely preterm (<28)	62	0.6	62	0.3	124	0.4	
Very preterm (28-32)	117	1.1	110	0.6	227	0.8	
Preterm (32-36)	771	7.4	999	5.4	1770	6.1	
Term (37-40)	6778	65.1	12366	66.5	19144	66.0	
Post term (>40)	2682	25.8	5070	27.2	7752	26.7	<.001*
Birth weight	10395	100	18586	100	28981	100	
ELBW (<1000g)	57	0.5	63	0.3	120	0.4	
VLBW (<1500g)	84	0.8	72	0.4	156	0.5	
LBW (1500-2500g)	567	5.5	625	3.4	1192	4.1	
Normal (>2500g)	9687	93.2	17826	95.9	27513	94.9	<.001*
Mode of delivery	10412	100	18624	100	29036	100	
Vaginal, spontaneous	6445	61.9	12937	69.5	19382	66.8	
Vaginal, instrumental	2493	23.9	3112	16.7	5605	19.3	
Caesarian section	1474	14.2	2575	13.8	4049	13.9	<.001*
Complications of labour and delivery	5449	52.3	7641	41.0	13090	45.1	<.001*
Plurality (Yes)	325	3.1	161	0.9	486	1.7	<.001*
Tests of significance using chi-square							
*Significant at .05 level							

Previous psychiatric disorders

In total, 4.2% (n=1209) of the women had received any psychiatric disorder diagnoses, 0.2% (n=61) a previous manic episode or a bipolar disorder diagnosis, 2.1% (n=621) a depression diagnosis, 2.8% (n=824) an anxiety disorder diagnosis and 0.4% (n=122) a personality disorder diagnosis during the five years prior to childbirth. There were no statistically significant differences between the IVF or the control group for any of these diagnoses but those in the control group (0.1%; n=26) were more likely than those in the IVF group (0.04%; n=4) to have a history of schizophrenia or other psychotic disorder diagnosis (p=.015).

Postpartum psychosis

In total, 106 (0.4%) of the women had been diagnosed with a PPP. No statistically significant differences were found in PPP prevalence between the women in the IVF group (0.3%; n=29) and the control group (0.4%; n=77) ($p=.169$). While 26 (0.1%) of the women received a psychotic disorder diagnosis, 40 (0.1%) were diagnosed with mania or bipolar disorder and 9 of the women (0.03%) received the diagnosis severe mental and behavioural disorders associated with the puerperium during the first year postpartum.

Table 4. Study II; Postpartum psychosis: Significant results of the multiple logistic regression			
	Postpartum psychosis (F20-31, F531)		
Covariates	OR	p	C.I.
Any psychiatric disorder (F20-43, F60)			
No (reference level)	40.726	<.001*	23.866-69.496
Schizophrenia or psychotic disorder (F20-25, F28-29, F53)			
No (reference level)	324.125	<.001*	131.327-799.962
Bipolar disorder or mania (F30-31)			
No (reference level)	516.128	<.001*	264.251-1008.090
Depression (F32-39)			
No (reference level)	27.465	<.001*	16.227-46.488
Anxiety disorder (F40-42)			
No (reference level)	12.940	<.001*	7.402-22.619
Personality disorder (F60)			
No (reference level)	27.272	<.001*	11.805-63.003
*Significant at the $\leq .05$ level			

The multiple logistic regression analyses showed that any previous psychiatric diagnosis or specifically a psychotic disorder, bipolar disorder or mania, depression, anxiety disorder or personality disorder diagnosis were significant predictors of PPP (Table 4). There were no statistically significant differences in the risk of being diagnosed with PPP between the IVF and control group ($p=.646$) or depending on maternal age ($p=.058$), marital status ($p=.774$), highest level of education ($p=.689$), gestational diabetes ($p=.912$), preeclampsia ($p=.884$), gestational length ($p=.544$), birth weight ($p=.230$), multiple birth ($p=.313$), mode of childbirth ($p=.768$) or any complication of labour and delivery ($p=.586$).

Study III

Sociodemographic variables

While there were no statistically significant differences between the groups in employment status, the women who had biological and/or adoptive children were more likely than those who had remained childless to be married/cohabiting (Table 5). However, those who had biological children were less likely than the other parental status groups to have remained with the same partner as the time of treatment. Those who had biological children were less likely than those who were childless/had adopted children to be aged ≥ 45 years (Table 5).

Table 5. Study III; Demographics: Prevalence and chi-square tests											
	No children		Biological children		Adoptive children		Biological+adoptive children		Total		
	n	%	n	%	n	%	n	%	n	%	p
	95	20.2	259	55.1	91	19.4	25	5.3	470	100	
Age at follow-up											<.001*
<45	20	21.1	123	47.5	28	30.8	10	40	181	38.5	
≥ 45	75	78.9	136	52.5	63	69.2	15	60.0	289	61.5	
Missing	0		0		0		0		0	0.0	
Marital status											<.001*
Married/cohabiting	55	58.5	240	93.0	91	100.0	25	100.0	411	87.4	
Separated/divorced/other	39	41.5	18	7.0	0	0.0	0	0	57	12.1	
Missing	1		1		0		0		2	0.4	
Same partner											<.001*
Yes	54	90.0	175	70.6	90	98.9	24	96.0	343	73.0	
No	6	10.0	73	29.4	1	1.1	1	4.0	81	17.2	
Missing	35		11		0		0		46	9.8	
Employment status											.369
Yes	66	78.6	189	78.8	75	87.2	19	79.2	349	74.3	
No	18	21.4	51	21.3	11	12.8	5	20.8	85	18.1	
Missing	11		19		5		1		36	7.7	
Tests of significance using chi-square. *Significant at .05 level. The percentages do not in all cases reach 100% due to missing data. Some percentages do not add up to 100% because of rounding.											

Self-rated mental health

Differences between age and employment groups, parental and marital status groups and same or different partner groups were assessed for the 9 primary dimensions of the SCL-90. Compared to those without children, those who had biological children were less likely to report symptoms of depression ($p=.009$) and those who had biological or adoptive children

were less likely to report symptoms of phobic anxiety ($p=.017$). Those who were aged ≥ 45 were more likely to exhibit symptoms of depression ($p=.030$) or phobic anxiety ($p=.021$) than those who were in the younger age group. Those who were employed were more likely than the unemployed to report symptoms of depression ($p=.017$), anxiety ($p=.004$), phobic anxiety ($p=.003$) and obsessive compulsion ($p=.018$). Women who were married/cohabiting were less likely than those who were separated/divorced to report symptoms of depression ($p=.030$), anxiety ($p=.042$) or obsessive compulsion ($p=.042$). Those who had changed partners since the time of treatment were more likely to exhibit obsessive compulsive symptoms ($p=.002$). There were no statistically significant differences for somatisation, interpersonal sensitivity, hostility, paranoid ideation and psychoticism.

In regard to the global indices, those who had remained childless scored higher than those who had biological and/or adopted children but the differences were, after Bonferroni corrections of the significance level, only statistically significant for GSI ($p=.022$) (Table 6). Initial analyses showed significant differences between the childless group and each of the other parental status groups for GSI but after Bonferroni corrections the only remaining significant difference was between those who were childless and those who were biological parents (Table 6). Subgroup analyses showed no significant differences between the three groups of women with biological, adopted and biological and adopted children.

Table 6. Study III; Global indices: One-way ANOVA by parental status									
	GSI			PSDI			PST		
Children	Mean	SD	p	Mean	SD	p	Mean	SD	p
No children (ref)	.52	.50		.58	.05		28.87	1.89	
Biological	.40	.43	.004*	.45	.93	.018	24.83	1.15	.039
Adopted	.41	.42	.043	.45	.05	.061	24.83	1.94	.141
Biological and adopted	.37	.41	.041	.46	.09	.214	24.36	3.68	.264
			.022			.101			.295
SD= Standard deviation, GSI = Global Severity Index, PSDI = Positive Symptom Distress Index, PST = Positive Symptom Total Level of significance $p<.05$. Bonferroni corrected significance level $p=.008$. * = significant value.									

Compared with an aged-matched reference group, the women in the study population were at increased risk of somatisation ($p<.001$), obsessive compulsive symptoms ($p=.020$) and depressive symptoms ($p=.017$). There were no statistically significant differences for the remaining primary dimensions. In regard to the global distress indices there were no significant differences for the GSI and the PST but the women who had previously undergone IVF scored higher than the reference group on PSDI indicating that these women had reported more intense symptoms ($p<.001$). The magnitude of the differences was, using Cohen's distance, found to be under the cut-off for symptoms of obsessive compulsion and depression, small for somatisation and medium for PSDI.

Study IV

Sociodemographic variables

In total, 11.5% of the participants were childless. Those who were parents were more likely to be married (45.8%; $n=200$) or widowed (47.1%; $n=206$) than the childless (24.6%; $n=14$ vs 38.6%; $n=22$) ($p<.001$). There were no statistically significant differences in gender ($p=.670$) or highest level of education ($p=.298$) across the parental status groups. The only information available for the non-participants was gender and living situation. While there were no statistically significant differences in gender ($p=.074$) between participants and non-participants, the non-participants (22.2%; $n=20$) were more likely than the participants (11.1%; $n=55$) to live in institutional care ($p=.006$). Out of the 496 participants, 11,7% ($n=58$) received help filling out the questionnaire.

Psychological well-being

No differences across the parental status groups for loneliness, depressive symptoms, life satisfaction or sense of meaning in life were found in the chi-square analyses (Table 7). In total, 8.2% reported that they often, and 31.6% that they sometimes, felt lonely. However, among those who experienced loneliness, 80.4% reported that their feelings were neither strong nor weak, quite or very weak. About one third of the participants scored above the cut-off value for depressive symptoms on the GDS-15. In total, 87.7% reported a very or quite good satisfaction with life and 84,1% that their lives were to the highest degree or quite meaningful. Those who were parents were significantly more likely than those who were childless to experience higher levels of happiness (Table 7).

Table 7. Study IV; Psychological well-being: Distribution and chi-square tests							
	Childless		Parents		Total		
	n	%	n	%	n	%	p
Rate of feelings of loneliness	57		430		487		.734
Often	7	12.3	33	7.7	40	8.2	
Sometimes	18	31.6	136	31.6	154	31.6	
Rarely	18	31.6	132	30.7	150	30.8	
Never, Would like more time alone	14	24.6	129	30.0	143	29.4	
Strength of feelings of loneliness	36		230		266		.857
Very strong	2	5.6	7	3.0	9	3.4	
Quite strong	5	13.9	38	16.5	43	16.2	
Neither strong nor weak, quite or very weak	29	80.6	185	80.5	214	80.4	
Depression GDS-15	57		437		494		.721
Score <5p	37	64.9	294	67.3	331	67.0	
Score ≥5p	20	35.1	143	32.7	163	33.0	
Life satisfaction	38		310		348		.323
Very good	11	28.9	132	42.6	143	41.1	
Quite good	20	52.6	142	45.8	162	46.6	
Neither good nor bad, quite or very bad	7	18.4	36	11.7	43	12.3	
Sense of meaning in life	38		308		346		.229
To the highest degree meaningful	8	21.1	105	34.1	113	32.7	
Quite meaningful	20	52.6	158	51.3	178	51.4	
Neither meaningful nor meaningless, quite or very meaningless	10	26.3	45	14.5	55	15.9	
Happiness	38		308		346		.038*
To the highest degree happy	6	15.8	95	30.8	101	29.2	
Quite happy	19	50.0	150	48.7	169	48.8	
Neither happy nor unhappy,	6	15.8	43	14.0	49	14.2	
Quite or very unhappy	7	18.4	20	6.5	27	7.8	
Tests of significance using chi-square. *Significant at .05 level. Some percentages do not add up to 100% because of rounding.							

When the parental status groups were subdivided into groups by living situation (out in the community or institutional care), the chi square tests showed that those who lived in institutional care had a poorer self-rated health ($p=.007$) and were more likely to feel lonely ($p=.008$) and depressed ($p<.001$), irrespective of parental status.

Social network and self-rated health

The chi-square tests showed no statistically significant differences in self-rated health across the parental status groups ($p=.469$). The majority of the participants reported that their self-rated health was good (48.4%; $n=167$) or ok (31.6%; $n=109$). Neither was there any differences in living situation ($p=.728$). While 88.8% ($n=438$) lived out in the community, 6.1% ($n=30$) lived in residential care and 5.1% ($n=25$) in nursing homes. Those who were parents (86.4%; $n=374$) were more likely than those who were childless (62.5%; $n=35$) to have relatives close by ($p<.001$). There were no statistically significant differences in contact with friends or neighbours. In total, 88.5% ($n=424$) of the participants had friends close by ($p=.524$) and 29.6% ($n=142$) were in close, or had some, contact (56.7%; $n=272$) with their neighbours ($p=.981$). Those who were childless (50.9%; $n=27$) were more likely than those who were parents (26.5%; $n=112$) to report not receiving any help ($p<.001$). Among those who did receive help, children/grandchildren (43.4%; $n=183$) were the greatest source of help to their parents while those who were childless were almost equally likely to receive help from a spouse (17.0%; $n=9$), siblings (15.1%; $n=8$) or friends (15.1%; $n=8$).

Logistic regression analyses

Loneliness

The single logistic regression analyses showed that living in residential care compared to out in the community increased the risk of loneliness. These differences disappeared when other variables were controlled for in the multiple logistic regression analyses (Table 8). These analyses showed that being male, married compared to widowed, having a good self-rated health and living in the community compared to a nursing home increased the risk of loneliness (Table 8).

Table 8. Study IV; Loneliness, depression and happiness: Multiple logistic regression analyses									
	Loneliness			Depression			Happiness		
	p	OR	CI	p	OR	CI	p	OR	CI
Parental status									
Childless (ref)									
Parent	.563	1.27	.56-2.87	.466	1.65	.43-6.28	.536	.70	.21-2.24
Marital status									
Married (ref)									
Unmarried	.133	.50	.20-1.24	.576	1.46	.39-5.45	.031*	4.43	1.15-17.14
Widowed	<.001***	.24	.14-.42	.861	1.08	.46-2.51	.249	1.89	.64-5.54
Gender									
Woman (ref)									
Man	.020*	1.87	1.11-3.16	.596	.80	.35-1.84	.403	1.51	.58-3.94
Living situation									
In the community (ref)									
Residential care	.122	1.09	.400-3.00	.026*	1.37	.40-4.73	.24	2.53	.73-8.72
Nursing home	.041*	.16	.03-.93	.007**	8.22	1.77-38.23	.14	2.70	.41-17.84
Self-rated health									
Good (ref)									
Bad	.01*	.522	.31-.87	<.001***	4.77	2.22-10.25	<.001***	4.51	1.81-11.25
Constant									
OR = Odds ratio, CI: Confidence interval, 95% for OR. P<.05*, P<.01**, P<.001***									

Depression

The single, but not the multiple, logistic regression analyses showed that women, compared to men, were at increased risks of depressive symptoms above the GDS 15 cut-off. In the multiple logistic regression analyses, living in nursing homes or residential care and experiencing a poor self-rated health increased the risk of depressive symptoms above the GDS-15 cut-off (Table 8). The results for living situation were not significant in the single logistic regression analyses and were thus a result of interaction with other covariates.

Happiness

The significant differences in degree of happiness found in the chi-square tests for parental status, and in the single logistic regression analyses for residential care, disappeared when other factors were controlled for in the multiple logistic regression analyses. The bi- and multiple logistic regression analyses showed that being unmarried, compared to married, increased the likelihood of happiness (Table 8). Poor health was positively associated with happiness (Table 8).

The correlation analyses only showed a high collinearity between marital status and gender.

General discussion

Summary of principal findings

While there is some research on the consequences of infertility and its treatment on mental health and well-being in the postpartum period, studies on PPD have used questionnaires or symptom-rating scales rather than psychiatric diagnoses to identify cases and have often failed to control for the most important risk factor of PPD; a history of mental illness. There are no previous studies on the possible effect of infertility and its treatment on PPP risk. In addition, few studies extend beyond the first years after treatment and only a couple have studied psychological well-being in women with or without children as late as twenty years after infertility treatment. Little is known of how childlessness affects psychological well-being in the oldest old and thus the population that is likely to be frailest and most dependent on others. This thesis provides useful additions to the knowledge of postpartum mental health and long-term effects on psychological well-being in women who have undergone IVF treatment as well as the influences of childlessness on psychological well-being in elderly men and women.

The results of this thesis indicate that primiparous women who give birth after IVF treatment are not at increased risk of receiving a postpartum psychiatric disorder diagnosis such as PPD that requires in or outpatient psychiatric care, or PPP, compared with women who give birth after spontaneous conception. Neither does the risk of suicide appear to be increased in these women the first year after childbirth. In the present thesis, PPD and PPP cases were identified using ICD diagnostic codes and most major risk factors, such as previously diagnosed psychiatric disorders, were controlled for. The results confirm those of previous studies in showing a history of mental illness to be the major risk factor for PPD and PPP and that

women who undergo IVF treatment are less, or for some psychiatric disorders equally, likely than women who conceive spontaneously to have previously been diagnosed with a psychiatric disorder.

In regard to the long-term adjustment to infertility and IVF treatment, most women report a good mental health about twenty years after treatment. However, the results indicate that these women have a slightly increased risk of some adverse psychological symptoms and that this risk is further increased among those who remain childless. In addition, the results of this thesis are in accordance with several previous studies in showing that childlessness might increase the risk of having a social network of low support potential in old age. In spite of these findings, childlessness does not appear to have an adverse effect on psychological well-being in the oldest old.

Methodological considerations

Studying psychological well-being and mental health entails a series of potential methodological difficulties, some of which are discussed below.

Questionnaires and symptom rating scales vs register data

The majority of the previous studies on psychological well-being or mental health in relation to involuntary childlessness, infertility or IVF treatment have used a variety of questionnaires or self-report symptom rating scales to identify cases, only some of which are validated.

While a few of these instruments, such as the EPDS, have relatively good sensitivity and specificity when screening for depression (203), the use of others is not as well-established. In some studies, conclusions are drawn regarding the presence or absence of psychiatric

disorders when the participants have scored above a certain cut-off point on a symptom rating scale or higher than a control group. As previously mentioned, none of the studies on the risk of PPD in women after IVF treatment that were included in the review by Ross et al. (138) used diagnostic assessments or psychiatric diagnoses to identify cases. Brockington stated that “A positive score on a self-rating questionnaire needs to be followed by an interview clarifying the symptom of depression and coexisting psychiatric disorders” (86). Hence, it is difficult to know how well the cut-off points on symptom rating scales would measure up to psychiatric diagnoses received after an assessment by a medical professional according to DSM-V criteria.

These methodological issues are also relevant for the studies included in this thesis. In the present Study III, the SCL-90 was used to assess mental health problems and in Study IV, the GDS-15 was used to screen for depressive symptoms. The SCL-90 is a psychological symptom inventory measuring self-perceived mental health (196, 197) while the GDS-15 is a questionnaire commonly used to screen for depressive symptoms in the elderly (201). While these are validated, widely used screening instruments, it is important to note that conclusions regarding risk of psychiatric disorders cannot be drawn using these methods, only about risk of higher levels of symptoms compared with control groups or the general population. In addition, a study-specific questionnaire was used in Study IV to assess loneliness, social network, demographics and living situation and a structured interview to assess satisfaction with life, sense of meaning in life and happiness. Since the questionnaire and interview protocol are not validated, the results from Study IV, depression data from the validated GDS-15 being the exception, should be interpreted with caution.

The identification of cases using psychiatric diagnoses retrieved from registers also entails some methodological issues. While the diagnoses retrieved for Studies I and II were collected from the widely-used, validated Swedish NPR, it is of course probable that there are some diagnostic and reporting errors among the register data. Ludvigsson et al. (186) reported in their review study on NPR validation a general positive predictive value (PPV) of 85-95%. For psychiatric diagnoses the PPV ranged from 75 to 95% in all studies but one. Validation was, in these cases, performed using source data (patient charts) or by comparisons to other registers. Hence, it is not possible to be certain that all psychiatric diagnoses included in these studies are correct. While studies that have used questionnaires or symptom rating scales to define cases cannot draw conclusions regarding the occurrence of psychiatric disorders, it must be noted that conclusions from Studies I and II can only be drawn for the occurrence of psychiatric diagnoses rather than disorders.

Some of the studies referenced in the introduction to this thesis have used ICD-10 psychiatric diagnoses to identify cases when studying the prevalence of psychiatric disorders, (44, 68, 69, 98, 99, 116, 117, 122, 124, 140). These studies have used large, sometimes nationwide, registers from countries such as Denmark, Finland and Sweden. Most registers only cover hospitalizations and, in some countries, psychiatric outpatient visits but unfortunately not diagnoses from general practice. Contrary to the problems that arise from the use of self-report symptom rating scales and questionnaires, the use of diagnostic codes from register data will likely result in the exclusion of less severe cases of disorders such as PPD, while disorders that always require hospitalization, such as PPP, should be less affected. Therefore, the present Study II should not be affected by this methodological problem while it is relevant for Study I. Meanwhile, the scope of Study I was restricted to severe PPD that require in- or outpatient psychiatric care, not including women with PPD of a less severe form with

diagnoses from general practice. Hence, the results of Study I can only be generalized to severe PPD cases.

Variations in diagnostic codes to identify cases

The diagnoses selected to identify cases of PPD and PPP differ between studies. Since neither DSM-V nor ICD-10 offer specific diagnostic codes, only a "peripartum specifier", for postpartum psychiatric disorders, the diagnostic codes selected to represent PPP vary to a great extent. The range of diagnoses include manic episode (ICD-10 diagnostic code F30), bipolar disorder (F31), schizophrenia (F20), other psychotic disorders (F21-29) and even depressive disorders since severe MDD with psychotic symptoms (F32.3 and F32.3W) can be difficult to separate from disorders in the psychotic spectrum. Some studies also use the "mental and behavioral disorders associated with the puerperium" (F53) diagnoses. For PPD, the diagnostic codes used mostly stem from the ICD-10 diagnostic codes F32-39, sometimes only including F32-33. The F53 diagnoses can also be used for PPD, especially when it cannot be specified what kind of disorder from which the patient suffers. It is also possible that ICD-10 diagnosis F25.1, "Schizoaffective disorder depressive type", and F31.3-31.5 "Bipolar disorder, depressive episode" are sometimes included in the PPD definition. There might be an especially large mix of diagnoses when different versions of the ICD are included since translation between the different versions is complicated.

In Studies I and II, the diagnostic codes were chosen to match those of most previous studies while causing minimal overlap between PPD and PPP. For PPD ICD-10 diagnostic codes F32-39 were used, while for PPP the diagnostic codes identifying cases were F20-29 (Schizophrenia, Schizotypal and Delusional disorders), F30-31 (Manic episode and bipolar disorder) and F531 (Severe mental and behavioral disorders associated with the puerperium).

It could be argued that the ICD-10 code for “Bipolar disorder, depressive episode” (F31.3-31.5) and the “Mental and behavioral disorders associated with the puerperium” (F53) diagnoses should have been included in the range of diagnoses specifying PPD. However, this would most likely have resulted in a significant overlap with PPP. The choice to include the F53 diagnosis in Study II rather than Study I was based on the use of diagnostic codes in previous studies. Meanwhile, “Severe depressive episode with psychotic symptoms” (F32.3) was included in the range of diagnoses specifying PPD which might result in an overlap with PPP. In addition, the inclusion of all bipolar disorder diagnoses in the PPP range of diagnostic codes might result in overlap with PPD. However, due to the close association between PPP and bipolar disorder, this is most likely a problem of lesser magnitude. In regard to Study II, diagnostic codes emanated from the ICD-10, -9 and -8. Although the WHO ICD translation charts were used, the translation process is complicated due to large changes in the diagnostic systems between the different versions, especially ICD-8 to -9. Hence, it is possible that some errors have been made in the translation process. However, this was performed by one of the co-authors and audited by another in order to minimize these types of errors.

Time period for diagnostic criteria and long-term follow-up

Another consideration in regard to the identification of cases is the time period used. Previous studies have used inclusion periods ranging from four weeks to one year to identify psychiatric disorders postpartum. The difficulties in choosing an adequate period of time to specify the postpartum period is exemplified by the DSM-V and the ICD-10 which use four and six weeks respectively. In the present Studies I and II the longer time period of one year was chosen, with the support of some previous studies (87, 92, 93), in order to include all cases of PPD and PPP. While the debut of postpartum psychiatric disorders, especially PPP, often occur in the first days or weeks after childbirth, using a shorter time period might still

result in exclusion of many cases since it may take some time before a final and proper diagnosis is set. However, it is possible that this longer time period results in inclusion of cases that should not be classified as having a postpartum onset.

Study III also suffers from methodological issues regarding timing due to the differences in time of follow-up which ranged from 20-23 years. While a potential difference of three years can appear short, it is possible that only some of these women have started to experience the “grandparent phase” which has been shown in a previous study to increase the risk of adverse mental health consequences (160).

All the methodological considerations mentioned above might of course influence the accuracy, validity and reliability of the results in the present thesis. In addition, these methodological variations between studies result in difficulties when attempting to compare the results of this thesis to those of previous studies.

General issues regarding registers

The data on which Studies I and II are based on were collected from large population-based registers. This method makes it possible to include large numbers of participants, the size of the populations forming major strengths of these studies. However, including large populations might cause small differences, which do not have clinical relevance, to become statistically significant. The registers used in Studies I and II are validated and include 97-99% of births, in the case of the MBR, and almost all births after IVF pregnancies, in the case of the IVF register. However, the IVF register does not include information about unsuccessful IVF treatment, childbirth after other forms of infertility treatment or IVF treatment performed in other countries. As a result, there might be women in the control

group who have previously undergone unsuccessful IVF treatment or given birth after other forms of infertility treatment performed in Sweden or who have returned to Sweden to give birth after having undergone IVF treatment in another country. In addition, some demographic data were missing from the registers for a part of the Study I and II populations.

While register-based studies are often unparalleled in regard to the potential size of the study populations, using these kinds of registers might have some negative consequences for the research field as a whole. As the registers only exist in some western, and primarily northern countries, most of these studies are conducted on participants of only a few nationalities. Hence, the conclusions drawn from these studies are from populations that are likely to be similar in regard to cultural and sociodemographic factors. In addition, it is likely that health care systems in these countries have great similarities for example in regard to criteria for acceptance into IVF treatment and treatment funding. These factors might result in problems with generalizability to the rest of the world.

Principal findings in relation to previous research

Postpartum psychiatric disorders after IVF pregnancy

Studies I and II did not find any evidence of an increased risk of receiving a PPD or PPP diagnosis in women who give birth after IVF treatment compared to those who give birth after spontaneous conception. Instead there were indications that the women who had conceived spontaneously were at increased risk of receiving a PPD diagnosis but this difference was a result of interactions with confounding factors and disappeared in the multiple logistic regression analysis that included other covariates with a significant relationship to the outcome. While Study II is the first of its kind in examining IVF treatment

as a possible risk factor for PPP, the results of Study I are in accordance with those of most previous studies on IVF pregnancies and PPD risk (71, 74, 76, 79, 138, 142, 143, 146).

Unlike many previous studies (138), we were able to control for demographic variables, pregnancy and delivery factors as well as the strongest risk factor for PPD; a history of mental illness (110, 138). Since studies have found the risk of PPD to be equal in women who conceive using IVF treatment compared to those who give birth after spontaneous conception and since the prevalence of several PPD risk factors are generally lower in the population of women seeking infertility treatment, Ross et al. (138) speculated that studies controlling for these factors might find increased risks of PPD in women giving birth after IVF treatment. However, no such differences in the risk of receiving a PPD diagnosis between the IVF and the control group were found. Post-hoc power calculations of Studies I and II, focusing on the prevalence of PPD and PPP in the two groups, resulted in a power of approximately 92 for Study I and 75 for Study II. Usually, 80 is used as the default. Hence, while the power of Study I is good, the power of Study II is lower than the "normal" default but it is still of an acceptable level. Meanwhile, both studies should have been able to detect any significant differences between the groups which supports the negative findings of these studies.

The rationale behind the hypothesis that infertility and IVF treatment could function as risk factors for postpartum psychiatric disorders involves both hormonal and immunological pathways. Since infertility and its treatment can increase levels of stress (19, 21-23) and pregnancy-specific anxiety (71, 75), it has been hypothesized that this could result in HPA-axis hyper activation during pregnancy, which has been associated with PPD (134, 135). Immunological factors have primarily been implicated in PPP pathogenesis partly because of the similarities between PPP and preeclampsia such as shared risk factors (120, 133). The risk

of preeclampsia is increased in IVF pregnancies (8, 11, 13). While the present thesis found that the risk of preeclampsia was increased in the women who had undergone IVF treatment, the regression analyses did not show an association between preeclampsia and PPP nor between IVF pregnancies and PPP. In addition, the results of Study II confirmed the results of previous studies in showing that the risk of most pregnancy and delivery complications, including PTB (8-11, 13) and delivery by caesarean section (8, 10, 11), which some studies have identified as risk factors for PPP (97, 119), was higher in the women who had given birth after IVF treatment compared to those who had conceived spontaneously. However, no associations were found between these complications and PPP in the logistic regression analyses.

Risk factors for postpartum psychiatric disorders

In line with the results of previous studies, Study I showed that any previous psychiatric diagnosis, and specifically an affective disorder diagnosis, increased the risk of receiving a PPD diagnosis about 26 times (93, 109-111). Personality disorder diagnoses also emerged as potential risk factors for PPD, increasing the risk of receiving such a diagnosis 3.8-7.5 times. These results are in accordance with some previous studies which have shown an association between personality disorders and PPD (204, 205).

While there is ample evidence showing that a history of bipolar disorder is a major risk factor for PPP (88, 97, 98, 112, 113), only a few studies have found that a history of any psychiatric disorder (97), or specifically previous psychotic episode (97, 98), increases PPP risk. The results of Study II showed that the risk of receiving a PPP diagnosis was about 40 times higher in women with any previous psychiatric diagnosis than in previously healthy women. In comparison with women without previous psychiatric diagnoses, the risk of receiving a

PPP diagnosis was increased more than 300 times in women with a previous schizophrenia or a psychotic disorder diagnosis, more than 500 times in women with a previous manic episode or bipolar disorder diagnosis, almost 30 times in women with a previously diagnosed depressive episode or a personality disorder diagnosis, and was about 13 times higher in women with a previously diagnosed anxiety disorder. While there is support in previous studies for the results pertaining to bipolar disorder, and some for any psychiatric or psychotic disorders, the remaining diagnostic groups have not previously been implicated as PPP risk factors. An explanation for these results could be that women with severe mental health problems are likely to be at increased risk of comorbidity with other psychiatric disorders.

PPD and PPP prevalence

The PPD prevalence rates of 0.4% in the IVF group and 0.8% in the control group are of course miles away from the generally reported 13% (94, 95). However, studies reporting these higher prevalence rates have identified PPD cases using questionnaires or self-report symptom rating scales rather than psychiatric diagnoses according to DSM criteria. In addition, Study I only included women who had received a PPD diagnosis while in in- or outpatient psychiatric care. Hence, women with PPD diagnosed in general practice was not included in the present study. When Gaynes et al. (95) only included MDD, the PPD prevalence rates during the first year postpartum ranged from 1.0-5.9% and studies on PPD diagnosed by a physician during the first 6 weeks postpartum, or only including PPD hospitalizations the first post-partum year, have found prevalence rates ranging from 0.06 to 0.3% (101, 102). Study II found a PPP prevalence of 0.3% in the IVF group and 0.4% in the control group. These prevalence rates are slightly higher than the generally reported 0.1-0.2% (96-99). The discrepancies in PPD and PPP prevalence rates between studies are most likely caused by variations in PPD and PPP diagnostic criteria, the use of different ICD versions as

well as differences in the defined length of the postpartum period which ranges from four weeks to one year.

In regard to risk of suicide during the postpartum period, the results of Study I were encouraging in showing that none of the women in the IVF or the control group had committed suicide during the first year after childbirth. Although postpartum psychiatric disorders can in some unfortunate cases lead to suicide (106, 107), postpartum suicides are uncommon in absolute terms (206). In Sweden, there is an established routine in regard to screening for depression in new mothers. Hence, it is possible that this process has such a high sensitivity for identification of mental health problems that suicide prevention is adequately efficient. It is also possible that some cases would have been found had the focus of the studies been on suicide risk in PPD and PPP cases.

Previous psychiatric disorders

Studies I and II showed statistically significant, albeit somewhat conflicting, differences between the IVF group and the control group in regard to previous psychiatric diagnoses from in- or outpatient psychiatric care. Study I showed that the women who had conceived spontaneously were significantly more likely to have previously been diagnosed with a bipolar disorder, depression, personality disorders and most anxiety disorders than were those in the IVF group. While no statistically significant differences between the groups were found for schizophrenia or other psychotic disorder diagnoses, these diagnoses were more prevalent in the control group. The lack of statistically significant differences between the groups was most likely due to low numbers of women with previous schizophrenia or other psychotic disorder diagnoses.

Meanwhile, the results of Study II only showed a significant difference for schizophrenia or psychotic disorder diagnoses which were more prevalent in the control group. No statistically significant differences were found between the IVF and the control group in regard to any previous psychiatric diagnosis, a previous manic episode or bipolar disorder diagnosis, depression, anxiety or personality disorder diagnoses. These results are in accordance with those of Yli-Kuha et al. (44) who studied hospitalizations due to psychiatric disorders in women before and after infertility treatments comparing them to the general population. They found that women undergoing infertility treatment had less psychiatric morbidity than those in the control group across all diagnostic subgroups but that the results were only significant for psychotic disorders (44).

The discrepancies in the results of Studies I and II in regard to previous psychiatric diagnoses can be accounted for by the smaller population and earlier conclusion of the study period in Study I. These differences can be seen as indications of an increasing tendency for women with previously diagnosed psychiatric disorders to apply, and be accepted, for IVF treatment as these forms of treatments become increasingly common. The exception appears to be women with a history of schizophrenia or other psychotic disorders, results which are in accordance with those of Ebdrup et al. (139) who showed lower prevalence rates of psychotic disorders in women undergoing IVF treatment compared with the general population. Stewart et al. (62) found in their study of women seeking infertility treatment that while a lower proportion of the women who had a history of mental illness chose to enter infertility treatment, 25% of these women had started treatment. Hence, previously diagnosed mental illness did not always pose as a barrier for infertility treatment.

Studies have shown that psychotic (139, 207) as well as affective (30, 207, 208) disorders can have a negative effect on fertility due to negative effects of the conditions as well as their treatments. This could explain the low prevalence rates of 0.1% for schizophrenia or other psychotic disorder diagnoses and of 0.1%-0.2% for bipolar disorder diagnoses in the total population of women in Studies I and II. These numbers can be compared to prevalence rates of about 0.5% for schizophrenia (209) and 0.6 % for bipolar disorder (210) in the general population. However, previous studies on prevalence rates in women undergoing infertility treatment was 0.3-0.4% for schizophrenia and other psychotic disorders and 0.1% for bipolar disorder (44, 139). The small differences in psychotic disorder prevalence between the present thesis and the previous studies by Ebdrup et al. (139) and Yli-Kuha et al. (44) could be caused by differences in inclusion criteria. While these previous studies included all women who had undergone infertility treatment, only those with successful treatment was included in the present thesis, the chance of which is reduced in women with severe mental health problems (30, 139).

The results of this thesis are generally in accordance with those of previous studies in showing that while infertile women might suffer from increased levels of stress (19, 21-23) and symptoms of anxiety and depression, they are not necessarily at increased risk of depressive or anxiety disorders (44). While the prevalence rates for previous depression diagnoses were 1.1-2.3% in Studies I and II, previous studies have found prevalence rates of MDD at about 4.7% in the general population (211). These differences are likely due to the lack of diagnoses from general practice in the Swedish NPR. Previous studies on the prevalence of depression diagnoses in women undergoing infertility treatment have found rates ranging from 0.7% to 0.9% (44, 140). The slightly higher prevalence rates found in this

thesis could be explained by differences in the selected diagnostic codes (140) or the inclusion of only in-patient psychiatric diagnoses in some studies (44).

The finding in this thesis that women who give birth after IVF treatment appear to have fewer previous mental health problems compared to those who conceive spontaneously is in line with the “healthy patient effect” hypothesis posed by several authors of previous studies (19, 44, 62, 140). This hypothesis states that those who choose to confront the emotional demands of infertility treatment are psychologically more robust than women who choose to not seek treatment for their infertility or those who give birth spontaneously. This effect might mitigate the influences of other risk factors that infertility and its treatment can give rise to and thus help explain the lack of differences between the IVF and control group in PPD and PPP risk.

Long-term consequences of infertility and IVF treatment

The results of Study III showed that women who had experienced IVF treatment about 20 years previously generally had few symptoms of mental illness. Meanwhile, those who had experienced infertility and IVF treatment were at slightly increased risks of some adverse mental health symptoms. There were statistically significant differences for depressive, obsessive-compulsive and somatisation symptoms as well as an increased strength of the reported symptoms in the women who had previously undergone IVF treatment. These results are in accordance with those of Gameiro et al. (159) in showing that the risk of adverse mental health symptoms can be increased in women many years after infertility treatment (159), but that most women adjust well after infertility treatment, irrespective of its outcome (158, 164).

Since the time of treatment, a majority of the women had become biological or adoptive parents while only about 20% had remained childless. In accordance with the results of some previous studies on the long-term effects of unsuccessful IVF treatment (20, 149-152), there were indications that those who had remained childless were at increased risk of some adverse mental health consequences compared to mothers. Those who had remained childless scored higher on the GSI than those who were biological parents, indicating a higher mean level of mental health problems. In addition, there were significant differences in symptoms of depression and phobic anxiety, the risk of which was increased in the group of childless women. In regard to clinically relevant mental health problems, some previous population-based studies that have included women who had undergone infertility evaluation or treatment 8-35 years previously, have found increased risks of hospitalization due to some psychiatric disorders in childless women compared to mothers (44, 69) but that this risk was not increased compared to the general population (44). Hence, while women who do not have children after treatment might, many years later, be at increased risk of some symptoms of adverse mental health, this risk primarily appears to be increased when compared to mothers rather than in absolute terms to the general population. While Study III found that only biological parents had a lower risk of depressive symptoms compared to the childless, both biological and adoptive parents had a lower risk of phobic anxiety. Most previous studies have shown that the positive long-term effects of parenthood found in some studies are not dependent on whether the children were biological or adopted (144, 151, 152).

Study III also showed that the childless women were more likely than parents to be divorced or separated, and more likely than biological parents to be 45 years or older. In turn, being divorced or separated increased the risk of depressive, anxiety and obsessive-compulsive symptoms while a higher age increased the risk of symptoms of depression and phobic

anxiety. Thus, an interaction with these demographic factors might account for at least some of the differences between the parental status groups. Biological mothers were also more likely than the childless women to have changed partners since the time of treatment, a factor which increased the risk of obsessive compulsive symptoms. It should also be noted that the differences in age, and thus age at the start of treatment, and change in partners could account for the biological mothers' success in conceiving.

Previous studies have shown the importance of coping skills to overcome the grief process after unsuccessful treatment (155) and to come to terms with an unsuccessful treatment since sustaining a child-wish has a negative influence on psychological well-being (164). Studies have also shown that symptoms of adverse mental health tend return to baseline levels after a few years (144, 157). However, even when the use of coping skills has been successful, entering the "grandparent phase" might revoke previous negative feelings associated with the IVF and its treatment (160). The scope of Study III did not include the use of coping skills or the sustenance of a child-wish. It could however be hypothesized that the women in this study had adjusted well to their current parental statuses, since most women experienced few symptoms of adverse mental health, but that some negative effects of infertility and its treatment remained, or perhaps had reappeared as their peers were starting to become grandmothers.

Long-term consequences of childlessness on psychological well-being and social network

Parental status, marital status, gender and psychological well-being

The results of Study IV indicate that childlessness does not appear to influence psychological well-being in the oldest old. The childless Swedish 85-year olds were not more likely than

parents to feel lonely and the feelings of loneliness they experienced were not stronger than those of the 85-year old parents. There were no differences in the risk of experiencing depressive symptoms above the chosen cut-off value on the GDS-15 nor were there any differences in sense of meaning in life or life satisfaction. While the chi-square tests indicated that childlessness negatively influenced happiness, these differences disappeared when confounding factors were controlled for. Hence, these results are in line with most previous studies in suggesting that the childless elderly do not differ from elderly parents in psychological well-being (167, 168, 170-173, 175). Koropecj-Cox (85) concluded that parenthood in itself is not a guarantee for absence of loneliness and depression in old age, but that the benefits of parenthood on psychological well-being depend on the quality of the parent-child relationship and that the effects of childlessness depends on whether it is voluntary or involuntary (85). These factors were unfortunately beyond the scope of Study IV. Hence, it is possible that differences between parental status groups in psychological well-being would emerge if these factors had been controlled for.

While no evidence was found for an association between parental status and psychological well-being in the elderly, there were some indications that marital status and gender influenced psychological well-being. The risk of loneliness was almost doubled in men while no significant differences between men and women were found for depression and happiness. These results are contrary to some previous studies which have shown that men are less likely than women to feel depressed and lonely (167).

Unexpectedly and contrary to the results of previous studies (168, 169, 178), the results of Study IV indicated that those who were married were at increased risk of feelings of loneliness compared to the widowed while there were no differences between the married and

the unmarried. It could be hypothesized that those who were widowed were to a greater degree looked after by family and friends while the married individuals were expected to find company in their spouse, to whom relationship quality is likely to vary. Furthermore, the unmarried were about four times more likely than those who were married to rate themselves as happy. Previous studies have suggested that unmarried individuals have greater social abilities (165, 174) that can be used to find other occupations or relations than to a spouse and that this might be a positive factor in later life.

The effects of self-rated health and living situation on psychological well-being

In addition, being of good self-rated health increased the risk of loneliness. This is contrary to previous expectations that the elderly who are more frail would suffer greater negative effects on psychological well-being (170) and to previous studies showing that poor self-rated health is a risk factor for loneliness (168, 178). In regard to living situation, the chi-square tests showed that those living in institutional care were at increased risk, while the multiple logistic regression analyses showed indications of a decreased risk of loneliness in those living in nursing homes compared to out in the community. These differences could be explained by differences in categorization of the housing variable between the two analyses. Given that the chi-square tests combining living situation and parental status resulted in small sample sizes and the multiple logistic regression analyses also controlled for other factors, the logistic regression analyses should be considered more trustworthy. It could be hypothesized that elderly who are in poor health or who live in nursing homes are supported by more providers of formal and informal care which could result in reduced feelings of loneliness. Meanwhile, in accordance with previous studies, being of poor self-rated health (168, 171, 172, 178) and living in nursing homes functioned as risk factors for depressive symptoms. Conversely, being in poor health was positively associated with happiness, results which are difficult to

explain in light of poor self-rated health being a risk factor for depressive symptoms. It is possible that health is not the most important determinant of happiness in the elderly and that those who are in poor health receive more care and attention from the people around them which might have contributed to their happiness.

As previously mentioned, some authors have hypothesized that elderly individuals who are 80 years or older would be affected by childlessness to a greater degree since they are more likely to experience a decrease in health and function (170, 177) and thus become more dependent on others. While we were able to study the “oldest old” and compare the childless to those who were parents while controlling for major confounding factors such as gender, marital status and self-rated health, a larger percentage of those who chose not to participate lived in institutional care. Hence, we were not able to fully investigate the effects of childlessness on this group of elderly individuals who might experience a greater decrease in health and function and thus become more frail. When the childless and parents were subdivided into groups depending on whether they lived out in the community or in institutional care, the results showed that those who lived in institutional care had a poorer self-rated health and were more likely to feel lonely and depressed than those who lived out in the community. As mentioned above, the results did not hold for loneliness when other factors were controlled for in the multiple logistic regression analyses. These results were independent of parental status and are thus in line with those of Chang et al. (171) who did not find any differences in psychological well-being between disabled, and thus more frail, elderly that were parents or childless. In addition, Hansen (165) concluded that the effect of parenthood on psychological well-being in the elderly is weak in welfare states, even when the very old and those living alone are included.

However, it must be noted that the population of 85-year olds included in Study IV did not appear to be very frail and that there were no differences in self-rated health between the childless and parents. Only 2% (n=7) of the participants rated their health as bad and 11.2% (n=55) lived in residential care or nursing homes. Another study on the ELSA-85 population showed that these individuals to a great extent still managed self-care and usual activities and had, despite multi-morbidity, a good self-rated health when evaluated on a visual analogue scale (VAS) (199). Hence, these 85-year old might still be healthy enough to be able to compensate for not having children and/or a spouse by filling their lives with other things that was meaningful to them.

Living situation, social network and support

The results of Study IV showed that the childless elderly were not more likely than those who were parents to live in institutional care. These results are contrary to those of previous studies that have shown an increased risk of institutionalized housing in the childless American, Australian and Welsh elderly (179, 183, 184). These contrasts can be explained by cultural differences as well as changes over time in the expectation of how much care children of elderly adults should provide their ageing parents. In Sweden, the health care and social security systems function well. There are home care services and nursing homes run by the municipalities that can support the elderly. Children are not expected to have their ageing parents reside with them but might be expected to provide some help and support. This was demonstrated in a previous study by Larsson et al. (181) on Swedish 81-year olds which showed that those who were parents were more likely than those who were childless to receive informal support while the childless compensated by receiving more formal support from health care services.

In accordance with the results by Larsson et al. (181), Study IV also found that the childless elderly were less likely to receive help from informal sources. Just over half of those who were childless reported that they did not receive any such help compared to just over a quarter of those who were parents. Since parents, in addition to having children, were more likely to be married or cohabiting, it can be assumed that parents have a greater number of people available to provide help. In addition, while we found evidence of the old assumption that children are the greatest source of support to their ageing parents (165, 166), the help given to the childless came from their friends, spouse or siblings. The great likelihood of these individuals being of advanced age themselves could explain why those who were childless received less help. In accordance with some previous studies (173, 174, 180), the present study showed that while those who were parents were more likely than the childless to have relatives close by, the childless elderly had not compensated by being in more contact with their neighbours or having friends close by (169, 180).

Limitations

Confounding factors

Since risk factors for adverse mental health effects vary greatly in nature, some can be estimated or measured in registers while others can only be gathered using questionnaires or even require a qualitative approach. Hence, none of the studies included in this thesis provides a full coverage of all possible confounding factors. In Study I we were not able to control for some known PPD risk factors such as antenatal depression and anxiety, stressful life events, social support or the quality of the marital relationship and in Study II we were not able to control for family history of PPP or bipolar disorder since this information is not available from the registers. Some of these factors are likely to favor the IVF group of women since

they are generally psychologically and socially well-adjusted and could thus have acted as confounding factors. Since only primiparous women were included, primiparity and history of PPP could not have acted as confounders but this limitation in scope instead decreases the generalizability of Studies I and II.

In Study III we were not able to control for possible confounding factors such as mental health or negative life events before the start of IVF treatment or during the 20 years that had passed since. Since previous studies have found that the prevalence of psychiatric morbidity is decreased in women seeking infertility treatment (44) it is possible that these factors favored the women who had undergone IVF treatment compared to the general population and thus might have influenced the results. Also, no information on parental status or fertility history was available for the reference group. It is possible that some of these women had previously undergone IVF treatment. In Study IV questions regarding attitude towards childlessness, whether the children of those who reported being parents were alive or dead, biological or stepchildren and the quality of the parent-child relationship were not included. Naturally these factors might have influenced the results but increasing the number of included questions could have resulted in a decrease in response rate. Since general psychological well-being is likely to be a product of many aspects in life, it would most likely be impossible to control for all potential confounding factors.

In addition, the 85-year olds included in Study IV were able to retain the help of a relative, friend or caretaker if physically unable to fill out the questionnaire. This of course entails a risk that the person helping out filled out the questionnaire answered as they believed the participant to feel rather than having the participant provide the information and/or that their interpretation of the question influenced the response of the participant.

Cross-sectional studies

Studies III-IV are cross-sectional, which is why conclusions regarding cause and effect cannot be drawn. For example, it is possible that the childless elderly in Study IV had chosen to remain childless due to adverse mental health and that these factors masked true differences between the childless and parents. These cross-sectional studies can only provide information on the psychological well-being of the individual at the time of filling out the questionnaire or symptom rating scale. In the SCL-90 instrument, the women are asked to rate their symptoms to represent the past week. However, since there was no follow-up or longitudinal data, we are not able to know whether our results would have persisted in the weeks, months or years to come.

Non-participants

While the register-based Studies I and II are not affected by non-participation, 7% of the approached women in Study III and 15% of those who received the postal questionnaire in Study IV chose not to participate. Since little or no information was available for these individuals it is possible that the results are skewed due to potential differences in the distribution of sociodemographic factors or the selection of individuals with higher levels of well-being. However, this rate of non-participation is very low. As only 7% of the cohort in Study III chose to not participate, these effects are most likely quite small. In regard to Study IV, we know that the non-participants were more likely to live in institutional care, hence it is possible that the 85-year olds who were the frailest and most reliant on others were not included in this study, thus resulting in an overly positive view of the health and well-being of older adults. Due to this low participation rate of institutionalized individuals, the results pertaining to housing must be regarded with caution as the confidence intervals are large. Naturally, this also reduces the generalizability of the results. Due to information missing

from the registers, some sociodemographic information was missing in Study I and II and might therefore have skewed the results.

Small numbers

In Study I and II numbers for some diagnostic groups, for example schizophrenia and psychosis and bipolar disorder were small, hence resulting in large confidence intervals which is why these results must be regarded with caution. In Study IV, the number of childless individuals was small, thus decreasing the power of the study. This might have contributed to the lack of significant differences found between the parents and the childless individuals in psychological well-being.

Conclusions

While involuntary childlessness, infertility and its treatment can cause stress and have a negative effect on psychological well-being, results of this thesis indicate that these factors do not appear to increase the risk of receiving a PPD or PPP diagnosis from in- or outpatient psychiatric care or suicide during the first year postpartum. It is possible that any negative effects of infertility and its treatment would have been mitigated by the “healthy patient effect”, meaning that those who choose to enter and are accepted to infertility treatment are generally psychologically robust with few major PPD and PPP risk factors. This thesis has shown some evidence of this effect since those who had given birth after IVF treatment were less likely than mothers who had conceived spontaneously to have previously been diagnosed with some of the more severe psychiatric disorders. In accordance with the results of previous studies, the results of this thesis indicate that a history of mental illness is to be regarded as the major risk factor for postpartum psychiatric disorders.

In the long-term perspective, there were indications that women who had undergone IVF treatment twenty years previously, especially those who had remained childless, could be at increased risk of some symptoms of mental illness. It is possible that these symptoms and negative emotions had recently been revoked in these childless women since they were just about to enter a period of time in their lives when their peers are likely become grandparents. However, the results indicated that most women appear to adjust well psychologically, whether or not they had been successful in fulfilling their parenthood goals.

When they reach old age, childless individuals might have social networks of less support potential and do not appear to compensate for the lack of children and, in some cases a spouse, by increasing their contact with friends or neighbours. However, they are not more likely to end up living in institutional care and do not experience more feelings of loneliness, depression or unhappiness compared to parents. These results might be due to that the majority of the participants were in good health and that most lived out in the community which might enable them to cope with their childlessness.

To summarize, the results of this thesis suggest that while involuntary childlessness, infertility and its treatment can have some negative effects on psychological well-being in women as late as twenty years after treatment, the risk of receiving a postpartum psychiatric disorder diagnosis is not increased in women who give birth after IVF treatment, most women report a good mental health 20 years after treatment and psychological well-being in childless elderly individuals does not appear to be negatively affected even though their social networks can have less support potential.

Ethical considerations

Written consent was obtained from the participants of Studies III and IV. These individuals were informed in writing that participation was voluntary and that they were free to withdraw their participation at any time during the study. However, receiving a request for participation in a study on infertility and IVF treatment could have negative consequences for the approached individuals. First, the request could serve as a reminder of this potentially difficult period of time in the person's life thus revoking negative emotions. Second, even though the letter asking for participation was put in a sealed envelope and addressed to the potential participant, information might by accident be revealed to other members of the household. It is possible that some women had not informed their children or new partners of their infertility history, but might be called upon to do so when this letter arrived.

Since Studies I and II are register-based, the individuals included in these studies were not given the possibility to decline the use of their information. According to current Swedish legislation, it is the Regional Ethical Review committee that is to give or decline their ethical approval after having weighed the risk of violating the integrity of the participants in register-based studies against the benefits that society will gain from the research project. However, register data are anonymized and reported on a group, rather than an individual level, which is why it is unlikely that studies will cause any negative consequences for the individual except for some studies on very rare disorders and hence a small number of cases. In the present studies, this is not likely to have been a problem.

The Studies included in this thesis were approved by the Regional Ethical Review Board, Linköping, Sweden. For Studies I and II the numbers were 03-556, 03-557, 07-M66 08-08-M 233-8, 2010/403-31, for Study III number 03-338 and for Study IV number 141-06.

Clinical implications

As it was shown in Studies I and II, previously diagnosed psychiatric disorders are major risk factors for postpartum psychiatric disorders. Hence, there is a need for vigilance when encountering women with a history of mental illness who are planning to become, or who currently are, pregnant. In maternal health care and before the start of infertility investigation and treatment, the occurrence of psychiatric disorders should be screened for. In case such a history is detected, the woman should be followed closely in the postpartum period.

As infertility treatment becomes more common and increasingly accessible, women with a history of mental illness might not refrain from entering treatment as they may have done before. When comparing the results of Studies I and II there was some evidence to support this theory since the percentage of women with some previous psychiatric diagnoses who gave birth after IVF treatment was higher in Study II, which was concluded later, than in Study I. The acceptance into treatment of increasing numbers of women with a history of adverse mental health might reveal consequences of infertility and its treatment that have not been seen before.

Although more studies are needed to confirm these findings, Study III indicates that women who go through IVF treatment, and specifically those remain childless after unsuccessful infertility treatment, constitute a vulnerable group even later on in life. Awareness of the increased risks of some negative psychological symptoms is important for gynaecologists at the time of infertility treatment, as well as during follow-up, and for any health care officials, when encountering middle-aged women who suffer from depressive and anxiety symptoms. Questions asked by health care professionals regarding fertility history could add some pieces

of the puzzle when determining the cause of mental health problems in women who seek healthcare.

Future perspectives

Future studies on the consequences of infertility and its treatment on mental health or psychological well-being should be careful when selecting instruments to screen for symptoms of disorders or identify cases. Preferably, chosen instruments should be validated with a good sensitivity and specificity. If the number of instruments used to assess symptoms is reduced, this field of research will benefit in that conclusions in review studies and meta-analyses can be drawn more easily. In addition, caution should be taken when interpreting results and studies should be clear in expressing when and how symptoms were assessed or cases identified.

There is a need of more studies on PPD in women who have undergone IVF treatment, preferably using diagnoses set by a health care professional rather than symptom rating scales, and if possible including diagnoses from general practice as well as psychiatric care. Since Study II was the first in studying the risk of PPP in women after IVF pregnancies, more studies are needed to verify these results. In addition, more studies are needed on PPD and PPP risk factors and their magnitudes in order to increase the chances of preventing these disorders. For example, Studies I and II indicated that personality disorders are risk factors for postpartum psychiatric disorders but these results are in need of verification. It would also be interesting to study risk of PPD or PPP for different subgroups of infertility treatment such as gamete donation or intracytoplasmic sperm injection (ICSI) and between different types of infertility; female, male, mixed or unexplained.

Studies on the effects of infertility and its treatment should if possible be longitudinal and extend beyond the first years after treatment. More information is needed on the long-term influences on psychological well-being by infertility and its treatment, possible fluctuations during different phases in women's lives and risk factors for adverse outcomes so that the women who have not been able to cope and adjust to their post-treatment parental statuses can be identified. While there are not enough studies on the effects of infertility and its treatment in women, there are even fewer studies on these influences on mental health in men, in the short as well as the long-term perspective.

More studies should also focus on the effect of parental status on psychological well-being in the elderly while controlling for attitude towards childlessness during their childbearing years as well as in old age, whether any children they have are alive or dead, biological or stepchildren and to further determine general factors that have the greatest influence on psychological well-being in the oldest old.

Acknowledgements

I would like to start by directing a great big thank you to my main supervisor **Gunilla Sydsjö** who, besides being a positive, encouraging, experienced, knowledgeable and simply amazing supervisor, also has become a close friend. I am so glad that I knocked on your door that day!

I have also been fortunate enough to work with my associate supervisors **Ann Josefsson** and **Mats Hammar** who always have insightful comments on hand and who have been great sources of support during these years. I have learnt a lot from working with you. Thank you!

During my years as a PhD student I have also received invaluable advice, on statistics and other topics, and assistance in collecting register data from statistician **Marie Bladh**.

Thank you also to **Jan Marcusson**, **Ewa Wressle** and **Katarina Nägga** for our collaboration on Study IV.

I am ever so grateful to **Jan Brynhildsen**, **Caroline Lilliecreutz**, **Susanne Liffner**, **Elizabeth Nedstrand** and **Maria Sarberg** for taking the time to review my thesis and for offering me their invaluable advice. Thank you!

A special thank you to **Jenny Alwin** who, besides being a great friend, has been truly excellent in helping me prepare for this day by reviewing my thesis and with other dissertation-related queries.

I would also like to thank **Adam Sydsjö** for his friendship, encouraging words and for many lovely dinners spent discussing research and other important matters at his and Gunilla's home.

I am very grateful to **the participants of Studies III-IV** for agreeing to participate and for taking the time to fill out the questionnaires.

I would also like to thank **those responsible for the upkeep of the national registers**.

I am grateful to **the Medical Research Council of Southeast Sweden**, **the County of Östergötland** and **the Family Janne Elgqvist Foundation** for providing funding for Studies III-IV included in this thesis.

I would like to thank my parents **Bosse** and **Britta** for their ongoing support and encouragement during all my years at school, university and as a doctoral student.

I have also been blessed with a wonderful extended family, **Birgitta**, **Malin**, **Henrik** and **Stella**, and many kind and positive **friends** who have helped me in moments of frustration and encouraged me when encouragement was due. Thank you all so very much!

A special thank you to my dear friend **Solveig** who has been exposed to more than her fair share of the frustrating moments and has been called upon for encouragement and support at a great many times during the past years.

Thank you also to my lovely little son **Karl** for not crying that much and sleeping quite a lot at night, thereby allowing his mother to complete her thesis.

I would not have been able to complete this thesis without the support of my beloved husband **Björn**. You are always a great source of support and encouragement as well as a great sounding board. I am so grateful that you never try to limit me in my (sometimes overly optimistic) endeavors.

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Papers I-IV

Papers

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