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a longitudinal cohort study on stress and depression

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Pregnancy outcomes after recurrent pregnancy loss – a longitudinal cohort study on stress and depression

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Running title Distress in RPL and outcome

Abstract

Research Question: Are self-reported symptoms of stress and depression associated with pregnancy outcomes within the first year after referral to a tertiary recurrent pregnancy loss unit?

Design: Prospective cohort study with online questionnaires using the Major Depression Inventory (MDI) and Cohen's Stress Scale (PSS) at referral and after one year. The study was conducted between 2010 and 2014. A total of 301 women with recurrent pregnancy loss completed the first questionnaire. One year after referral, 185 women (61%) completed a follow-up questionnaire.

Results: A score above the threshold for major depression on the MDI at referral was not a predictor for outcome in the first pregnancy after referral; OR (95% CI) for live birth 1.71 (0.66; 4.44), nor was increasing scores on the PSS: OR 0.98 (95% CI 0.94; 1.02). At follow-up, women who had achieved a pregnancy which ended with the birth of a live born child had significantly lower scores on both the MDI: 13.45 (11.05) versus 11.04 (11.07), difference -2.41 (95% CI -4.60; -0.23) and the PSS: mean 17.69 (7.59) versus 13.03 (6.83), difference -4.66 (95% CI -6.04; -3.28), respectively. This was not the case for women who did not have a successful pregnancy. Women with recurrent pregnancy loss after a child were less likely to report symptoms corresponding to major depression than women with only losses (n=7 (5%) vs. 19 (12%), p=0.04).

Conclusions: Self-reported emotional distress did not impact future chance of live birth in this cohort. A live born child decreased emotional distress.

Key words Recurrent pregnancy loss, depression, stress, prospective cohort study

Key message In this longitudinal cohort study of women with recurrent pregnancy loss, self-reported emotional distress was not a predictor for future pregnancy outcomes, but a live born child decreased emotional distress.

Introduction

Involuntary childlessness due to reduced fertility is a severe low-control stressor (Schmidt 2006) where the couple can do little or nothing to influence the nature or the outcome of their situation (Terry & Hines 1998). Reduced fertility affects both couples who are infertile, e.g. those who have not achieved a clinical pregnancy after > 12 months' attempt with regular, unprotected sexual intercourse (Zegers-Hochschild et al. 2017) and couples with recurrent pregnancy loss (RPL). Several studies have documented that depressive symptoms and psychological stress are common conditions among women with RPL (Andalib et al. 2006, Craig et al. 2002, Kolte et al. 2015, Li et al. 2012, Mevorach-Zussman et al. 2012, Nakano et al. 2013, Rowsell et al. 2001, Stirtzinger and Robinson 1989, Sugiura-Ogasawara et al. 2002, Sugiura-Ogasawara et al. 2013, Toffol et al. 2013). However, whether this impacts future pregnancy outcomes is less clear. A study of 61 Japanese women with RPL showed that depression increased the risk of subsequent pregnancy loss in RPL patients (Sugiura-Ogasawara et al. 2002). Another study showed higher stress levels among women with RPL (N=45) than controls (N=40), but also that higher stress levels were associated with a better chance of live birth in the first pregnancy after referral for women with RPL (Li et al. 2012).

We have described differences in perceived stress and major depression between 301 newly referred patients with RPL and 1813 participants in the Soon Parents Study (Kolte et al. 2015). Compared with the Soon Parents Study participants, significantly more RPL patients fulfilled the criteria for major depression; 8.6% (N=26) vs. 2.2% (N=40); adjusted OR 5.53 (95% CI: 2.09; 14.61), using the Major Depression Inventory (MDI). Furthermore, significantly more patients had a high perceived stress level on the Perceived Stress Scale (PSS): 41.2% (N=124) versus 23.2% (N=42) in the comparison group, adjusted OR 1.59 (95% CI: 1.03; 2.44) (Kolte et al. 2015).

The present study is a follow-up study of the RPL patients in the above-mentioned study. Our primary research questions are: 1) Is major depression or increasing scores on the perceived stress scale predictors

for outcome of first pregnancy after referral? 2) Does a pregnancy ending with a live birth after referral decrease scores on the MDI or the PSS one year after referral compared with scores at referral? 3) Are there differences in reported stress and depressive symptoms between women with a child before RPL (secondary RPL) and women with RPL without a previous live birth (primary RPL)? 4) Does mode of conception impact psychometric scores?

Materials and methods

The present study is a follow-up study of a previous publication, where the cohort is described in detail (Kolte et al. 2015). The cohort consists of 301 patients who had experienced ≥3 consecutive pregnancy losses (early miscarriages or non-visualized pregnancy losses) before referral to the Danish RPL Unit at Copenhagen University Hospital, Rigshospitalet. One year after referral, all participants received a follow-up questionnaire with the MDI and Cohen's PSS as well as supplementary questions regarding pregnancies after referral. The clinical staff in the RPL Unit was not informed about individual patients' participation in the study, so medical investigation and treatment was not influenced by the study. Patients were offered referral to their general practitioner based on their psychometric scores by AMK, but no psychological treatment was offered at the RPL Unit. Information on whether patients received treatment for mental distress was not gathered.

The MDI is a validated and widely used scale of self-reported depressive symptoms. The scale comprises 10 items on a 6-point Likert scale. Scores range from 0 (no depression) to 50 (extreme depression). The scale corresponds directly with the ICD-10 definition of depression and with the DSM-IV definition of major depression, including an additional question on low self-esteem. The scale and the classification system are described in detail elsewhere (Olsen et al. 2003). The PSS is a validated scale of perceived stress, designed to measure how uncontrollable, unpredictable and overwhelming respondents find their lives. It contains 10 items on a 5-point Likert scale, and scores range from 0 (no stress) to 40 (extreme stress). Usage and

calculation of scores are described elsewhere (Cohen et al. 1983, Cohen and Williamson 1988). The PSS is not a diagnostic tool and comparisons can only be made between individuals in a given study.

From the Danish RPL Unit's database we extracted information on patients' routine medical investigations at referral. As 'abnormal findings' in the medical work-up we included uterine abnormalities, karyotype abnormalities (patient and partner), cycle length (shorter than 21 days or longer than 34 days) and presence of lupus anticoagulant.

We dichotomized outcome of pregnancies after referral into 'live birth' or 'no live birth'. Women who were pregnant at time of follow-up were allocated based on the outcome of that pregnancy. Women who did not become pregnant in the first year after referral were not included in the analyses of pregnancy outcomes after referral. Pregnancies and deliveries were divided by mode of conception (spontaneous conception or conception after medically assisted reproduction (MAR) treatment.

Non-respondent analysis

We wanted to evaluate whether there were any systematic differences between respondents and non-respondents of the second questionnaire. Therefore, we compared number of live born children before and after referral; number of pregnancy losses before referral; outcome of pregnancies in the first year after referral, number of women who did not become pregnant after referral; MDI and PSS scores at referral; age; education; household income; country of origin; working or unemployed; daily smoking and alcohol intake between respondents and non-respondents of the second questionnaire. These data were drawn from the first questionnaires and the RPL Unit's database.

Statistics

Normally distributed parameters were compared with Student's T-test, presented as mean differences and 95% confidence intervals (95% CI). If Levene's Test for Equality of Variances was significant ($p<0.05$), equal variances were not assumed. For non-normally distributed parameters, we used the Mann-Whitney U Test

with results presented as the test value *U* and p-values. Distributions of scores were evaluated by visual inspection. P-values <0.05 were considered significant.

For binary outcomes we used the χ^2 test and logistic regression as appropriate.

Major depression was analysed as a dichotomous independent variable with live birth as the dependent variable. In a separate analysis, we analysed PSS scores at referral as a continuous independent variable with live birth as the dependent variable. We ran both unadjusted logistic regression analyses and analyses adjusted for number of pregnancy losses before referral and maternal age. As we previously found that MDI and PSS scores were correlated (Kolte et al. 2015), we chose to do separate analyses and not include both MDI and PSS in the same logistic regression analysis.

All statistical analyses were performed using IBM Statistical Package for Social Sciences, version 22 (IBM, Armonk, New York, USA).

Results

Of the 301 participants in the original study 5 were lost to follow-up (2%). Of the remaining 296 women, 64 (22%) did not become pregnant in the first year after referral. The first pregnancy after referral ended as a pregnancy loss for 130 women (56%) and in a live birth in 102 cases (44%). During the first year after referral, 72 women (31%) had only experienced one or more pregnancy losses and 160 (69%) had a pregnancy which ended with a live birth. 185 women (61%) completed the follow-up questionnaire.

Association between medical investigations and MDI and PSS scores at follow-up

Among the 185 respondents of the second questionnaire 112 (61%) had a normal medical work-up; 40 (21%) had an incomplete work-up; 5 (3%) had an abnormal karyotype, 11 (6%) had irregular menstrual cycles and 17 (9%) had an abnormal uterine anatomy. None of the participants were positive for the lupus anticoagulant. Compared with all respondents of the first questionnaire there were no statistically

significant difference in the percentages of the different abnormal results, nor the percentage of women with normal or abnormal results (data not shown).

There was no association between abnormal results of medical investigations and psychometric scores at follow-up, neither for each abnormal result nor for all abnormal results combined, see supplementary table 1.

Mode of conception and emotional distress

Women who had conceived by medically assisted reproduction (in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and/or insemination) at least once before referral did not have significantly different mean scores on neither the MDI nor the PSS than women who had conceived spontaneously (supplementary table 2).

Predictive value of MDI and PSS scores at referral

Among women with major depression at referral, 23 (89%) became pregnant in the first year after referral, which was comparable to the rest of the cohort, of which 209 (77%) became pregnant, p=0.22. In the first pregnancy after referral, 16 (70%) of the women with major depression had a live born child vs. 114 (55%) in the rest of the cohort; adjusted OR (95% CI) for live birth: 1.71 (0.66; 4.44). Thus, major depression was neither a predictor for obtaining a pregnancy, neither for the chance of live birth in the first pregnancy after referral. At referral, 122 women reported high stress levels, defined as >18 on the PSS. Of these, 98 (80%) obtained a pregnancy in the first year after referral. Among women with lower self-reported stress levels, 134 (77%) became pregnant, p=0.50. Likewise, PSS scores at referral did not impact the likelihood of a live born child in the first pregnancy after referral; adjusted OR (95% CI) for live birth: 0.98 (0.94; 1.02) for each step of increased PSS score (Table 1).

Changes in MDI and PSS scores according to outcome

Among women who had a child after referral (n=100), both MDI and PSS scores were significantly lower at follow-up than at referral: MDI scores mean (SD): 13.45 (11.05) versus 11.04 (11.07), difference -2.41 (95% CI -4.60; -0.23) and PSS scores: mean 17.69 (7.59) versus 13.03 (6.83), difference -4.66 (95% CI -6.04; -3.28). This was not observed for the patients who did not have a live birth (n=58) or did not become pregnant in the first year after referral (n=27) (Table 2).

MDI and PSS scores according to live born children before referral

Fewer women with secondary RPL fulfilled the criteria for major depression at referral than those with primary RPL: 7 (5%) vs. 19 (12%), p=0.04. Mean scores on the PSS were not statistically significantly different; secondary RPL: Mean score 16.04 (SD 6.42), primary RPL: Mean score 17.28 (SD 7.40); mean difference 1.23 (95% CI -0.36; 2.89).

At follow-up women with primary RPL had a significant decrease in scores on the MDI, mean difference (95% CI) -3.11 (-5.55; -0.67), which women with secondary RPL did not report, mean difference 0.55 (-1.78; 2.88). The difference between the groups was significant: -3.66 (95% CI: -7.05; -0.26). Both groups had a significant decrease in reported stress levels, -3.48 (-5.00; -1.96) and -1.98 (-3.40; -0.55), respectively. The difference between the groups was not statistically significant, mean difference -1.50 (-3.60; 0.60), see also Table 3.

Non-respondent analysis

Significantly more of the non-respondents of the second questionnaire had not achieved a pregnancy in the first year after referral, compared to the respondents. However, significantly more of the non-respondents' pregnancies in the first year ended in a live birth (81% vs. 63%, p=0.006).

Non-respondents were more often of non-Danish ancestry, had a shorter education and lower household income. All other investigated parameters were comparable in the two groups, including MDI and PSS scores at referral (Supplementary Table 3).

Discussion

In this study of women with RPL we did not demonstrate a prognostic impact on reproductive outcome of symptoms of depression or perceived stress. Having a live born child after referral decreased both depressive symptoms and reported stress levels in this cohort.

Pre-natal or pre-conception mental illness, as well as obstetrical complications and stressful events may be risk factors for post-partum depression (O'Hara and McCabe 2013). Therefore, it may seem paradoxical that we find lower scores on the MDI among women who have a child after referral than among women who do not. To us this suggests an association between their at referral unfulfilled wish to have a child and emotional distress, which is seemingly alleviated by a live born child. This is further supported by our finding of a lower prevalence of symptoms of major depression among women with secondary vs. primary RPL. It is however a limitation that we do not have information on whether the women with depressive symptoms or high stress levels at baseline subsequently received treatment. Our study would have benefited from a comparison group of women without RPL who were also trying to conceive. This was unfortunately not available.

To our knowledge, there have not been published other studies which have investigated the impact of a live birth on maternal mental health among women with RPL. A systematic review on women who conceived after ART did not show significantly higher self-reported depressive symptoms compared with women who conceived spontaneously (Ross et al. 2011). In contrast, a Danish register-based study showed that a live birth is a risk factor for depression among women who have undergone ART treatment, especially in the first 42 days after delivery (Sejbaek et al. 2015). It should however be noted that as the Sejbaek et al study is register based, only clinical depressions treated at a psychiatric department are included and the study population is also different. Major depression can be defined as “A period of two weeks or longer during which there is either depressed mood or loss of interest or pleasure, and at least four other symptoms that reflect a change in functioning” (National Institute of Mental Health 2018). The

MDI was developed specifically to cover the diagnostic criteria in both the European ICD-10 and the North American DSM-IV definitions of depressive disorders (Olsen et al. 2004). Online questionnaires have benefits in that they are easy to administer; the participants can access them when it is convenient for them and they do not have to return an answer sheet by post or come to a scheduled appointment. However, the inability for the researcher to control when the questionnaire is completed may be a limitation. Questionnaire based studies have inherent limitations due to e.g. recall bias, response bias, a desire to be a good 'subject' etc. However, the MDI has been validated against the WHO-recommended Present State Examination (PSE) diagnostic interview, where it showed both high sensitivity and specificity (Bech et al. 2001, Olsen et al. 2003).

As the questionnaires were sent out before the first consultation at the RPL unit and precisely one year later, the time span between pregnancies and psychometric measurements will have varied. A study where administration of questionnaires is timed by pregnancies would be interesting, but unfortunately not possible in the setting of the present study. Face-to-face interviews in addition to the online questionnaires would have provided important information and studies of the women's partners are sorely lacking.

Stress and depression are major causes of personal hardship as well as societal expenses (Marcus et al. 2012) and maternal stress may have negative effects on the future health of her unborn child through fetal programming (Babenko et al. 2015). Depression has been associated with non-communicable disease such as heart disease (Nicholson et al. 2006), perhaps through a pro-inflammatory state causing both depression and cardiovascular disease (Wright et al. 2014). This is supported by the association between depression and circulating levels of pro-inflammatory cytokines, most notably interleukin-6, tumor necrosis factor α and c-reactive protein (Dowlati et al. 2010, Kohler et al. 2017).

Sporadic pregnancy losses as well as RPL have likewise been associated with an increased risk of cardiovascular disease, with immunological and endocrinological disturbances proposed as causal factors (Oliver-Williams et al. 2013). Decreased vagal tone, manifested by diminished heart rate variability has

been demonstrated among women with stress and depression (Kim et al. 2005) and is associated with increased cardiac mortality (Makikallio et al. 2001). Decreased heart rate variability has been demonstrated among women with RPL (Kataoka et al. 2015). In this study, indices of lower heart rate variability were also associated with scores on the Kessler-6 and the perinatal grief scale among women with RPL. The results from these studies highlight the emerging and complex interplay between inflammation, cardiovascular health, mental disease and reproductive failure (Frazier et al. 2018, Nakamura et al. 2008, Raison et al. 2006). Maternal immune tolerance of the fetus is essential for a successful pregnancy and evidence is gathering that stress in all forms may influence the necessary adaptive changes, deregulating this complex system, as reviewed by Nepomnaschy et al. (Nepomnaschy et al. 2007). It would have strengthened our if we had had biological markers of emotional distress, making it possible to investigate the role of the hypothalamic-pituitary-adrenal axis in RPL and the interaction with emotional distress.

Our results are conflicting with a previous study of 61 women where depression led to a higher risk of loss in the next pregnancy (Sugiura-Ogasawara et al. 2013). Their study of 61 women with two prior miscarriages used a different scale to investigate depressive symptoms, namely the SCL-90R and combined with semi-structured interviews. They had a 22% miscarriage rate in the next pregnancy and found that miscarriage was significantly associated with depressive symptoms on the SCL-90R (Sugiura-Ogasawara et al. 2002). In their publication from 2012, Li et al. found that women with RPL who had a live birth in the next pregnancy after assessment scored lower in the positive affect domain of the Positive and Negative Affect Schedule (PANAS) than those who miscarried again, indicating that symptoms of depression increased the likelihood of a live birth (Li et al. 2012). The authors also measured NK cell numbers and cortisol but found no correlation with self-reported emotional distress. The authors conclude that moderate stress may improve outcome after RPL. There can be multiple reasons why our results differ from other published studies; populations, screening tools, definitions of RPL, study design, follow-up length and study size all differ.

It seems clear that large, well-planned studies on pregnancy outcomes, major depression, perceived stress and later risk of non-communicable disease, especially coupled with measurements of biomarkers before, during and after pregnancy are sorely lacking in women with RPL.

To our knowledge, our study is by far the largest study of stress, depression, RPL and subsequent outcomes, but is still limited by the number of included patients. Follow-up of the group of women who did not respond to the second questionnaire was based solely on information in the RPL Unit's database and could therefore be incomplete. However, in the group of respondents of the second questionnaire there were no significant discrepancies between the information proved by the patients and that in the database (data not shown). Therefore, we found it reasonable to include the non-respondents' data in the analysis of pregnancies after referral. The results of the non-respondent analysis indicate that they may have had less contact with the RPL Unit in the intervening year as they 1) were less likely to have been pregnant and 2) were more likely to have had a birth in the year after referral. There may also be a socio-demographic aspect as they were more likely to have an immigrant background and a lower socio-economic position than respondents.

In conclusion, we found that major depression and perceived stress among women with RPL were not predictors for chance of live birth after referral. Women who had a positive pregnancy outcome had lower levels of self-reported stress and depressive symptoms after one year. More longitudinal studies with repeated measurements of emotional distress are needed to firmly conclude the putative impact of emotional distress on outcome after RPL and the risk of post-partum emotional distress in this patient group. Future longitudinal studies would benefit from including face-to-face interviews, the women's partners, measurements of biomarkers such as TNF-α, IL-6, CRP and cortisol.

Authors' roles

AMK initiated and performed the study, performed all statistical analyses and wrote the paper. LRO provided the questionnaires, contributed to data interpretation and critically revised the manuscript. OBC and LS contributed to data interpretation and critically revised the manuscript. HSN supervised AMK in data analysis, participated in data interpretation and critically revised the manuscript. All authors approved the final manuscript.

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Conflicts of interest

None declared.

Ethics approval

According to Danish legislation, questionnaire studies are exempt from IRB approval. The Danish RPL Unit's database is approved by the Danish Data Protection Agency, registration number 2009-41-3686.

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Author bio

Astrid Marie Kolte is a medical doctor and obtained her PhD on recurrent pregnancy loss in 2016. She is currently a postdoctoral researcher at Copenhagen University Hospital Rigshospitalet. She has published on several aspects in recurrent pregnancy loss such as stress, depression, immunology, genetics and evolution.

Tables

Table 1 - Chance of live birth in the first pregnancy after referral according to Perceived Stress Scale (PSS) and Major Depression Inventory (MDI) scores at referral

	Unadjusted analysis, OR (95% CI)	Adjusted analysis, OR (95% CI)[b]
PSS score[a]	0.98 (0.95;1.02)	0.98 (0.94; 1.02)
Major depression on MDI	1.91 (0.75; 4.82)	1.71 (0.66; 4.44)

[a]Per step increase
[b]Adjusted for age and number of pregnancy losses prior to referral

Table 2 - Changes in Perceived Stress Scale (PSS) and Major Depression Inventory (MDI) mean scores at referral and one year later depending on pregnancy outcomes within the first year after referral

	Referral *Mean (SD)*	Follow-up *Mean (SD)*	Mean difference (95% C.I.)[a] *Referral vs. follow-up*
Perceived Stress Scale			
Live birth (N=100)	17.69 (7.69)	13.03 (6.83)	-4.66 (-6.04; -3.28)
Only pregnancy losses (N=58)	16.91 (7.18)	15.93 (7.28)	-0.98 (-2.89; 0.92)
No pregnancies (N=27)	13.93 (7.25)	14.15 (7.96)	0.22 (-2.27; 2.72)
Major Depression Inventory			
Live birth (N = 100)	13.45 (11.05)	11.04 (11.07)	-2.41 (-4.60; -0.23)
Only pregnancy losses (N 58)	12.50 (9.66)	11.74 (10.55)	-0.76 (-3.80; 2.86)
No pregnancies (N=27)	12.96 (12.19)	13.59 (11.81)	0.63 (-5.19; 6.45)

[a]Paired samples T-test

Table 3 - Changes in Perceived Stress Scale (PSS) and Major Depression Inventory (MDI) mean scores at referral and one year later depending on type of recurrent pregnancy loss (RPL)

	Referral *Mean (SD)*	Follow-up *Mean (SD)*	Mean difference (95% C.I.)[a] *Referral vs. follow-up*
Perceived Stress Scale			
Primary RPL	17.63 (7.78)	14.16 (7.65)	-3.48 (-5.00; -1.96)
Secondary RPL	16.01 (7.09)	14.04 (6.71)	-1.98 (-3.40; -0.55)
Major Depression Inventory			
Primary RPL	14.78 (11.82)	11.67 (11.19)	-3.11 (-5.55; -0.67)
Secondary RPL	11.04 (8.98)	11.58 (10.82)	0.55 (-1.78; 2.88)

[a]Paired samples T-test