

Infertile women who screen positive for depression are less likely to initiate fertility treatments

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STUDY QUESTION: Are infertile women who screen positive for depression less likely to initiate infertility treatments?

SUMMARY ANSWER: Infertile women who screen positive for depression are less likely to initiate treatment for infertility.

WHAT IS ALREADY KNOWN: Infertility imposes a psychological burden on many couples. Depression and anxiety have been demonstrated in ~40% of infertile women, which is twice that of fertile women. Further, the psychological burden associated with infertility treatment has been cited as a major factor for discontinuation of infertility care.

STUDY DESIGN, SIZE, DURATION: Prospective, observational study in a clinical-based cohort of 416 women who completed a questionnaire after the new patient visit, from January 2013 until December 2014 inclusive.

PARTICIPANTS/MATERIALS, SETTING, METHODS: All new female infertility patients ($n = 959$) seen between January 2013 and December 2014 at University of North Carolina Fertility received an electronic questionnaire to screen for mental health disorders and to evaluate their perception of mental health disorders on infertility.

MAIN RESULTS AND THE ROLE OF CHANCE: Of 959 surveys sent, 416 women completed the questionnaire (43%). The prevalence screening positive for depression, using the NIH PROMIS screening tool, was 41%. Sixty-two percent of all women initiated infertility treatment, and of these, 81% did so within 4 months. In multivariate analysis, women who screened positive for depression had 0.55 times the odds of initiating treatment for infertility (95% CI: 0.31–0.95). Similarly, women who screened positive for depression had 0.58 times the odds of initiating infertility treatment within 4 months (95% CI: 0.35–0.97), which was the time of censoring from the most recent patient evaluated. Women who screened positive for depression were less likely to pursue treatment with oral medications or IVF ($P = 0.01$ and $P = 0.03$, respectively), as compared to women who did not screen positive for depression.

LIMITATIONS, REASONS FOR CAUTION: Questionnaire-based evaluations may result in a lower prevalence of psychological disorder as some participants feign emotional well-being. Although we did not identify differences in women who responded to our survey and those who did not, responder bias may still be present. In addition, infertility is a couple's disease. However, this study only included psychological evaluation of the female partner. We have no information about the women's previous treatment.

WIDER IMPLICATIONS OF THE FINDINGS: Screening for depression is important in the infertility patient population, as further evaluation and psychological interventions may improve compliance with fertility treatments, quality of life, and potentially, the overall chance of pregnancy.

STUDY FUNDING/COMPETING INTERESTS: None.

Key words: depression / depression screening / mental health / female infertility / infertility treatment

Introduction

Infertility imposes a psychological burden on many couples. Most infertile couples believe that infertility induces considerable life stress

(Mahlstedt *et al.*, 1987; Cousineau and Domar, 2007). In addition, patients with infertility are more likely to suffer from a psychiatric illness than fertile patients (Noorbala *et al.*, 2009; Domar, 2015). Specifically, depression has been demonstrated in ~40% of infertile

women, which is twice that of fertile women (Domar *et al.*, 1992; Chen *et al.*, 2004).

Although previous studies have evaluated the association between psychological disorders and infertility, the outcome of interest in these studies is traditionally pregnancy. Attempts to reduce the psychological stress associated with infertility have been associated with higher quality of life and higher pregnancy rates, but not a decrease in the rate of patient drop out (Domar *et al.*, 2015; Frederiksen *et al.*, 2015). Further, the psychological burden associated with infertility treatment has been cited as a major factor for discontinuation of infertility care (Domar, 2004; Gameiro *et al.*, 2012). Previous studies evaluating the association between depression and initiation of fertility treatments have yielded mixed results (Malcolm and Cumming, 2004; Brandes *et al.*, 2009; Eisenberg *et al.*, 2010; Lopes *et al.*, 2014). In the only evaluation in US couples, 20% of couples who did not pursue treatment after an initial evaluation for infertility cited 'emotional stress' as the primary reason and scored higher on a screen for depression than women who pursued treatment (Eisenberg *et al.*, 2010).

The objective of this study is to determine if screening positive for depression, with a brief, validated questionnaire, is correlated with pursuing treatment for infertility. No studies have prospectively evaluated time to infertility treatment initiation or differences in type of infertility treatment in women who screen positive for depression as compared to those who do not. We hypothesize that women who screen positive for depression at after the initial consultation will be less likely to initiate infertility treatment. Thus, the identification of women who would benefit from further evaluation and psychological interventions may improve compliance with fertility treatments and potentially, the ultimate outcome of pregnancy.

Materials and Methods

All new infertility patients seen between 1 January 2013 and 31 December 2014 at University of North Carolina Fertility received an electronic questionnaire to screen for mental health disorders and to evaluate their perception of mental health disorders on infertility. Women age 18–41 years who were seeking infertility treatment and had the ability to read and speak English were included in the study. Email addresses were provided by patients who consented to email correspondence. The electronic questionnaire was sent after the new patient visit at our institution (although patients may be in various stages of infertility care and treatment if they had previously seen another provider). Data regarding patients' demographic and medical information were extracted from the medical record. Estimated annual income was calculated using an income tax database by home zip code (Melissa Data, 2016).

The questionnaire was developed using a validated tool for depression and by reproductive specialists familiar with mental health disorders and infertility. Questions were generated with the objective of evaluating patient perception of mental health disorders and infertility and to screen for depression. The questionnaire included 12 questions (multiple choice or Likert scale responses) assessing patient perception of the impact mental health disorders have on infertility and identification of barriers for mental health care. Screening for depression was performed using the National Institutes of Health Patient Reported Outcomes Measurement Information System (PROMIS) 4-item short form (Pilkonis *et al.*, 2011). This validated measure includes four questions, each with a Likert scale, and standardized method for scoring (see Supplementary Table S1). Possible scores are integers, between 4 and 20. Depression was dichotomized, per scoring protocols, as present when a subject scored more than

8 on the NIH PROMIS depression short form. The survey also included further questions regarding some demographic information (race, marital status, education level) and pregnancy and fertility history. The questions were reviewed by physicians for content and by non-physicians for clarity.

Subjects were prospectively evaluated via chart review to determine the timing of initiating treatment for infertility. Time to treatment was defined as months from initial new patient consultation to initiation any of the following infertility treatments: fertility medications, intrauterine insemination, IVF or fertility surgery. Only women who had treatment recommended by their physician were included in the analysis (for example, if expectant management was recommended, women were excluded). In order, to take into account patients who were most recently seen, treatment was dichotomized for analysis as both (i) initiation of any infertility treatment and (ii) initiation of any treatment within 4 months (as censoring occurred at 4 months from the most recently seen patient).

Statistical analysis

Descriptive statistics were generated for all variables, and bivariate analyses were conducted using Student's *t*-test and Pearson's X^2 for continuous and categorical variables, respectively. Bivariate analyses were conducted to evaluate the differences between women who screened positive for depression and those who did not and the differences between those who pursued infertility treatment and those who did not. A logistic regression model evaluated the odds of initiating infertility treatment by status of depression screening. The full model included all variables that were associated with the exposure, a risk factor for the outcome and not on the causal pathway. A change in the effect method was used to remove variables that were not confounders. The final model included the following covariates: age, education level, BMI and duration of infertility. For modeling, age and BMI were continuous variables; education was categorized into three categories: less than a college degree, college degree and at least some graduate work; and duration of infertility was categorized into three categories: <1 year, 1–2 years and >2 years. All analyses were carried out with the use of STATA statistical software (version 13.0; StataCorp LP, College Station, TX, USA).

Ethical approval

This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Results

Of 959 surveys sent, 416 women completed the questionnaire, yielding a response rate of 43%. There were no significant demographic differences, as obtained by the medical record, between women who did and did not respond. Overall, 50% of women in this study were <35 years. Most participants were Caucasian (80%) and highly educated (86% with at least a college degree). The majority of the women were overweight (BMI > 25) or obese (BMI > 30) (58%) and had been attempting conception for more than 2 years (57%). The most common infertility diagnoses were unexplained (33%), anovulation (21%), male (17%) and diminished ovarian reserve (14%) (Table 1).

Fifty percent of women with infertility reported feeling depressed most or all of the time. The prevalence of screening positive for depression in our cohort, as determined by a positive PROMIS depression screen, was 41%. Women who screened positive for depression were more likely to be nulliparous, of a higher BMI, and with a duration of infertility more than 2 years, as compared to women without

Table I Patient characteristics overall and stratified by screening for depression.

	Overall (n = 416)	Negative depression screen (n = 174)	Positive depression screen (n = 122)	P value
Age (years)				
<35	50	50	53	
35–37	19	21	18	
38–40	15	17	12	
>40	16	12	17	0.28
Age (years)	35.1 (5.3)	34.9 (6.1)	34.6 (5.4)	0.54
Race				
Caucasian	80	82	78	
Other	20	18	22	0.40
Married	92	94	89	0.12
Education				
Less than college degree	14	10	19	
College degree	39	39	41	
At least some graduate work	47	51	40	0.93
Income				
< \$40 000 per year	9	6	14	
\$40 000–80 000 per year	30	25	38	
> \$80 000 per year	61	69	48	<0.01
BMI (kg/m ²)	27.5 (7.4)	26.7 (8.2)	29.1 (7.4)	<0.01
BMI (kg/m ²)				
<18.5	1	2	1	
18.5–24.9	41	44	34	
25–29.9	22	23	25	
>30	36	32	41	0.25
Parous	54	71	30	<0.01
Prior pregnancy loss	41	38	45	0.26
Infertility diagnosis				
Unexplained	33	38	30	
Anovulation	21	22	22	
Male	17	17	16	
Diminished ovarian reserve	14	14	13	
Other	15	9	19	0.30
Duration of infertility				
<1 year	10	12	5	
1–2 years	33	37	29	
>2 years	57	51	66	0.02

Data are mean (SD) or %.

depression (Table I). No difference in infertility diagnosis was detected between women who did and did not screen positive for depression.

After the initial new infertility consultation, 62% of women initiated infertility treatment. Of those that did initiate treatment, the mean time to treatment was 3 months. Eighty-one percent of women who initiated treatment did so within 4 months of initial evaluation. Women who initiated treatment were more likely to be <35 years of age, Caucasian, married, parous and with a normal BMI as compared to women who did not ever initiate treatment (Table II). In addition, diagnosis significantly differed between women who pursued treatment and those who

did not ($P = 0.04$), with women who pursued treatment more commonly having a diagnosis of anovulation and male factor infertility.

Thirty-six percent of women who screened positive for depression initiated infertility treatments, as compared to 64% of women without depression ($P = 0.02$). Of women who did initiate fertility treatments, women who screened positive for depression were significantly less likely to pursue treatment with oral medications or IVF as compared to women who screened negative (Table III). In multivariate analysis, after adjusting for age, education level, BMI and duration of infertility, women who screened positive for depression had 0.55 times the odds of

Table II Unadjusted associations between each patient characteristic and initiation of fertility treatment.

	No fertility treatments (n = 155)	Initiated fertility treatments (n = 257)	P value
Age (years)			
<35	39	57	
35–37	18	20	
38–40	19	13	
>40	26	10	<0.01
Age (years)	36.5 (6.1)	34.5 (5.4)	<0.01
Race			
Caucasian	68	85	
Other	32	15	<0.01
Married	84	96	<0.01
Education			
Less than college degree	21	11	
College degree	37	41	
At least some graduate work	42	48	0.08
Income			
< \$40 000 per year	15	7	
\$40 000–80 000 per year	28	30	
> \$80 000 per year	57	63	0.11
BMI (kg/m ²)	28.3 (7.1)	27.0 (7.2)	0.08
BMI (kg/m ²)			
<18.5	1	2	
18.5–24.9	35	45	
25–29.9	19	24	
>30	45	29	0.01
Parous	40	61	<0.01
Prior pregnancy loss	44	40	0.48
Infertility diagnosis			
Unexplained	30	34	
Anovulation	10	21	
Male	14	18	
Diminished ovarian reserve	22	14	
Other	24	13	0.04
Duration of infertility			
<1 year	9	10	
1–2 years	27	37	
>2 years	64	53	0.22

Data are mean (SD) or %.

Table III Fertility treatment type, stratified by screening for depression.

	Negative depression screen (n = 174)	Positive depression screen (n = 122)	P value
Oral medications	62	47	0.01
Injectable medications	30	23	0.19
Intrauterine insemination	33	25	0.17
IVF	29	19	0.03

Data are in %.

Table IV Unadjusted and adjusted odds ratios^a for patients initiating treatment for infertility who screen positive relative to those who screen negative for depression.

	Odds ratio (95% CI)
Initiating treatment	
Unadjusted	0.54 (0.32–0.90)
Adjusted ^b	0.55 (0.31–0.95)
Initiating treatment within 4 months	
Unadjusted	0.57 (0.36–0.92)
Adjusted ^b	0.58 (0.35–0.97)

^aBased on a logistic regression model.

^bAdjusted for age, duration of infertility, BMI and education level.

Discussion

Overall, screening positive for depression was common (41%) in our cohort. Women who screened positive for depression were more likely to be overweight or obese, nulliparous and with a longer duration of infertility than women who screened negative. Most women in our cohort initiated treatment for infertility. However, women with a positive depression screen were significantly less likely to initiate treatment for infertility than women who screened negative, even after adjusting for age, education level, BMI and duration of infertility.

The prevalence of a positive depression screen in our cohort (women seeking initial infertility evaluation) was 41% as determined by validated questionnaire. Similarly, a study evaluating a similar study population to ours (Caucasian and well-educated), at initial infertility evaluation (n = 448) reported a prevalence of major depressive disorder of 39.1% as determined by structured interview (Holley et al., 2015). A similar prevalence (28%) was found in infertile patients undergoing IVF (Pasch et al., 2012). The rate of a positive depression screen in our cohort is consistent with that reported studies, likely giving support for the validity of the NIH PROMIS tool in this population.

In our study, women who screened positive for depression were more likely to be overweight or obese, nulliparous and trying to conceive for over 2 years. In contrast, Holley et al. (2015) did not find a

initiating treatment for infertility (95% CI: 0.31–0.95) (Table IV). Similarly, women who screened positive for depression had 0.58 times the odds of initiating infertility treatment within 4 months (95% CI: 0.35–0.97).

significant association with depression and either duration of infertility or number of failed treatment cycles. A study by [Volgsten et al. \(2010\)](#) reported that infertile women with an anxiety or depression were more likely to be overweight (BMI > 30 kg/m²) than infertile women without psychiatric diagnosis. Given our findings that patients with obesity, nulliparity and a long duration of infertility may be more likely to have depression, careful consideration should be given to carefully screen such women for the presence of depression.

Our study revealed an association between a positive depression screen and failure to initiate infertility treatment. Previous studies evaluating the association between psychological distress and initiating treatment for infertility have been mixed. [Malcolm and Cumming \(2004\)](#) evaluated Canadian women who did not pursue infertility treatment ($n = 329$) via telephone interview, and 'emotional distress' was cited as the reason for discontinuation in only 1.2% of couples. Further, [Lopes et al. \(2014\)](#) found that Portuguese women ($n = 291$) with psychological maladjustment (as determined using the Fertility Quality of Life scale) still reported high intentions to proceed with infertility treatment. In contrast, in a large cohort of women undergoing infertility treatment in the Netherlands ($n = 1391$), [Brandes et al. \(2009\)](#) found that 45% of women dropped out before starting any form of infertility treatment after initial evaluation, with 11% citing emotional distress as the principal reason after telephone follow-up. [Eisenberg et al. \(2010\)](#) evaluated 434 couples after initial infertility evaluation and found that 13% did not undergo any treatment for infertility. Twenty percent of those not pursuing treatment cited 'emotional stress' as the reason, and a higher score on the depression screen (20-item Center for Epidemiologic Studies Depression Scale, CES-D) was correlated with not pursuing treatment. Our findings are similar as women who screen positive for depression, as determined by a validated tool, are less likely to initiate treatment for infertility in a US population. We also specifically identified that these women are significantly less likely to pursue treatment options with oral medications or IVF as compared to women who screened negative.

While emotional distress is frequently cited as a reason for discontinuation of infertility treatment, financial burden is also an important factor in many cases. The impact depression and emotional stress have on treatment decisions may best be evaluated in areas with subsidized coverage for IVF to exclude financial restrictions. In the previously discussed study by [Brandes et al. \(2009\)](#), 34% of women discontinued further infertility treatment due to emotional distress. In 974 couples from Sweden, 54% of women discontinued treatments before completion of the three covered IVF cycles, most commonly due to psychological burden (26%) ([Olivius et al., 2004](#)). Further, [Domar et al. \(2010\)](#) evaluated US women with insurance coverage for three IVF cycles ($n = 47$), with a drop-out rate of 34% before the last cycle. The most cited reason for discontinuation of care was emotional, with 39% of women reporting psychological burden and needing a break. In contrast, [Van Dongen et al. \(2015\)](#) recently evaluated Dutch couples undergoing IVF ($n = 667$) and found no association between depression (as determined by the validated SCREENIVF tool) and discontinuation of treatment, although lack of social support was associated with treatment drop-out. However, it appears that even when the financial burden of costly infertility treatment is removed, couples with a higher level of psychological stress or depression are less likely to continue with additional treatment for infertility.

Strengths of this study include the use of validated measures of psychological assessment and the prospective nature of our evaluation.

Although not previously used in an infertile population, the PROMIS depression form has been validated for use in screening for depression in diverse patient populations ([Choi et al., 2014](#); [Stone et al., 2015](#); [Schalet et al., 2016](#)). Prior studies have correlated the PROMIS short forms for depression with other standard measures of depression screening, including the Zung depression scale, the CES-D and the 9-item Patient Health Questionnaire ([Hung et al., 2015](#); [Kim et al., 2015](#)). In addition, our electronic questionnaire had a good response rate without demographic differences noted between women who did and did not respond. Our study is also the first to investigate the difference in treatment type pursued based on screening positive for depression.

Our study is not without limitations. Questionnaire-based evaluations may result in a lower prevalence of psychological disorder as some participants feign emotional well-being ([Cousineau and Domar, 2007](#)). Therefore, the true prevalence of depression in our study population may be higher than stated. In addition, infertility is a couple's disease. However, this study only included psychological evaluation of the female partner. Further, the financial strain of infertility treatment may dictate the ability to pursue treatment. However, it is difficult to account for an individual's financial status, as it may not be intrinsically tied to reported income and patients often decline to answer questions about income. We opted to include education in our model, as educational level and financial status are frequently correlated and a significant difference was seen between the educational levels in women with and without depression in our cohort. In addition, many women present to a fertility clinic at different time periods in their fertility journey. Although we evaluated patients for depression after the new patient visit, it is important to note that women may have pursued infertility evaluation or treatment before presenting to us for care. Thus, we are truly evaluating the association between screening positive for depression and the initiation of fertility treatments at a new clinic. In addition, no correction was made for multiple comparisons.

In summary, our study reveals that infertile women who screen positive for depression are less likely to initiate treatment for infertility. As the relationship between infertility and depression is complex, better understanding of the lasting impact of depression on infertility is crucial. As women with a positive depression screen are less likely to initiate infertility treatment, the importance of provider evaluation at initial visit should be stressed. Although screening positive for depression is not equivalent to a clinical diagnosis of depression, appropriate screening for depression will help to identify women who may benefit from further evaluation and psychological interventions which may improve compliance with fertility treatments, thus helping to achieve the ultimate goal of pregnancy.

Supplementary data

Supplementary data are available at [Human Reproduction online](#).

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Author's roles

N.M.C. provided contributions to design, data analysis and interpretation, manuscript drafting, revising and final approval of the version to be submitted for publication. H.S.H. provided contributions to data analysis and interpretation and manuscript revision and final approval of the version to be submitted for publication. J.E.M. provided contributions to design, data analysis and interpretation, critical manuscript revising and final approval of the version to be submitted for publication.

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Conflict of interest

All authors have no conflicts of interest to disclose.

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