

Infertility-related stress and the risk of antidepressants prescription in women: a 10-year register study

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STUDY QUESTION: Is the first-time redeemed prescription of antidepressants predicted by the level of infertility-related stress in women seeking ART treatment?

SUMMARY ANSWER: Infertility-related stress in the personal and marital domains and general physical stress reactions were significant predictors of a first redeemed prescription of antidepressants after ART treatment in this 10-year follow-up cohort study.

WHAT IS KNOWN ALREADY: The literature has found inconsistent findings regarding the association between infertility-related stress and later psychological adjustment in fertility patients. The association between infertility-related stress and later prescription of antidepressants had never been explored in long-term cohort studies.

STUDY DESIGN, SIZE, DURATION: All women ($n = 1169$) who participated in the Copenhagen Cohort Multi-centre Psychosocial Infertility (COMPI) cohort study in the year 2000 (questionnaire data) were linked with the register-based Danish National ART-Couple (DANAC) I cohort, which includes women and their partners having received ART treatment from 1 January 1994 to 30 September 2009. The study population were among other national health and sociodemographic registers further linked with the Danish National Prescription Registry.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women initiating ART treatment were followed until they had redeemed the first prescription of antidepressants or until 31 December 2009. Logistic regression analyses were conducted to test the association between general physical stress reactions and infertility-related stress in the personal, marital and social domains, respectively, and a future redeemed prescription of antidepressants. Age, education level, marital status, number of fertility treatments prior to study inclusion and female infertility diagnosis were included as covariates in the adjusted analyses. Further, the analysis was stratified according to childbirth or no childbirth during follow-up.

MAIN RESULTS AND THE ROLE OF CHANCE: The final sample consisted of 1009 women with a mean age of 31.8 years. At study inclusion, women had tried to conceive for an average of 3.45 years. At 10-year follow-up, a total of 13.7% of women had a first redeemed prescription of antidepressant medication. The adjusted odds ratio (OR) showed that high general physical stress predicted the later prescription of antidepressants (adjusted (adj) OR = 2.85, 95% confidence interval (CI) 1.96–4.16). Regarding infertility-related stress domains, high personal stress (adj OR = 2.14, 95% CI 1.46–3.13) and high marital stress (adj OR = 1.80, 95% CI 1.23–2.64) were significantly associated with the later prescription of antidepressants. Social stress was not significantly associated with the future redeemed prescription of antidepressants (adj OR = 1.10, 95% CI 0.76–1.61). Among women not having achieved childbirth during follow-up, the risk of a first-time prescription of antidepressants associated with infertility-specific stress was higher compared to the risk among women having childbirth during follow-up.

LIMITATIONS, REASONS FOR CAUTION: This study did not account for potential mediating factors, such as negative life events, which could be associated with the prescription of antidepressants. Second, we are not able to know if these women had sought psychological support during follow-up. Additionally, antidepressants might be prescribed for other health conditions than depressive disorders.

WIDER IMPLICATIONS OF THE FINDINGS: Our results suggest that women presenting high infertility-related stress in the personal and marital domains were at higher risk of redeemed first-time prescription of antidepressants after ART, independently of having delivered a child or not after initiation of ART treatment. Women would benefit from an initial screening specifically for high infertility-related stress. The COMPI Fertility Problem Stress Scales can be used by clinical staff in order to identify women in need of psychological support before starting ART treatments.

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Introduction

Extensive evidence has shown support for the psychological and social impact of infertility on women, men and couples. Some studies documented poor psychological adjustment to infertility diagnosis (for a review see [Luk and Loke, 2015](#)) and to fertility treatments (e.g. [Boivin and Takefman, 1995](#); [Klonoff-Cohen et al., 2001](#); [Williams et al., 2007](#); [Moura-ramos et al., 2010](#); [Vahratian et al., 2011](#); [Wichman et al., 2011](#)). Longitudinal studies have shown that female depression seems to increase after unsuccessful treatment ([Verhaak et al., 2007](#)). A recent systematic review and meta-analysis found that patients with failed treatments and who ended treatment without achieving parenthood presented poor mental health ([Pasch et al., 2012](#); [Gameiro et al., 2014](#); [Gameiro and Finnigan, 2017](#)); however this adjustment tended to improve with time since treatment ([Gameiro and Finnigan, 2017](#)). A register-based study in Denmark found that women engaged in ART treatments with no live birth had a lower risk of being clinically diagnosed by a psychiatrist with a unipolar depression compared to those with live birth, as delivery is a risk factor for depression postpartum ([Sejbaek et al., 2015](#)). However, a Swedish cross-sectional study found that 20–23 years after IVF women were at increased risk of depression, especially those who remained childless and/or without a partner ([Vikström et al., 2015](#)). Another study found that women treated for infertility had less psychiatric disorders than controls ([Yli-Kuha et al., 2010](#)).

Antidepressant use has been increasing in the majority of European countries ([OECD, 2013](#)). Antidepressants prescription is used for moderate to severe depressive disorder, but also for other conditions such as anxiety, insomnia, panic disorders and neuropathic pain ([Sindrup et al., 2005](#); [Wong et al., 2016](#)). In the field of fertility care, ~30% of women engaged in ART treatments fulfill criteria for mental health disorders ([Volgsten et al., 2008](#)) and 41% for depression in particular ([Crawford et al., 2017](#)) based on self-report evaluations. Women reporting higher depression did not seek medical advice for infertility to a similar extent as women without depression ([Herbert et al., 2010](#); [Crawford et al., 2017](#)), and they initiated fewer ART treatment cycles and had a lower number of live births compared to those without a clinical depression diagnosis ([Sejbaek et al., 2013](#)). Although the use of antidepressants in women undergoing IUI treatment was not associated with pregnancy rates, it was associated with increased risk of pregnancy loss ([Evans-Hoeker et al., 2018](#)). The only study investigating antidepressant use among patients undergoing

IVF found that the diagnosis of depression and the treatment with antidepressants before IVF was associated with reduced pregnancy rates ([Cesta et al., 2016](#)). This is of particular relevance since antenatal depression is associated with increased risk of postpartum depression, which has negative consequences for the woman's and child's health ([Rwakarema et al., 2015](#)). Post-partum depression can negatively influence the mother-child relationship, and the use of antidepressants during pregnancy and breastfeeding has been associated with increased risk for poor child development ([Brummelte and Galea, 2016](#)). In addition, a history of previous unsuccessful treatments seems to be associated with a higher risk of depressive symptomatology during pregnancy and after delivery ([Agostini et al., 2018](#)). Even though the risk of postpartum depression is not higher in women undergoing IVF, there is an increased risk in the case of previous history of mental illness ([Vikström et al., 2017](#)). Acting in a preventive way might diminish the negative influence of psychological strain on reproductive outcomes as well as preventing the negative consequences of depression for women and their children. Given the importance of prevention and early detection of psychosocial issues in people undergoing fertility treatments, knowing the link between pre-levels of stress and specifically infertility-related stress and future antidepressants prescription is crucial. This will be of great value since screening for stress at the beginning of treatment will enable fertility staff to understand patient needs and offer additional care accordingly, creating an opportunity to act in a preventive way and thus restrain the need for antidepressants. The majority of studies investigating the predictive role of infertility-related stress on later development of maladjustment has been focused on self-reported outcome measures (for a review see [Rockliff et al., 2014](#)). Self-reported mental health outcome measures can be biased by social desirability, i.e. study participants might answer what they think they are expected to state. In our study, we used register-based data on the first-time redeemed prescription of antidepressants as outcome, which can be considered an indicator of psychological strain. Around 90% of prescriptions of antidepressants in Denmark are managed in primary health care (general practitioners) and the remaining 10% in secondary care (psychiatrists at hospitals) ([Eplöv et al., 2005](#)). By using prescription data, we were able to include minor or moderate depression and not only the most severe depressions diagnosed and treated by a psychiatrist.

The present study aims to explore the predictive role of general physical stress and more specifically the role of infertility-related

stress when initiating ART treatment, on the risk of a later first-time redeemed prescription of antidepressants in a 10-year follow-up cohort study of women initiating ART treatment in the year 2000–2001 in Denmark. In addition, since the literature showed contradictory findings regarding the link between achieving childbirth or not and later psychological strain, knowing if having a child influences the relation between infertility stress and the later prescription of antidepressants would help to clarify this question.

Material and Methods

Setting

Between 1994 and 2006, fertility treatment performed by a medical doctor was accessible only for women in a heterosexual partnership (Danish Ministry of Health, 1997). In the public health care system only couples with no common children and with female age up to 40 years old are offered ART treatments (up to three 'fresh cycles') and an unlimited number (in practice 3–6) of IUI treatment cycles. In the private health care system, women up to 45 years of age are offered treatments. Since 2007, medical doctors have permission to offer fertility treatments to single women and lesbian couples as well. Fertility clinic staff provide the routine psychosocial care, and no psychologists to offer professional psychosocial services are employed at public fertility clinics in Denmark.

Study Population

This study is part of the Copenhagen Cohort Multi-centre Psychosocial Infertility (COMPI) Research Programme established in the year 2000. This research program includes a number of cohort studies aiming at investigating the psychosocial and medical issues of infertility and fertility treatment (Schmidt, 2006; Schmidt *et al.*, 2013). For this study, we used data from the COMPI Infertility Cohort and the Danish National ART-Couple (DANAC) I Cohort (Schmidt *et al.*, 2013).

The COMPI Infertility Cohort includes a consecutive sample of all new couples initiating ART treatment at one of five specialized fertility clinics in Denmark (Schmidt, 2006). Between January 2000 and August 2001, all couples entering treatment for the first time at one of four large public hospital-based specialized fertility clinics and one specialized private clinic received a sealed, pre-addressed, stamped envelope immediately before their first treatment attempt, including questionnaires about their reproductive history and psychosocial self-report measures such as infertility stress and coping. In total 1406 couples were invited to participate, and 83% (1169/1406) of the women participated. In 2010 we established the national register-based DANAC I Cohort that includes all women and their partners living in Denmark who had received ART treatment from 1 January 1994 to 30 September 2009 at public as well as private fertility clinics (Schmidt *et al.*, 2013). Each person living in Denmark has a unique personal identification number, which is the key variable in all national health registers, giving unique opportunities for cross linkage between registers. The DANAC I Cohort was linked with a number of national register data on health (somatic health, the National Patient Register; psychiatric health, the Danish Psychiatric Central Research Register); the Danish Medical Birth Register; the Danish Register of Causes of Deaths; national socio-demographic data as well as data on redeemed prescriptions of medication from the Danish National

Prescription Registry. The COMPI Infertility Cohort was linked with the DANAC I cohort making it possible in this study to combine self-reported data from the questionnaire-based COMPI Infertility Cohort with national register-based data on redeemed prescription of antidepressant medication. This register covers individual-level data on all dispensed prescriptions drugs sold in Danish community pharmacies since 1994 (Kildemoes *et al.*, 2011), being the only way to buy antidepressants in Denmark. All redeemed prescriptions are recorded in this register using automated bar-code data entry from community pharmacies, i.e. indicating that medication was bought. For this study, registers of antidepressants prescriptions (Anatomical therapeutic chemical classification code N064) until 31 December 2009 were collected. We considered the first registered redeemed prescription of antidepressants after the answer to the COMPI questionnaire at study inclusion as outcome in the analysis. Women who already had delivered and/or adopted at cohort study inclusion ($n = 124$) and women with prescription of antidepressants prior to answering the COMPI questionnaire at cohort study inclusion ($n = 36$) were excluded from the analysis.

Ethical approval

The COMPI Infertility Cohort study complying with the Helsinki II Declaration was assessed by the Scientific Ethical Committee of Copenhagen and Frederiksberg Municipalities (KF 01-107/99) and was approved by the Danish Data Protection Agency (J.nr. 1999-1200-233; 2001-41-1486; 2005-41-5694). The DANAC I Cohort study was approved by the Danish Data Protection Agency (J.nr. 2008-41-2076), the National Board of Health (J.nr. 7-505-29-1658/1) and the Danish Medical Agency and Statistics Denmark (J.nr. 703481).

Measures

Predictors

The COMPI Fertility Problem Stress Scales (COMPI-FPSS, Schmidt *et al.*, 2005; Schmidt, 2006) is a self-report instrument that includes 14 items assessing the impact of infertility on the personal domain (e.g. 'It is very stressful for me to deal with this fertility problem'), social domain (e.g. 'How much stress has your fertility problem placed on your relationships with your family?') and marital domain (e.g. 'How much stress has your fertility problem placed on your marriage?'). Items are rated on 4- or 5-point Likert scales and were originally developed for the Danish population. High scores indicate higher stress, and high stress was defined as the highest third (Schmidt *et al.*, 2005). COMPI-FPSS is a widely used instrument to measure the infertility-specific stress and was in a cross-cultural validation study in seven countries found to be a reliable measure for both genders (Sobral *et al.*, 2017). It was also found to be good at screening for depression and anxiety (Pedro *et al.*, 2019). The Cronbach's alphas in the COMPI Infertility Cohort of women were 0.81 for the total score and range from 0.73 to 0.81 for the three domains (Schmidt, 2006).

'Physical Stress Reactions' is composed of nine items originally from the Stress Profile Questionnaire (Setterlind and Larson, 1995) rated on a 5-point Likert scale. Higher scores indicated more severe stress reactions, and high stress was defined as the highest third. This measure has shown good psychometric properties and had been used to explore the stress in the context of chronic health diseases (Hallman *et al.*, 2001), including infertility (Peronace *et al.*, 2007; Boivin *et al.*, 2018).

The Cronbach's alpha in the COMPI Infertility Cohort of women was 0.74.

Covariates

Control variables were retrieved from the Danish Medical Birth Register, the socio-demographic population registers at Statistics Denmark and COMPI questionnaire. Education was defined as the level of education, and marital status was defined as married or living together. Female cause of infertility (defined as 'blocked tubes' and/or 'irregular or anovulation' as infertility diagnosis) and the number of prior treatments (including IUI, IVF and ICSI) were also included in the analysis. National register data on childbirth during follow-up were used to conduct stratified analysis.

Statistical Analysis

All analyses were conducted in Statistical Analysis Software (SAS), SAS Institute, version 9.4. Descriptive statistics were conducted to characterize the sample. Chi-square tests were used to explore the association between high stress (the highest third) and study population characteristics. Logistic regression analyses were used to test the association between infertility stress and physical stress and the future redeemed, first-time prescription of antidepressants. Potential confounders were selected both based on previous studies (Sejbaek et al., 2015; Martins et al., 2018) and using a directed acyclic graph. Age, education, marital status, female cause of infertility and number of fertility treatments prior to study inclusion were included as covariates in the adjusted analyses. Stratified analyses were conducted to explore the estimates among the groups of women who had delivered a child or not during follow-up.

Results

Participants

Table I depicts the participants' sociodemographic characteristics at study inclusion and the association with high stress. The final sample consisted of 1009 women with a mean age of 31.78 years ($SD = 3.63$). The majority had vocational training or further education after high school. At study inclusion, the women had been together with their partners on average for 7.82 years ($SD = 3.73$), and 61% were married. The participants had tried to conceive for an average of 3.45 years ($SD = 1.16$). A total of 41% had a diagnosis of partner's decreased semen quality, 27% blocked tubes and 14% ovulatory problems. At study inclusion, women had already undergone on average 4.19 treatments ($SD = 2.80$), mainly insemination treatment cycles. An increasing number of fertility treatment attempts prior to study inclusion was associated with a significantly larger proportion reporting high stress in the personal, marital and social domain. Long further education was significantly associated with a larger proportion reporting high stress in the personal domain. High marital stress was significantly associated with an increasing number of years trying to conceive. High social stress was significantly associated with an increasing number of years being partners and cohabitating as marital status (vs. married women). A total of 12% had severe depressive symptoms at study inclusion measured by the Mental Health Inventory-5 from the Short Form (SF-36). However, the register linkage of the COMPI Infertility Cohort with the Danish Psychiatric Central Research Register showed

that no one had a clinical diagnosis of depression provided by a psychiatrist.

Stress and prescription of antidepressant medication

A total of 13.7% (138/1009) had a first-time redeemed antidepressant medication prescription at follow-up. Table II presents mean and SD for the general physical stress and infertility-stress variables. The average time between women's answer to the COMPI Infertility Cohort questionnaire and the first-time prescription of antidepressants medication was 5.7 years ($SD = 2.7$).

Table III presents the crude and adjusted OR for the association between general physical stress, infertility-related stress and the later redeemed prescription of antidepressants. High general physical stress predicted the later prescription of antidepressants (adj OR = 2.85, 95% confidence interval (CI) 1.96–4.16). Regarding infertility-related stress domains, high personal stress (adj OR = 2.14, 95% CI 1.46–3.13) and high marital stress (adj OR = 1.80, 95% CI 1.23–2.64) were significantly associated with the later prescription of antidepressants. Social stress was not significantly associated with the future prescription of antidepressants (adj OR = 1.11, 95% CI 0.76–1.62). Among women who did not deliver a child during follow-up, the association between stress and antidepressants was markedly stronger than among those with a childbirth during follow-up in the case of personal stress (OR 3.48, 95% CI 1.49–8.10 vs. OR 1.89, 95% CI 1.22–2.95) and marital stress (OR 4.05, 95% CI 1.73–9.49 vs. OR 1.50, 95% CI 0.97–2.33).

Discussion

Women engaged in ART and reporting high personal and marital stress at the beginning of treatment at a specialized fertility clinic were at almost twice the risk of redeeming the first-time prescription of antidepressants during 10 years of follow-up after initiating treatment compared to women reporting lower levels of infertility-related stress. This follow-up study included women from the COMPI Infertility Cohort who had initiated ART treatment between 2000 and 2001. This is the first study in Denmark exploring the relationship between self-reported general physical stress and infertility-related stress and antidepressants prescription in women engaged in ART.

A total of 13.7% of our sample had redeemed the first-time prescription of antidepressants during follow-up. A study from Sweden reported a lower percentage (3.5%) of women using antidepressants before and after ART treatments (Cesta et al., 2016). This difference might be related to different prescriptions rules and procedures between these countries; prescriptions in Denmark are initially given 1 month at a time and in Sweden 3–6 months (Cesta et al., 2016). Another study found that 5.7% of women undergoing IUI treatment reported being using antidepressant medication (Evans-Hoeker et al., 2018). Our percentage for prescription of antidepressants is considerably higher than the overall percentage of clinically diagnosed unipolar depression of 2.6% found in the DANAC I Cohort among women having received ART treatment (Sejbaek et al., 2013). As antidepressants are prescribed to people suffering from moderate depression and also to some extent used for other indications than depression, these differences in percentages between prescription of antidepressants and clinical diagnosis of unipolar depression provided

Table 1 Baseline study population characteristics and the association with high stress.

	Mean (SD)	N (%)	High physical stress (%)	High personal stress (%)	High marital stress (%)	High social stress (%)
Age	31.78 (3.63)					
≤30 years		389 (39)	37	37	37	37
31–34 years		435 (43)	31	31	39	31
≥35 years		185 (18)	36	31	36	36
Years together with partner <i>n</i> = 29 missing	7.82 (3.73)					
≤5		318 (32)	31	35	36	31*
6–10		431 (44)	36	33	39	41*
≥11		231 (24)	37	33	38	40*
Years trying to have a child <i>n</i> = 15 missing	3.45 (1.16)					
0–2		215 (22)	34	28	30*	31
3–5		576 (58)	33	36	40*	40
≥6		203 (20)	38	34	40*	38
Total number of treatments	4.19 (2.80)					
0		454 (45)	34	24**	30**	33*
1–4		346 (34)	32	40**	40**	41*
≥5		209 (21)	38	42**	52**	41*
Infertility diagnosis^a <i>n</i> = 14 missing	-					
Blocked tubes		265 (27)	34	32	34	34
Irregular or anovulation		140 (14)	40	36	43	41
Decreased semen quality		409 (41)	33	31	37	40
No cause proven		265 (27)	34	37	44*	40
Other causes		181 (18)	38	37	40	38
Education <i>n</i> = 39 missing	-					
Basic school education		146 (15)	40	36*	38	35
Higher school education		69 (7)	30	30*	33	36
Vocational training		403 (42)	32	28*	35	34
Short further education		61 (6)	36	36*	41	44
Medium length further education		212 (22)	36	39*	39	40
Long further education		79 (8)	33	42*	47	49
Marital status <i>n</i> = 36 missing	-					
Married		593 (61)	33	35	37	33*
Cohabiting		380 (39)	36	31	39	40*

The Copenhagen Multi-centre Psychosocial Infertility Research Programme (COMPI), *N* = 1009 women.

^aPossible to report more than one infertility diagnosis.

*Chi-square *P*-value <0.05.

**Chi-square *P*-value <0.01.

by a psychiatrist or even between studies exploring rates of antidepressant use (e.g. due to different prescription times) were expected. We see the first-time prescription of antidepressants as an indicator for

seeking help in the health care system for a psychological strain. Hence, our finding that infertility-related stress is a predictor of later first-time prescription of antidepressant medication is in line with recent

Table II Baseline infertility-related stress and general physical stress.

	Mean (SD)	Min-max score	N (%) highly stressed	Threshold for high stress
COMPI-FPSS				
Personal stress	1.38 (0.78)	0.0–4.0	337 (33.4)	> 1.78
Social stress	0.57 (0.65)	0.0–3.0	378 (37.5)	>0.7
Marital stress	0.98 (0.80)	0.0–3.5	383 (38.0)	> 1.1
Physical stress reactions	19.73 (14.18)	0.0–77.8	344 (34.1)	>24

N = 1009 women. The COMPI Infertility Cohort.

Note: COMPI, Copenhagen Multi-centre Psychosocial Infertility Research Programme; COMPI-FPSS, COMPI Fertility Problem Stress Scales. Possible score: personal stress (range 0–4.0), social stress (range 0–3.0), marital stress (range 0–3.5), physical stress reactions (range 0–100).

Table III The association between high infertility-related stress domains, high physical stress and later redeemed first-time prescription of antidepressants for all sample and stratified analyses based on childbirth during follow-up.

	N (crude/adjusted analyses)	N with AD prescription	Crude OR	Adjusted OR*	P-value adj OR	Childbirth, N = 792	No childbirth, N = 178
						Adjusted OR*	Adjusted OR*
Personal stress	1009/970	138	1.96 (1.36–2.82)	2.14 (1.46–3.13)	<0.01	1.89 (1.22–2.95)	3.48 (1.49–8.10)
Social stress	1009/970	138	1.09 (0.75–1.57)	1.11 (0.76–1.62)	0.59	0.99 (0.64–1.53)	1.93 (0.84–4.44)
Marital stress	1009/970	138	1.60 (1.12–2.30)	1.80 (1.23–2.64)	<0.01	1.50 (0.97–2.33)	4.05 (1.73–9.49)
Physical stress reactions	1009/970	138	2.86 (1.98–4.12)	2.85 (1.96–4.16)	<0.001	2.94 (1.91–4.54)	2.35 (1.04–5.32)

OR with 95% CI. The COMPI Infertility Cohort. Note: AD, redeemed prescription of a first-time antidepressant medication; COMPI, Copenhagen Multi-centre Psychosocial Infertility Research Programme.

*Adjusted for age, marital status, education, number of fertility treatments prior to study inclusion, female cause of infertility.

evidence showing the connection between stress and psychological adjustment in people undergoing fertility treatments. A longitudinal study found that stress appraisals before treatment significantly predicted depression following IVF treatment (Knoll et al., 2009). More specifically, infertility-related stress was found to be associated with emotional distress (Moura-Ramos et al., 2012; Gana and Jakubowska, 2016) and severe depressive symptoms (Peterson et al., 2014). Our results showed that general stress and also infertility-related personal and marital stress predicted the later first time-redeemed prescription of antidepressants; social infertility-related stress did not. This result indicates that the stress attributed to infertility has a significant impact on the later need for treatment with antidepressant medication in the follow-up. In addition, the social dimension of COMPI-FPSS explores how much stress the fertility problem affects the relationship with family and friends. In our sample, the social impact of infertility does not appear to play an important role in the risk of a subsequent antidepressant prescription. It could be that stress should be in a person's very close relationships (partner, family) to have an impact on the need for prescription of antidepressants compared to stress in relation to people of a bit more distance (friends, co-workers). In fact, the impact of marital issues on individual psychosocial adjustment in both the general population and patients undergoing ART has been studied. Marital conflict was associated

with increased depressive symptoms in the general population (Proulx et al., 2009), and Whisman and Uebelacker (2009) found a bidirectional effect of marital dissatisfaction and depressive symptoms. Infertility-related stress was associated with marital distress (Gana and Jakubowska, 2016) and seems to negatively affect the stability of marital relationships (Martins et al., 2014). These studies all showed a relationship between marital issues and poor psychological adjustment.

Our results also showed that personal and marital infertility stress are predictors of later prescription of antidepressants, whether these women had delivered or had not delivered a child during follow-up. As already suggested in other studies, this might indicate that psychological strain might be related to other issues, such as coping skills in the management of infertility diagnosis and/or treatment demands and failures (Pasch et al., 2012; Gameiro and Finnigan, 2017). This finding reinforces the importance of screening for psychological strain at the beginning of treatment. Furthermore, it emphasizes the potential importance of offering psychological support for those presenting higher stress at the beginning, given the fact that this strain seems to remain even after women achieved the goal of motherhood.

More specifically, the risk for the first-time prescription of antidepressants was higher for those who had not delivered a child, which is in line with the finding of a higher risk of adverse outcomes for those

that went through failed treatments without achieving childbearing (e.g. Pasch *et al.*, 2012; Gameiro and Finnigan, 2017; Martins *et al.*, 2018). One of these studies revealed that failed treatments lead to worse mental health and well-being; however no differences were found when comparing those who had a child or not (Gameiro and Finnigan, 2017), suggesting that higher risk of poor mental health is related to the unfulfillment of childbearing goals characterized by a sustained child-wish (Gameiro *et al.*, 2014). Counseling should focus on the childbearing goals, promoting balanced decision-making regarding going through new treatments (since repeated treatments increased the chance of achieving a pregnancy; Pinborg *et al.*, 2009) or not. For those who do not consider other alternatives, psychologists can have a role in facilitating the bereavement of not achieving a pregnancy and counseling and supporting on the exploration of other ways to achieve parenthood or to establish other life-goals. For example, the Three Tasks Model of Adjustment to Unmet Parenthood Goals (Gameiro and Finnigan, 2017) gives therapeutic tools that can be the target on psychosocial care to promote acceptance and meaning-making of the unmet parenthood goals and pursuing new life goals, in order to promote better adjustment. Since these patients seem to be at higher risk of the future need of antidepressants, fertility clinics should offer follow-up appointments to make sure they have easy access to psychosocial care and intervention, in case of need.

Our study has strengths that should be highlighted. First, we linked the COMPI Infertility Cohort with national register data on medication, including a complete registration of all women who had undergone ART treatments between 1994 and 2009 and with later first-time redeemed prescription of antidepressants in a long follow-up. To the best of our knowledge, this is the first study investigating the role of an infertility-specific stress measure on the later prescription of antidepressants using a 10-year follow-up cohort study and using a general stress measure as reference. The COMPI-FPSS has been recognized as a feasible tool to screen for clinically relevant anxiety and depression (Pedro *et al.*, 2019). The use of COMPI-FPSS also contributes to the clarification of the source of infertility-related stress since it is organized in three domains of stress: personal, marital and social stress. Pre-treatment screening of infertility-related stress might be of great importance for identifying people in need of psychological support. A study revealed that Screen-IVF could correctly assess who would be at risk of maladjustment, even though it included a short follow-up after one treatment cycle (Verhaak *et al.*, 2010). In addition, the combination of both self-reported measures and medical record data can be of great value. Medical records can be seen as more rigorous than self-report since it is less likely biased by social desirability. The fact that we assessed specifically the prescription of antidepressant medication rather than psychiatric depression diagnosis might enable detection of less severe depressive conditions and a more realistic picture of who and how many might be at risk since prescriptions can be made by a general practitioner and not only by psychiatrists.

Despite the large sample size and the possibility to study the antidepressants redeemed prescription received for all women undergoing ART treatment included in the COMPI Infertility cohort, some bias might occur given that participation in the COMPI Infertility cohort was voluntary. However, the high response rate of 83% among women and the diversity of educational level in the sample reassure the possible generalization of the results to the population of women

in ART treatment. Unfortunately, we were not able to control for other negative life events that can explain the need for antidepressant medication. Future studies might explore the role of, for example, the death of close family members, which has a potential psychological impact in life. In addition, no national register data on seeking professional psychological services are available in Denmark. As there are no psychologists employed at fertility clinics in this country, fertility patients in need of professional psychological support have to approach private services with out-of-the-pocket payment. Finally, the outcome measure in our study was the recorded redemption of the prescription, not actual use of the prescribed antidepressant. However, since the registry includes all antidepressants prescriptions redeemed at community pharmacies in Denmark (i.e. indicating that medication was bought), we can presume that they had effectively used this medication.

Our study emphasizes the importance of screening for infertility-related stress before ART treatments and the need to include mental health professionals in fertility care. As mentioned previously, in Denmark there are no psychologists employed at fertility clinics, which may prevent delivery of preventive and effective management of psychological issues in patients undergoing treatment. The COMPI-FPSS can be used as screening measures to predict emotional/psychological problems at the beginning of treatments and thus potentially prevent, through psychological intervention, the need to use antidepressants. Our results support the hypothesis that the need for use of antidepressants is related to infertility/fertility treatment since the COMPI stress measurement scales were specifically designed to measure stress related to infertility. In addition, the instrument is a short and reliable measure and easy to use in fertility care by healthcare professionals (Pedro *et al.*, 2016; Sobral *et al.*, 2017). Because the COMPI-FPSS are organized according to three domains (personal, social, marital, respectively), it permits discrimination of the source of stress. This gives mental health professionals cues to develop and direct psychological support and better understand the patient's needs. In this way, all women would benefit from being screened for psychosocial issues at the beginning of ART treatments and from receiving personalized intervention covered by public hospitals focused on coping with the stress of infertility and particularly with treatment failure. Based on our results, focusing on marital and personal stress domains would be beneficial in reducing later psychological strain and hence reducing or preventing future need for antidepressants.

Authors' roles

JP, DV, GM, CH, MVM and LS designed the study. DV, GM and CH performed the data analysis. All authors contributed to interpretation of the results. JP and DV drafted the manuscript. All authors made significant contributions critically revising the manuscript and approved the final version for submission.

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Conflict of interest

The authors have no conflict of interest.

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