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Psychiatric disorders among women and men in assisted reproductive technology (ART) treatment. The Danish National ART-Couple (DANAC) cohort: protocol for a longitudinal, national register-based cohort study

Lone Schmidt,[1] Ida Hageman,[2] Charlotte Ørsted Hougaard,[1] Camilla Sandal Sejbaek,[1] Maria Assens,[1] Ninna Hinchely Ebdrup,[1] Anja Pinborg[3]

For numbered affiliations see end of article.

Correspondence to
Dr Lone Schmidt;
lone.schmidt@sund.ku.dk

ABSTRACT

Introduction: There are complex causal associations between mental disorders, fertility treatment, fertility treatment outcome and infertility per se. Eating disorders cause endocrine disturbances, anovulation and thereby infertility, and research has shown that infertility as well as unsuccessful assisted reproductive technology (ART) treatment are potential risk factors for developing a depression on a long-term basis. Despite the fact that worldwide more than 400 000 ART treatment cycles are performed every year, the causal associations between mental disorders, use of medication for mental disorders and ART treatment in both sexes have only been sparsely explored.

Method and analysis: The main objective of this national register-based cohort study is to assess women's and men's mental health before, during, and after ART treatment in comparison with the mental health in an age-matched population-based cohort of couples with no history of ART treatment. Furthermore, the objective is to study the reproductive outcome of ART treatment among women who have a registered diagnosis of a mental disorder or have used medication for mental disorders prior to ART treatment compared with women in ART treatment without a mental disorder. We will establish the Danish National ART-Couple (DANAC) cohort including all women registered with ART treatment in the Danish in vitro fertilisation Register during 1994–2009 (N=42 915) and their partners. An age-matched population-based comparison cohort of women without ART treatment (n=215 290) and their partners will be established. Data will be cross-linked with data from national registers on psychiatric disorders, medical prescriptions for mental disorders, births, causes of deaths and sociodemographic data. Survival analyses and other statistical analyses will be conducted on the development of mental disorders and use of medication for mental disorders for women and men both prior to and after ART treatment.

INTRODUCTION

Worldwide more than 400 000 assisted reproductive technology (ART) cycles are performed every year.[1] Mental illness, infertility and outcome of fertility treatment are related in complex causal associations; mental illness can lead to infertility and vice versa, and similar counter activity is seen between mental illness and the outcome of fertility treatment. A prospective cohort study on the entire Danish population born after 1950 showed significantly lower first-child fertility rates for both women and men, who had previously been admitted to psychiatric hospital due to severe mental disorders.[2] The incidence rate ratio of parenthood after at least one psychiatric admission varied between 0.18 and 0.70 for different psychiatric diagnoses including schizophrenia, bipolar disorder, unipolar disorder and others compared with women and men without a psychiatric admission. A recent population-based Finnish study found that childless women with infertility experience had an increased risk of dysthymia and anxiety compared with women without infertility. Furthermore, infertile childless men experienced a significantly poorer quality of life compared with men without infertility.[3] In a review, Williams et al[4] concluded that unsuccessful fertility treatment is a risk factor for developing severe depressive symptoms and possibly major depression. In women, eating disorders affect luteinising hormone and follicle-stimulating hormone levels and can have prolonged impact on reproductive functions and fertility.[5] Studies based on smaller clinical samples of female patients

with infertility showed a higher prevalence of eating disorders among infertile female patients compared with the background population.[6] [7] Also, psychiatric disorders are potential risk factors for adverse pregnancy outcomes[8] as well as a risk factors of having negative attitudes towards pregnancy and difficulties in handling motherhood.[9] [10] Furthermore, treatment for psychotic disorders can be related to impaired fertility by, for example, increased levels of prolactin due to medication.[11]

Apart from two large studies, the scientific literature addressing mental disorders in infertile populations receiving fertility treatment is limited. Yli-Kuha *et al*[12] investigated psychiatric morbidity before and after fertility treatment in more than 9000 Finnish women who purchased drugs for in vitro fertilisation (IVF) during 1996–1998. Women who received fertility treatment had fewer hospitalisations due to psychiatric disorders compared with women receiving no fertility treatment, which suggests a healthy patient effect. A Danish cohort study on more than 51 000 women with primary or secondary infertility, who were referred to hospitals or private fertility clinics during 1973–1998 with follow-up until 2006, reported that women with no child delivery had more than twofold increased risk of suicide compared with women who had at least one child.[13] Both studies are based solely on female populations who received fertility treatment before 1999, where only a few ART treatments were performed and none of the studies include specific details on the fertility treatment. Owing to the study period it must be assumed that majority of the study populations received milder infertility treatment methods. Hence no current large studies exist on ART female populations and mental disorders. Furthermore, to the best of our knowledge no large-scale cohort studies on psychiatric disorders among men in ART treatment have been published.

METHODS
Study design
The Danish National ART-Couple (DANAC) cohort will be a longitudinal cohort of women, and their partner, having received ART treatment from 1 January 1994 until 30 September 2009. The two main objectives of this register-based research project are to study psychiatric disorders and the use of drugs for mental disorders in women and men before, during and after ART treatment and to compare this with an age-matched background population of women with no history of ART treatment and their cohabiting male partner and to study whether reproductive outcome of ART treatment differs between ART patients with and without a mental disorder.

Registers included
In Denmark each resident receives a unique personal identification number (PIN) at birth or at the time of immigration. We will use data from the Danish IVF Register, the Danish Psychiatric Central Research Register, the Danish National Prescription Register, the Danish Medical Birth Register (MBR), the Fertility Database (FTDB), the Danish Register of Causes of Death and sociodemographic registers at Statistics Denmark in order to establish the DANAC cohort (table 1). This cohort is a further development of the Copenhagen Multi-centre Psychosocial Infertility (COMPI) Research Programme, which was initiated in 2000.[14]

The compulsory *Danish IVF Register* was established in 1994 and includes registration of all ART treatment cycles conducted at public and private fertility clinics; that is, IVF, intracytoplasmic sperm injection (ICSI), frozen/thawed embryo transfer (FET) and oocyte recipient cycles.[15] [16] The IVF Register is cycle-based and for each treatment cycle the female PIN code is recorded. For every ART treatment cycle, clinical and laboratory data as well as data on treatment outcomes are reported. From January 2007 onwards the register also includes data on non-ART treatment as, for example, intrauterine insemination cycles (IUI).

The Danish Psychiatric Central Research Register is unique and recognised worldwide as it contains information on psychiatric contacts systematically collected from 1938. Since 1969, data on all psychiatric admissions to psychiatric hospitals and wards in general hospitals in Denmark have been computerised. There are no private hospitals for adult psychiatry in Denmark, thus all resident contacts with psychiatric hospital settings (inpatient or outpatient) are registered. Since 1 January 1995 information about all outpatient contacts has also been included.[17] Until December 1993 the 8th revision of the International Classification of Diseases (ICD-8) was used and since January 1994 ICD-10 has been used. The register does not include contacts with private psychiatrists working outside hospital settings or general practitioners who treat many of the less severe psychiatric disorder patients. In order to make our data as complete as possible, we therefore decided to complement our study with data from The Danish National Prescription Register.

The Danish National Prescription Register is administered by Statistics Denmark. It was established in 1994 as an individual-level database and includes information on all prescribed, dispensed drugs sold in Denmark.[18] For this project only data on antipsychotic medicine (MN05A), antidepressive medicine (MN06A), anxiolytica (MN05B) and medication for alcohol dependency (MN07BB) will be extracted. The main reason for including data on medication is to be able to identify participants who received treatment for mental disorders without hospital contact. Hence we are able to identify milder forms of mental disorders.

The Danish MBR was established in 1968 to monitor the health of newborns and the quality of antenatal and delivery care and includes information on all deliveries in Denmark.[19]

The FTDB was established by Statistics Denmark in 1993 and includes data since 1980 on socioeconomic status and information on deliveries and children of the total population aged 15–49 years.[20]

Table 1 The register data which will be used in establishing the Danish National ART-Couple (DANAC) cohort

Name of register	Period of data inclusion	Main variables included

The Danish IVF Register	1 January 1994–30 September 2009	*For each ART treatment cycle*
		    Female age
		    Infertility diagnosis
		    Date of treatment
		    Type of treatment (IVF, ICSI, FET, oocyte recipient cycle)
		    Clinical pregnancy

The Danish Psychiatric Central Research Register	1969–2009	*Age*
		    Dates of admission and discharge
		    Start and end of outpatient treatment
		    Place of treatment
		    Mode of admission (acute or planned)
		    Main and comorbid psychiatric diagnoses (ICD-8 and ICD-10)

The Danish National Prescription Register	1994–2009	*For antipsychotic medicine (MN05A), antidepressive medicine (MN06A), anxiolytica (MN05B), medication for alcohol dependency (MN07BB)*
		    Anatomical therapeutic chemical classification (ATC) code
		    Date of dispensing
		    Number of prescription refills
		    Number of dose units in package
		    Indication for prescription

The Danish Medical Birth Register	1994–2010	*For women only*
		    BMI (from 2004)
		    Parity
		For each child born
		    Personal identification
		    Date of birth
		    Gender
		    Gestational age
		    Birth weight
		    Singleton/multiple birth
		    Congenital malformations
		    Live birth/still birth
		    Perinatal mortality

The Fertility Database	1995–2009	*For women only*
		    Date of birth
		    Parity
		    Singleton/multiple birth
		    Death of child

The Danish Register of Causes of Death	1995–2009	*For women and men*
		    Date of death
		    Primary cause of death (ICD-10)

Statistics Denmark Sociodemographic Registers	1995–2009	*Socioeconomic status*
		    Income
		    Social transfer income (maternal/paternal leave/unemployment/sickness leave)
		    Highest finalised education
		    Marital status
		    Cohabiting partner
		    Immigration/emigration

ART treatment, assisted reproductive technology treatment; BMI, body mass index; FET, frozen/thawed embryo transfer; ICD, International Classification of Diseases; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation.

The Danish Register of Causes of Death was established in 1875 and since 2007 death certificates have been submitted electronically to the National Board of Health.[21]

National Sociodemographic Registers were established in Statistics Denmark in 1995, and provide us with sociodemographic data and background information for the populations.

Objectives

We aim at investigating the following main research questions: (1) What is the prevalence of patients with a psychiatric disorder and the prevalence of prescribed, dispensed medication for mental disorders in the ART cohort and does the prevalence differ from the prevalence in an age-matched background population

without a history of ART treatments? (2) Is the existence of a psychiatric disorder or the use of medication for mental disorders prior to ART treatment a risk factor of a poorer outcome of ART treatment (e.g. pregnancy and live birth rates, gestational age, birth weight, congenital malformations) compared with women in ART treatment without psychiatric disorders? (3) Does the sociodemographic characteristics differ between women and men in ART treatment with a history of a psychiatric disorder/use of medication for mental disorders compared with women and men in ART treatment with no history of a psychiatric disorder/use of medication for mental disorders? (4) Is unsuccessful ART treatment a risk factor for later development of psychiatric disorders or use of medication for mental disorders? (5) Is ART treatment a potential risk factor for re-activating a prior psychiatric disorder? (6) Do causes of death (eg, for mental disorders) differ between ART-treated patients and the age-matched background population and between women and men in successful and unsuccessful ART, respectively?

Establishment of study cohort
DANAC cohort
A cohort of all women registered with at least one ART treatment, that is, IVF, ICSI, FET, oocyte recipient cycles during the period 1 January 1994 to 30 September 2009, in the IVF Register will be established. A total of 42 915 women are registered and of these women 30 502 (71%) are registered in the Danish MBR with at least one delivery during the period 1994–2010. The MBR does not include data on the use of medically assisted reproduction. To identify all deliveries after ART conception, we will combine the date of initiation of the ART treatment cycle with the date of a subsequent delivery. We will identify an ART delivery as a delivery with date of birth 140–308 days (20–44 gestational weeks) after the ART cycle initiation. If more than one ART cycle performed in the same woman matches the criteria of a subsequent birth, we will choose the ART cycle dated close to the delivery. All other deliveries will be categorised as non-ART deliveries, that is, children born after a non-treatment-related conception as well as children born after fertility treatment other than ART. Treatments such as ovulation induction and IUI were not recorded in the IVF Register until 2007, and hence it is not possible to identify children born after non-ART treatment in our cohort.

For each woman in the DANAC cohort five randomly selected age-matched comparison women from the background population will be identified (N=215 290) at Statistics Denmark. Women with any records in the IVF Register from 1 January 1994 onwards will be excluded from the comparison group.

In Denmark, the frequency of cohabitation without marriage is similar to the frequency of married couples.[22] On the basis of sociodemographic registers in Statistics Denmark we will identify the cohabiting/married partner for all women in the DANAC cohort. The partner is defined as the individual the woman is either married to or registered partner with (same sex couple). For unmarried women, a partner is defined in two different ways: (1) for women with a child and living together with the father of this child, the father is selected as the partner; (2) otherwise two individuals of opposite sex living at the same address will be classified as a consensual union if the age-difference between the woman and the man is less than 15 years and they are not closely related. If the woman shares address with more adult males, the man with the age close to the woman's age will be selected as her partner. For women in the DANAC cohort all partners (married/unmarried) in a consensual union from 1990 and onwards will be identified. If the woman had been in more consensual unions over time, only the man, with whom she was in a consensual union with at the date of initiation of the first ART treatment cycle will be selected when analysing data. During the period 1997–2007 medical doctors were allowed to offer fertility treatment only to heterosexual couples living together.

When comparing women and men in ART treatment with the age-matched control group without ART treatment we will select different subpopulations of the comparison group depending on the specific research question that is going to be investigated, for example, it will be necessary to distinguish between women who have given birth to children and those who have not.

Register-linkages
By using the PIN of all women and their cohabiting partners from 1990 onwards in the DANAC cohort, as well as from the age-matched comparison cohort, data will be linked with several national registers: the Danish Psychiatric Central Research Register, the Danish National Prescription Register, the FTDB, the Danish Register of Causes of Death, and sociodemographic registers at Statistics Denmark. As described, the DANAC cohort is also linked to the MBR in order to identify deliveries after ART. We will establish cohort data for each calendar-year during the periods described in table 1. Hence data regarding, for example, mental disorders and use of medication for mental disorders will be available before, during and after ART treatment.

STATISTICAL ANALYSIS
Common statistical methods will be applied for simple comparisons between study and control groups. Student t test will be used to compare parametric continuous data and non-parametric tests will be used if data is not normally distributed. A p value <0.05 will be considered statistically significant. In case of multiple testing a lower p value will be selected as significance level. Frequencies between groups will be compared with χ^2 tests. Incidence rate ratios will be calculated, and more advanced statistical methods appropriate for longitudinal cohort studies

as for example, Cox regression models and multivariate logistic regression analyses will be applied. When calculating risk time for the development of a mental disorder or the use of medication for mental disorders, we will exclude participants with incomplete data on migration and those who left Denmark without returning. As the DANAC cohort represents the complete national cohort of women treated with ART from 1994 to 2009, sample size calculations have not been performed as we will not be able to expand the study population if needed. To avoid selection bias, a comparison cohort of sufficient sample of five controls will be chosen per individual in the DANAC cohort. Adjustment will be made for a long row of confounders such as age, infertility diagnosis, number of ART treatment attempts, parity and sociodemographic factors.

PERSPECTIVES

For women, the reproductive age represents a period of increased risk of developing a mental disorder. Surprisingly little focus has been placed on mental problems during pregnancy and the implications for mother, fetus, child and partner. Having a mental disorder during pregnancy is stressful for the pregnant women, but it may also affect the fetus as for example, stress hormones like corticosteroids cross the blood–placenta barrier. Mental problems during pregnancy are related to, for example, suicidal behaviour, reduced participation in ante-natal healthcare, and increased use of tobacco and other drugs.

This study will enhance focus on mental disorders and use of medication for mental disorders in ART patients and hopefully increase the diagnosis and support to these vulnerable patients both before and during ART treatment as well as those who obtain childbirth and those who do not. Furthermore, this project will enhance focus on reproductive outcome after ART treatment among women with a mental disorder compared with women without a mental disorder.

It is our hope that mapping the prevalence of mental disorders in a cohort of infertile couples seeking ART treatment for their reproductive problems will increase the awareness of psychiatric morbidity in infertile populations and thereby increase the chance that psychiatric disorders are actually treated with obvious health benefits.

This large-scale, national research project among women and men in ART treatment investigates severe mental disorders leading to a contact registered in the Danish Psychiatric Central Research Register as well as the use of drugs prescribed for mental disorders. By including data on the use of medication for mental diseases also among participants not registered with a psychiatric diagnosis in the Psychiatric Register also less severe mental illness will be identified. The study will contribute substantially to the limited existing scientific literature on psychiatric morbidity in both men and women in relation to ART treatment. The project will provide information regarding differences in psychiatric morbidity over decades and causes of deaths among women and men in ART treatment compared with an age-matched background population with no history of ART. Furthermore, the study will reveal some of the complex causal associations between infertility and mental disorders and use of medication for mental disorders which will be hypothesis generating.

The data provides the possibility of exploring ART treatment as a potential risk factor for subsequent development of a mental health disorder as, for example, depression, and whether this potential association could be related to ART treatment success. In the future more register linkages would be of relevance, for example, to include data on female and male participants' somatic health (eg, BMI, chronic diseases and other factors) as well as data on the children's long-term health and well-being. It is especially intriguing to explore the health of ART children born of mothers and/or fathers with a mental disorder.

The main strengths of this project are the size of the cohorts, the possibilities of combining data from several national registers, and the large comparison group from the background population. Data will be obtained in a similar way on study and comparison populations thereby avoiding selection bias. Further, the registration of a diagnosis for a mental disorder is based on a medical doctor's clinical diagnosis and not on self-reported questionnaires. The limitations are those usually related to register-based research, including missing data and the quality of data. However, several studies have described that the national Danish health registers fulfil the quality criteria for scientific research. Another limitation to register research is the lack of detailed information on specific confounders. However, in this study we are aiming to combine data from several registers thereby obtaining information on most relevant confounders.

Author affiliations
[1]Department of Public Health, Section of Social Medicine, University of Copenhagen, Copenhagen, Denmark
[2]Psychiatric Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[3]Fertility Clinic, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Health (J.nr. 7-505-29-1658/1), the Danish Medical Agency, and Statistics Denmark (J.nr. 703481). The project follows the Helsinki II Declaration. Due to Law 503 1992 about Scientific Ethics Committee System in Denmark, register-based studies with no contact to participants do not need to apply for ethical approval. The data sets are stored at Statistics Denmark in a non-identifiable form. Only researchers approved by the first author LS and Statistics Denmark will have access to the data sets.

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