Psychiatric disorders in women with fertility problems: results from a large Danish register-based cohort study

B. Baldur-Felskov1, S.K. Kjaer1,2, V. Albieri3, M. Steding-Jessen3, T. Kjaer4, C. Johansen4, S.O. Dalton4, and A. Jensen1,*

1Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen 2100, Denmark 2Gynaecological Clinic, Juliane Marie Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen 2100, Denmark 3Statistics, Bioinformatics and Registry, Danish Cancer Society Research Center, Copenhagen 2100, Denmark 4Survivorship, Danish Cancer Society Research Center, Copenhagen 2100, Denmark

*Correspondence address. Tel: +45-3525-7693; Fax: +45-3525-7731; E-mail: allan@cancer.dk

Submitted on June 29, 2012; resubmitted on October 23, 2012; accepted on November 9, 2012

STUDY QUESTION: Do women who don’t succeed in giving birth after an infertility evaluation have a higher risk of psychiatric disorders compared with women who do?

SUMMARY ANSWER: The results indicated that being unsuccessful in giving birth after an infertility evaluation could be an important risk factor for psychiatric disorders.

WHAT IS KNOWN ALREADY: Several studies have investigated the association between fertility treatment and psychological distress, but the results from these studies show substantial variation and lack of homogeneity that may be due to methodological limitations.

STUDY DESIGN, SIZE AND DURATION: A retrospective cohort study was designed using data from a cohort of 98,320 Danish women evaluated for fertility problems during 1973–2008 and linked to several Danish population-based registries. All women were followed from the date of first infertility evaluation until date of hospitalization for the psychiatric disorder in question, date of emigration, date of death or 31 December 2008, whichever occurred first. Owing to the precise linkage between the infertility cohort and the Danish population-based registries, using the unique Danish personal identification number, virtually no women were lost to follow-up.

PARTICIPANTS/MATERIALS, SETTING AND METHODS: Information on reproductive status for all women in the infertility cohort was obtained by linkage to the Danish Medical Birth Registry. A total of 53,547 (54.5%) women gave birth after the initial infertility evaluation, whereas 44,773 (45.5%) women did not give birth after the evaluation. To determine psychiatric disorders diagnosed in the women after enrolment in the infertility cohort, the cohort was linked to the Danish Psychiatric Central Registry. A total of 4,633 women were hospitalized for a psychiatric disorder. The Cox proportional hazard regression model was applied to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association between parity status after the initial infertility evaluation and risk of hospitalization for various groups of psychiatric disorders, including ‘all mental disorders’ and six main discharge subgroups labelled: ‘alcohol and intoxicant abuse’, ‘schizophrenia and psychoses’, ‘affective disorders’, ‘anxiety, adjustment and obsessive compulsive disorders’, ‘eating disorder’ and ‘other mental disorders’.

MAIN RESULTS AND THE ROLE OF CHANCE: The incidence rate for all mental disorders was 393 cases per 100,000 person-years among women who did not succeed in giving birth after the infertility evaluation but only 353 cases per 100,000 person-years among women who succeeded in giving birth after the infertility evaluation. Women not giving birth after the infertility evaluation had an increased risk of hospitalization for all mental disorders (HR 1.17, 95% CI 1.11; 1.25), alcohol and intoxicant abuse (HR 2.02, 95% CI 1.69; 2.41), schizophrenia and psychoses (HR 1.46, 95% CI 1.17; 1.82) and other mental disorders (HR 1.42, 95% CI 1.27; 1.58) compared with women who gave birth after the infertility evaluation. In contrast, the risk of affective disorders (HR 0.90, 95% CI 0.81; 0.99) was decreased among women not giving birth after the infertility evaluation. Finally, the risk of anxiety, adjustment and obsessive compulsive disorders (HR 1.07, 95% CI 0.97; 1.17) as well as of eating disorders (HR 1.40, 95% CI 0.88; 2.22) was not significantly affected by parity status after the infertility evaluation.

LIMITATIONS, REASON FOR CAUTION: As only psychiatric conditions warranting hospitalization could be included in the present study, the true incidence of all psychiatric disorders among women with fertility problems is likely to be somewhat
Introduction

Worldwide, infertility affects 10–15% of couples where the woman is trying to conceive (Evers, 2002; Bonde and Olsen, 2008). In Denmark, the number of women treated with assisted reproductive techniques (ART) has increased steadily over the past 10 years, and in 2009 ~9% of the children born that year were conceived after ART (Danish Fertility Association, 2009). Thus, treatment with ART has enabled many infertile couples to become parents, probably making a positive difference to their lives, which is not the case for those couples with unsuccessful ART (Patrick et al., 2002).

Several studies have examined the psychological strain associated with fertility treatment (Eugster and Vingerhoets, 1999; Kee et al., 2000; Hammarberg et al., 2001; Lok et al., 2002; Chen et al., 2004; Ramezanadeh et al., 2004; Khademi et al., 2005; Verhaak et al., 2005; Karjane et al., 2008; Sbaragli et al., 2008; Volgsten et al., 2008, 2010; Drosdzol and Skrzypulec, 2009; Johansson et al., 2009, 2010; Noorbala et al., 2009; Gelbaya, 2010; Klemmeti et al., 2010; Yli-Kuha et al., 2010; Greil et al., 2011; Pasch et al., 2012). Many of these studies have reported a high prevalence of distress, depressive symptoms and psychiatric disorders in infertile women, where the risk of these symptoms seems to be positively correlated with length of fertility treatment and with negative results of the treatment. However, results from these studies show substantial variation and lack of homogeneity, which may be due to methodological limitations. Most studies were clinic-based and thus included a relatively low number of study subjects, which may have affected the precision of the risk estimates. In addition, diagnostic criteria in earlier studies were not uniform as they were based on information obtained from self-administered questionnaires and a variety of other instruments used to measure the mental health of the persons involved. Furthermore, many of the previous studies used a cross-sectional rather than a longitudinal design, which may hamper the evaluation of a causal association. To our knowledge, only two recent studies used population-based data to study the degree of mental disorders among women with fertility problems. In a cross-sectional study, Klemmeti et al. (2010) showed that childless women with fertility problems were at an increased risk of dysthymia and anxiety disorders compared with a control group of women without fertility problems. Furthermore, results from a case–control study by Yli-Kuha et al. (2010) showed that women who gave birth after fertility treatment had a lower risk of most groups of psychiatric diagnoses compared with women not giving birth.

Using data from a large Danish population-based cohort of women with fertility problems, we have previously found a 2-fold increased risk of suicide in women with fertility problems who were unsuccessful in giving birth compared with women with fertility problems who gave birth to at least one child (Kjaer et al., 2011). As suicide is often preceded by psychiatric disorders (Mortensen et al., 2000; Hawton and van Heeringen, 2009), the risk patterns of psychiatric disorders may differ between women with fertility problems who subsequently give birth and those who do not. Here, we aimed to study the risk of psychiatric disorders among women with fertility problems in Denmark, i.e. to investigate whether women not succeeding in giving birth after infertility evaluation have a higher risk of psychiatric disorders than do women who succeeded in having at least one child after infertility evaluation. To our knowledge, this study is the first to examine this association in a nationwide, population-based cohort study design.

Materials and Methods

Cohort identification

We initially used the established Danish Infertility Cohort consisting of 54 362 women ever referred to public Danish hospitals or private fertility clinics between 1963 and 1998 because of fertility problems. The cohort has previously been described in more detail (Kjaer et al., 1999; Jensen et al., 2007). In brief, the women were identified either from medical records or local computerized systems directly at the clinic, or through the Danish National Patient Registry, which contains information on all contacts to Danish hospitals since 1977, using codes 628 and DN97 in the International Classification of Diseases (ICD), 8th and 10th revisions, respectively. Subsequently, we updated the Danish Infertility Cohort by including women evaluated for infertility during 1 January 1999–31 December 2008 with information from both the Danish National Patient Registry and from the Danish IVF registry, which contains compulsory information on all IVF treatments in Denmark since 1 January 1994 (at the time of analysis updated to 31 December 2005). The updated Danish Infertility Cohort consists of 108 801 women evaluated for infertility during 1963–2008. All data were entered into a single database, with one record for each woman, including the initial date of infertility evaluation, the clinic’s name and the woman’s personal identification number.

The unique Danish personal identification number is a personalized number assigned to all residents in Denmark. It is included in all health registries and ensures accurate linkage of information between registries. Using the personal identification numbers, we linked the infertility cohort to the Danish Civil Registration System to determine dates of
emigration, deaths or disappearance. The register was established on 1 April 1968 and includes information on vital status (date of death, emigration or disappearance) for all residents in Denmark (Pedersen, 2011). We excluded 443 women because they immigrated to Denmark after their infertility evaluation and 14 women with other types of registrations errors. A further 476 women were excluded as we included only women aged 20–55 years in our study, leaving 107 868 women eligible for further analysis. The study was approved by the Danish Data Protection Agency.

**Ascertained of exposure status**

To obtain information on reproductive status for all women in the infertile cohort, we linked the cohort to the Danish Medical Birth Registry (Knudsen and Olsen, 1998). The Danish Birth Registry holds computerized information on all births in Denmark since 1 January 1973 and thus enables linkage between a woman and a child. Hence, we excluded 4876 women included in the infertility cohort between 1963 and 1973 as we had no valid information on the women’s reproduction before 1973.

Additionally, as women with a history of psychiatric disorders have a high risk of recurrence, some of the psychiatric diagnoses observed after their infertility diagnosis may have been due to an earlier psychiatric disorder and not to infertility. We therefore linked the infertility cohort to the Danish Psychiatric Central Research Registry (see detailed description of this registry in the Identification of outcomes section) and consequently excluded 4672 women who had been hospitalized for any psychiatric disorder before their first date of infertility evaluation. In total, 98 320 women evaluated for fertility problems during 1973–2008 were eligible for the final analyses.

In a subset analysis, we aimed to further adjust our risk estimates for socioeconomic factors (highest attained education and disposable income). To obtain this information, our cohort was linked with the CANULI (Social Inequality in Cancer Incidence and Survival in Denmark) database, which contains harmonized socioeconomic data for all residents in Denmark above the age of 30 years during 1990–2006 (Dalton et al., 2008). The data in the CANULI database are derived from the population-based Integrated Database for Labour Market Research in Statistics Denmark (Pedersen et al., 2011). This subset analysis comprised 61 514 women evaluated for infertility during 1990–2006.

**Identification of outcomes**

To determine psychiatric disorders diagnosed in the women after enrollment in the infertility cohort, the cohort was linked to the Danish Psychiatric Central Registry. This registry contains individual information on all admissions and discharges to Danish psychiatric hospitals (inpatient facilities), with dates, one main discharge diagnosis and up to three auxiliary discharge diagnoses since 1 January 1970. Since 1995, the registry has also held information on all outpatient contacts (Mors et al., 2011). Before 1995, all psychiatric diagnoses were reported according to the ICD-8 classification system (ICD, 8th revision) and after 1994 they were reported according to the ICD-10 classification system (ICD, 10th revision; Mors et al., 2011).

On the basis of ICD-10 and ICD-8 codes, we divided the psychiatric diagnoses into one main group labelled: ‘all mental disorders’ and six main discharge subgroups labelled: ‘alcohol and intoxicant abuse’, ‘schizophrenia and psychoses’, ‘affective disorders’, ‘anxiety, adjustment and obsessive compulsive disorders’, ‘eating disorder’ and ‘other mental disorders’. The classifications with ICD-8 and -10 codes are shown in Table I. For the analysis of all mental disorders, we used the first registered main discharge diagnosis for the women in question. Women who were hospitalized for different main discharge diagnoses could thus be included in more than one subgroup analysis.

**Table I Classification of psychiatric diagnoses in outcome categories (ICD-10 and ICD-8).**

<table>
<thead>
<tr>
<th>Category</th>
<th>ICD-10</th>
<th>ICD-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>All mental disorders</td>
<td>F00–F99</td>
<td>290–315</td>
</tr>
<tr>
<td>Alcohol and intoxicant abuse</td>
<td>F10–F19</td>
<td>291, 294.30, 303–304</td>
</tr>
<tr>
<td>Schizophrenia and psychoses</td>
<td>F20–F29</td>
<td>295, 297, 298.39</td>
</tr>
<tr>
<td>Affective disorders</td>
<td>F30–F39</td>
<td>296, 298.09–19</td>
</tr>
<tr>
<td>Anxiety, adjustment disorders and OCD</td>
<td>F40–F43</td>
<td>300</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>F50</td>
<td>306.50–59</td>
</tr>
<tr>
<td>Other mental disorders*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OCD, Obsessive compulsive disorder.

*Consists of all mental ICD-10 and ICD-8 codes not specified in the above-mentioned five subgroups.

**Statistical analysis**

The Cox proportional hazard regression model was applied to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association between parity status after infertility evaluation and risk of hospitalization for psychiatric disorders. Time in years since the date of entry into the cohort, i.e. first contact with a fertility clinic (infertility evaluation), was used as the underlying time scale so that each person contributed with person-years from time of entry until event of interest or censoring. Censoring date was given by date of emigration, date of death, date of hospitalization for schizophrenia, or 31 December 2008, whichever occurred first. A diagnosis of schizophrenia was used as a censor, except when we investigated the outcome schizophrenia and psychoses, on the assumption that schizophrenic patients could not be considered as having another psychiatric disorder (Dalton et al., 2002). From time of entry, the exposure was classified as a time-dependent variable such that women contributed exposure time in the infertile group until time of birth of the first child. From that date onwards, the woman contributed person-years to the fertile group.

Potential confounders included in the analysis were age on entry into the cohort (continuous variable), year of entry into the cohort (continuous variable) and parity status prior to the infertility evaluation (child yes/no). In the subset analysis, we also adjusted for socioeconomic position variables, i.e. highest attained education (categorized such as basic school/high school, vocational education, higher education, unknown) and disposable income (categorized such as lowest (first quartile), middle (second–third quartile), highest (fourth quartile)). However, this additional adjustment for socioeconomic position variables did not substantially alter the results, i.e. the magnitude of the risk estimates was virtually unchanged (data not shown); accordingly, these subgroup results are not presented further. A two-sided Wald $\chi^2$ test was used to evaluate the significance effect of the exposure variable (parity status after infertility evaluation) and a significance level of 5% was applied for all analyses. The statistical software program SAS (version 9.2, SAS Institute, Cary, NC, USA) using the PHREG procedure was used.

**Results**

Baseline characteristics for our study population are shown in Table II. A total of 53 547 (54.5%) women gave birth after the initial infertility evaluation, of whom 10 804 also had at least one child before the
A total of 44,773 (45.5%) women did not give birth after the evaluation but 12,384 of these women had at least one child before the infertility evaluation. The number of women entering the cohort increased steadily in the study period from 6,033 during 1973–1978 to 20,998 during 2004–2008. The mean age at first infertility evaluation was slightly lower (29.7 years) for women who gave birth after the infertility evaluation than for women who did not give birth after infertility evaluation (32.0 years).

The 98,320 women constituting the study population contributed 1,241,849 person-years of follow-up in the analysis of first hospitalization for any psychiatric disorder (608,692 person-years in women giving birth after the initial infertility evaluation and 633,157 person-years in women not giving birth after the infertility evaluation). In the analysis of all mental disorders, the median length of follow-up was 11.3 years (range: 0.0–36.0). A total of 4633 women were hospitalized for any psychiatric disorder, of which 2147 were observed in the group of women who gave birth after the infertility evaluation and 2486 were found in the group of women not giving birth after the infertility evaluation. The most common main discharge diagnoses were in the group of anxiety adjustment and obsessive compulsive disorders followed by affective disorders, and other mental disorders (Table III). The incidence rate for all mental disorders was 393 cases per 100,000 person-years among women who did not give birth after the infertility evaluation but only 353 cases per 100,000 person-years among women who gave birth after the infertility evaluation.

In all analyses, we adjusted for age and year of entry into the cohort as well as parity status before infertility evaluation. In the analysis of all mental disorders, increasing age on entry into the cohort was associated with a decreased risk of all mental disorders (HR 0.95, 95% CI 0.95; 0.96), whereas increasing year of entry into the cohort was associated with an increased risk (HR 1.03, 95% CI 1.03; 1.04). Women who had a child before the infertility evaluation had an increased risk of all mental disorders (HR 1.59, 95% CI 1.49; 1.69). Figure 1 shows HRs for the group of all mental disorders and selected main discharge groups in relation to the success of having a child or not after infertility evaluation. A statistically significant increased risk of all mental disorders was observed among women who did not give birth after the infertility evaluation compared with women who gave birth after the evaluation (HR 1.17, 95% CI 1.11; 1.25). In addition, the risks of alcohol and intoxicant abuse (HR 2.02, 95% CI 1.69; 2.41), schizophrenia and psychoses (HR 1.46, 95% CI 1.17; 1.82) and other mental disorders (HR 1.42, 95% CI 1.27; 1.58) were statistically significantly increased for women who did not give birth after infertility evaluation. The risk for abuse was even higher when restricting abuse to intoxicant abuse (HR 2.96, 95% CI 2.00; 4.37; data not shown). In contrast, women who did not give birth after infertility evaluation had a statistically significantly decreased risk of affective disorders (HR 0.90, 95% CI 0.81; 0.99), and the risk was further reduced when restricting analysis to unipolar depression alone (HR 0.87, 95% CI 0.78; 0.96) (data not shown). We also found an increased risk of eating disorders; however, this was not statistically significant (HR = 1.40, 95% CI 0.88; 2.22). Lastly, the risks of anxiety, adjustment and obsessive compulsive disorders were not markedly affected by the women’s parity status after infertility evaluation.

### Table II: Baseline characteristic for 98,320 Danish women evaluated for fertility problems, 1973–2008.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All n = 98,320 (100%)</th>
<th>Birth after infertility evaluation n = 53,547 (54.5%)</th>
<th>No births after infertility evaluation n = 44,773 (45.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth after infertility evaluation but not before</td>
<td>42,743 (79.8%)</td>
<td>12,384 (27.7%)</td>
<td></td>
</tr>
<tr>
<td>Birth before and after infertility evaluation</td>
<td>10,804 (20.2%)</td>
<td>32,389 (72.3%)</td>
<td></td>
</tr>
<tr>
<td>Birth before infertility evaluation but not after</td>
<td>12,384 (27.7%)</td>
<td>32,389 (72.3%)</td>
<td></td>
</tr>
<tr>
<td>No birth at any time</td>
<td>32,389 (72.3%)</td>
<td>32,389 (72.3%)</td>
<td></td>
</tr>
<tr>
<td>Year of infertility evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973–1978</td>
<td>6,033 (6.1%)</td>
<td>3,266 (6.1%)</td>
<td>2,767 (6.2%)</td>
</tr>
<tr>
<td>1979–1983</td>
<td>8,174 (8.3%)</td>
<td>4,360 (8.1%)</td>
<td>3,814 (8.5%)</td>
</tr>
<tr>
<td>1984–1988</td>
<td>8,270 (8.4%)</td>
<td>4,434 (8.3%)</td>
<td>3,836 (8.6%)</td>
</tr>
<tr>
<td>1989–1993</td>
<td>15,065 (15.3%)</td>
<td>9,111 (17.0%)</td>
<td>5,954 (13.3%)</td>
</tr>
<tr>
<td>1994–1998</td>
<td>19,742 (20.1%)</td>
<td>12,919 (24.1%)</td>
<td>6,823 (15.2%)</td>
</tr>
<tr>
<td>1999–2003</td>
<td>20,038 (20.4%)</td>
<td>13,737 (25.7%)</td>
<td>6,301 (14.1%)</td>
</tr>
<tr>
<td>2004–2008</td>
<td>20,998 (21.4%)</td>
<td>5,720 (10.7%)</td>
<td>15,278 (34.1%)</td>
</tr>
<tr>
<td>Median (year)</td>
<td>1996</td>
<td>1995</td>
<td>1998</td>
</tr>
<tr>
<td>Age at infertility evaluation (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28</td>
<td>29,075 (29.6%)</td>
<td>19,201 (35.9%)</td>
<td>9,874 (22.1%)</td>
</tr>
<tr>
<td>28–30</td>
<td>24,776 (25.2%)</td>
<td>14,919 (27.9%)</td>
<td>9,857 (22.0%)</td>
</tr>
<tr>
<td>31–33</td>
<td>20,675 (21.0%)</td>
<td>10,813 (20.2%)</td>
<td>9,862 (22.0%)</td>
</tr>
<tr>
<td>&gt;34</td>
<td>23,794 (24.2%)</td>
<td>8,614 (16.1%)</td>
<td>15,180 (33.9%)</td>
</tr>
<tr>
<td>Mean</td>
<td>30.8 years</td>
<td>29.7 years</td>
<td>32.0 years</td>
</tr>
</tbody>
</table>
We also investigated whether the risk of all mental disorders and the six main discharge subgroups associated with parity status after the infertility evaluation varied according to parity status before the infertility evaluation, i.e. whether there are any interactions between these two potential risk factors for all mental disorders and the six main discharge subgroups. However, the risk for all outcome groups associated with parity status after the infertility evaluation was not significantly affected by parity status before the infertility evaluation, as none of the interaction terms was statistically significant (all P-values >0.05; data not shown).

In a sub-analysis, we investigated whether the risk of hospitalization for a psychiatric disorder was affected by including women with multiple births in the analyses. However, when we restricted our analyses to women who gave birth to singletons after the infertility evaluation,
our results were virtually unchanged (data not shown). Finally, we also calculated HRs associated with years of follow-up since the first date of infertility evaluation (i.e. to assess a potential latency effect). However, our results revealed no consistent trend in HRs associated with increasing length of follow-up (data not shown).

Discussion

Using data from the largest cohort of infertile women compiled to date, we show a 17% increased risk of hospitalization for all mental disorders among women who did not give birth after an infertility evaluation compared with women who gave birth after the evaluation. For specific main psychiatric diagnosis groups, women not giving birth after the first evaluation for infertility were at an increased risk of alcohol and intoxicant abuse, schizophrenia and psychoses, and other mental disorders but at a decreased risk of affective disorders. The risk for all outcome groups associated with parity status after the infertility evaluation was not significantly affected by parity status before the infertility evaluation. Thus, our results indicate that being unsuccessful in giving birth after infertility evaluation may be an important risk factor for severe psychiatric disorders, which require hospitalization.

Our study has several strengths including a high statistical precision of the risk estimates stemming from the use of a large comprehensive cohort with almost 100,000 women evaluated for infertility and because of the large number of women with the outcomes of interest, i.e. hospitalization for psychiatric disorders observed during a mean follow-up of 12.6 years. Additionally, this study is the first to investigate the association between the women’s parity status after infertility evaluation and risk of hospitalization for psychiatric disorders using a longitudinal cohort design. Further strengths include the precise linkage between our cohort and several unique Danish population-based registries, which allowed hospitalization for psychiatric disorders to be included in our study; no women were lost to follow-up; all children born to the women in our cohort were identified; and we were able to adjust for potential confounders, including parity status before the infertility evaluation. Moreover, in a subpopulation, we were able to further adjust for socioeconomic position (highest attained education and disposable income), but this left our risk estimates virtually unchanged. Psychiatric diagnoses were measured using the ICD-8 and ICD-10 classification systems, which ensure a high reliability and validity of psychiatric morbidity. Another advantage is the exclusion of women with a prior history of hospitalization for psychiatric disorders, since women with a history of psychiatric disorders have a high risk of recurrence.

Several previous studies have reported increased risks of anxiety, mood disorders, depressive symptoms and actual psychiatric disorders in infertile women. However, the risk estimates show great variation, most likely due to substantial differences in study design and methodological limitations, including low numbers of study subjects and different diagnostic criteria. Our study design differs from most earlier studies in this research field as most studies have not compared women with fertility problems according to their parity status after fertility treatment in a within-cohort study design. Instead, they compared the relative risks between women with fertility problems and women without fertility problems (Eugster and Vingerhoets, 1999; Lok et al., 2002; Chen et al., 2004; Karjane et al., 2008; Sbaragli et al., 2008; Volgsten et al., 2008; Drosdzol and Skrzypulec, 2009; Noorbala et al., 2009; Gelbaya, 2010; Klemetti et al., 2010). To our knowledge, only results from 10 earlier studies (Kee et al., 2000; Hammarberg et al., 2001; Khademi et al., 2005; Verhaak et al., 2005; Johansson et al., 2009, 2010; Volgsten et al., 2010; Yli-Kuha et al., 2010; Greil et al., 2011; Pasch et al., 2012) could be compared with ours as their design was similar to ours, i.e. analysing the risk of distress, depressive symptoms and actual psychiatric disorders according to pregnancy/parity status after infertility evaluation/treatment. However, these studies also show substantial variation regarding diagnostic criteria and only a single case–control study from Finland by Yli-Kuha et al. (2010) used the ICD classification to classify psychiatric disorders. The other studies measured the mental health of the subject persons by using information obtained from self-administered questionnaires and a variety of other instruments, including telephone interviews and structured clinical interviews conducted by healthcare professionals. Unlike these studies, every woman hospitalized in our cohort was evaluated by a psychiatric specialist on admission, which further supports that no misclassification occurred in measuring the outcome.

For alcohol and intoxicant abuse, we found a more than 2-fold increased risk among women not giving birth after infertility evaluation compared with women who gave birth after the evaluation. This finding is supported by results from several of the 10 studies with a similar study design (Johansson et al., 2009, 2010; Yli-Kuha et al., 2010). For example, Yli-Kuha et al. (2010) reported a more than 2-fold reduction in alcohol and intoxicant abuse among infertile women with births compared with infertile women without births (OR = 0.38, 95% CI 0.18–0.80). Our results showed a 50% increased risk of hospitalization for schizophrenia and psychoses in the group of women not giving birth after the infertility evaluation. Among earlier studies with a similar study design, only the study by Yli-Kuha et al. (2010) specifically investigated psychotic disorders and they found no convincing association between risk of psychotic disorders and parity status among women with fertility problems. We found a 40% increased risk of eating disorders in the group of women who did not give birth after the infertility evaluation, although this risk was not statistically significant. The study by Yli-Kuha et al. (2010) is the only 1 of the 10 studies with a study design similar to ours and which investigated the risk of eating disorders. In line with our result, their study found a decreased risk of eating disorders among a group of infertile women who had given birth compared with infertile women without births, albeit not statistically significant (OR = 0.30, 95% CI 0.03–2.92) as in our study.

In contrast to the three aforementioned psychiatric diagnoses, we observed a small, but statistically significantly, 10% decreased risk of affective disorders, particularly depression, among women not giving birth compared with women successful in giving birth after the infertility evaluation. These results are in contrast with the results from the other studies with a similar study design investigating this topic (Kee et al., 2000; Khademi et al., 2005; Verhaak et al., 2005; Johansson et al., 2009, 2010; Volgsten et al., 2010; Yli-Kuha et al., 2010; Pasch et al., 2012). Hence, our result is not easily explainable and may be due to chance alone, especially because the upper limit of the 95% CI (0.99) is very close to 1.00, i.e. close to statistical insignificance. If real, however, one possible explanation for the observed decreased risk of affective disorders could be the high proportion of
multiple births among women with fertility problems. Studies investigating the mental health of women after multiple births have found an increased risk of symptoms of depression among mothers of twins compared with mothers of singletons (Vilkska et al., 2009; Ross et al., 2011). However, when we excluded all women with multiple births from our analyses, the risk estimate was virtually unchanged. The slightly reduced risk for hospitalization for affective disorders among women not giving birth after the infertility evaluation might also be explained by surveillance bias. Both during pregnancy and after birth, women in Denmark are scheduled to see their general practitioner and other healthcare professionals, and when the children grow older the women generally accompany their children to the annual visits with the general practitioner and one might hypothesize that symptoms of depression or other affective disorders are diagnosed more often in the women with children simply because of more appointments within the healthcare system. It is also possible that doctors and other practitioners are more inclined to hospitalize, or refer to outpatient clinics, women with young children. However, these explanations are of a more speculative character and need to be further investigated in order to be conclusive. Lastly, in contrast to results from most other studies with a similar study design (Kee et al., 2000; Verhaak et al., 2005; Johansson et al., 2009, 2010; Yli-Kuha et al., 2010; Pasch et al., 2012), but not all (Volgsten et al., 2010), we found no convincing associations between parity status after infertility evaluation and risk of anxiety, adjustment and obsessive compulsive disorders.

Some limitations of our study should be noted. As we only had information on psychiatric conditions so severe that they warranted hospitalization or outpatient care (from 1995 and onwards), we were unable to analyse the association between parity status after infertility evaluation and less severe psychiatric conditions. Consequently, the true incidence of psychiatric disorders among women with fertility problems is probably somewhat underestimated. Information on psychiatric outpatient treatment was first available from 1995; thus an unknown number of women with psychiatric outpatient contacts before 1995 are included in our analyses but would have been excluded or adjusted for had this information been available. This could potentially have led to misclassification of exposure data; however, the unintended inclusion of these patients may at most have led to a slight underestimation of the risk estimates. Furthermore, we did not have detailed information on ART for all cohort members; for this reason the association between the different modalities of ART, including type of treatment, number of treatment attempts, types of fertility drug and risk of psychiatric disorders was not assessed. In relation to this aspect, we had no information on why some women who had an infertility evaluation were not later found in the IVF registry. This would have been a valuable information as those women who choose to have ART (and therefore are more likely to give birth) may be qualitatively different from those who have an infertility evaluation but no further treatment. For example, it is possible that women who are less mentally healthy will refrain from ART. Hence, as women who receive ART are more likely to give birth compared with women evaluated for infertility but with no further treatment, our risk estimates may be slightly overestimated.

In conclusion, our results show that infertile women who did not give birth after infertility evaluation were at an increased risk for a variety of psychiatric disorders, including alcohol and intoxicant abuse, schizophrenia and psychoses and other mental disorders, compared with women who gave birth after the infertility evaluation. In contrast, the risk of affective disorders was significantly decreased among women with fertility problems not succeeding in giving birth. The risk of anxiety, adjustment and obsessive compulsive disorders was not associated with the woman’s parity status after infertility evaluation. If real, our findings of a 17% increase in risk of all psychiatric disorders associated with giving birth after the infertility evaluation would mean ~40 additional cases of all psychiatric disorders per 100 000 exposed women, i.e. women not succeeding in giving birth after the infertility evaluation. Consequently, even though this number may not be very high, clinicians and other healthcare personnel treating this group of women should nevertheless be aware of the potential risk modification of psychiatric disorders associated with unsuccessful fertility treatment. Furthermore, our results point to new aspects of follow-up of women with fertility problems who are unsuccessful in giving birth in order to prevent or identify and treat these possible psychological side effects.

Acknowledgements

We thank Peter Bo Aarslev for data management assistance and Carol Bang-Christensen for language assistance.

Authors’ roles

B.B.-F. designed the study, interpreted the data and drafted the manuscript. S.K.K., S.O.D. and C.J. made substantial contributions to conception and design of the study and interpretation of the data, and critically revised the manuscript for important intellectual content. V.A. analysed and interpreted the data and critically revised the manuscript for important intellectual content. M.S.J. performed acquisition of data and critically revised the manuscript for important intellectual content. T.K. interpreted the data and critically revised the manuscript for important intellectual content. A.J. made substantial contributions to conception and design of the study and acquisition and interpretation of the data, and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Funding

The study was supported by the Danish Cancer Society.

Conflict of interest

All authors report no potential conflicts of interest.

References

Dalton SO, Mellemkjær L, Olsen JH, Mortensen PB, Johansen C. Depression and cancer risk: a register-based study of patients


