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ORIGINAL ARTICLE ***Infertility***

Fertility-related quality of life from two RCT cohorts with infertility: unexplained infertility and polycystic ovary syndrome

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STUDY QUESTION: Does fertility-related quality of life (FertiQOL) differ by infertility diagnosis between women with polycystic ovary syndrome (PCOS) and their partners, compared with couples with unexplained infertility (UI)?

SUMMARY ANSWER: Women with PCOS report lower QOL than those with UI, whereas males with UI report lower QOL than males with PCOS partners.

WHAT IS KNOWN ALREADY: The fertility-specific QOL survey, FertiQOL, has been used to examine fertility-related QOL in a number of worldwide cohorts. Few data have addressed fertility-related QOL as a function of infertility diagnosis. Overall, men report better QOL than women with infertility, and there is variation in FertiQOL scores across different samples from different countries.

STUDY DESIGN, SIZE, DURATION: This was a prospective, cohort study derived from two concurrent, randomized clinical trials, and designed to examine QOL in infertile females with PCOS and UI at the time of enrollment compared with each other and their male partners; to compare concordance FertiQOL scores in this study across other worldwide cohorts; and to determine if baseline FertiQOL was associated with pregnancy outcome.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with PCOS and their partners ($n = 733$ and $n = 641$, respectively), and couples with UI ($n = 865$ women and 849 men) completed a validated fertility-specific QOL survey (FertiQOL) at the time of the study screening visit. PCOS women were randomized to either clomiphene citrate or letrozole treatment; couples with UI were randomized to clomiphene citrate, letrozole or gonadotrophin plus IUI. FertiQOL results were compiled by diagnosis (PCOS or UI) and compared by diagnosis and sex using Wilcoxon Rank-Sum testing. Relationships between baseline FertiQOL and pregnancy outcomes were examined using logistic regression. Multivariable models were performed to assess the association between FertiQOL scores and key participant characteristics.

MAIN RESULTS AND THE ROLE OF CHANCE: Women with PCOS had lower total FertiQOL scores (72.3 ± 14.8) than those with UI (77.1 ± 12.8; $P < 0.001$); this was true for each domain (except Relational). These differences were largely explained by variation in BMI, hirsutism, household income and age. Women had lower overall FertiQOL scores than their male partners. Males with PCOS partners had higher scores than males with UI (84.9 ± 10.2 versus 83.3 ± 10.8; $P = 0.003$). Scores were not consistently associated with conception or pregnancy outcome.

LIMITATIONS, REASONS FOR CAUTION: The use of multiple tests of association may have resulted in spurious statistically significant findings. Inherent sociodemographic differences between women with PCOS and those with UI largely account for the lower QOL in women with PCOS. Our study was unable to assess if changes in QOL affected pregnancy outcome as FertiQOL data were collected prior to treatment. Finally, the participants for both studies represent their local communities, but are not a population-based sample and thus firm conclusions about how representative these couples are to the general population must be made with caution.

WIDER IMPLICATIONS OF THE FINDINGS: Women with PCOS with elevated BMI and hirsutism scores and with lower socioeconomic status may require more, targeted psychosocial support than those with other diagnoses. Possible attribution of infertility to the male partner appears to result in a lower QOL. There appears to be substantial national variation in FertiQOL scores, with US-based cohorts reporting overall higher QOL.

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Introduction

Evidence supports the notion that infertility causes substantial personal distress (Menning, 1982; Mahlstedt, 1985; Greil, 1997; Schmidt *et al.*, 2005; Verhaak *et al.*, 2007; Peterson *et al.*, 2014). Fertility treatments compound stress levels by being time-consuming, expensive, requiring invasive procedures and raising a couple's expectations. The ability for couples to maintain a loving, mutually supportive relationship while enduring treatment depends, in part, on their ability to successfully address these substantial burdens (Tao *et al.*, 2012).

One way to gain knowledge about the stress imposed by infertility is by assessing quality of life (QOL). QOL, as defined by the World Health Organization, refers to: 'an individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' (Group, 1998; Skevington *et al.*, 2004). QOL instruments specific for a single fertility-related disease state (such as polycystic ovary syndrome [PCOS] or endometriosis) (Jones *et al.*, 2011; Bourdel *et al.*, 2015) have the advantage of assessing distressors specific to that particular diagnosis, but they cannot be used to compare QOL between women or couples with different diagnoses. There is contradictory evidence about the degree to which men and women's QOL is affected by an infertility diagnosis and treatment. Some evidence indicates that women report a lower QOL than men (Nachtigall *et al.*, 1992; Tuzer *et al.*, 2010; Hsu *et al.*, 2013; Huppelschoten *et al.*, 2013), while others find that men and women with infertility have similar QOL (Abbey *et al.*, 1991; Peronace *et al.*, 2007; Chachamovich *et al.*, 2009). The effect of an infertility diagnosis on men has been evaluated in several studies (Mousavi *et al.*, 2013). Men who are known to have infertility have been shown to report more negative emotion and have a greater sense of loss and stigma than men whose wives are known to be fertile (Nachtigall *et al.*, 1992), and to report a lower personal QOL if they had male factor infertility as opposed to unexplained or female factor (Smith *et al.*, 2009). Others have not demonstrated differences in QOL measures by male infertility diagnosis (Lee *et al.*, 2001; Holter *et al.*, 2007).

Poorer psychological function as measured by QOL has overall not been found to relate to a worse reproductive outcome in most studies (Domar *et al.*, 2015), but the topic remains controversial, with some studies reporting significant relationships between emotional distress and poor outcomes (Matthiesen *et al.*, 2011) and others reporting no relationship (Boivin *et al.*, 2011a). A recent systematic review indicated that further evaluation of psychosocial interventions to improve QOL during treatment was warranted, since stress is a modifiable factor and might be amenable to simple and inexpensive interventions that could improve prognosis (Frederiksen *et al.*, 2015).

The fertility-related QOL (FertiQOL) survey is a behavioral instrument specifically designed to assess the burden of infertility in men and women who are experiencing fertility problems (Boivin *et al.*, 2011b). One of its advantages is that it is not limited to a single diagnosis, as it was developed to be a comprehensive instrument useful for study in multiple populations worldwide (Boivin *et al.*, 2011b). The initial FertiQOL

was validated by an international infertility clinic sample (291 women and 75 men), and an online sample of 1014 women and 34 men (Boivin et al., 2011b). A subsequent Dutch sample of 583 women provided further validation (Aarts et al., 2011). Cronbach reliability statistics for the Core FertiQOL were 0.72 and for the Dutch validation study 0.72–0.91. Overall, 783 US-based infertility patients have been assessed to date; almost all have been female (Boivin et al., 2011b). Limited data exist assessing fertility-related QOL in males and females with either unexplained infertility (UI) or PCOS. It is important to understand whether there are diagnosis-specific differences in QOL to allow for optimal support of patients with infertility.

Using the FertiQOL, we sought to examine the impact of infertility in a cohort of over 3000 US-based participants in the NIH-funded Reproductive Medicine Network (RMN). Two concurrently collected cohorts were studied: (1) all men and women participating in the Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) trial and, (2) all men and women participating in the Assessing Multiple Intrauterine Gestations From Ovarian Stimulation (AMIGOS) trial. We sought to evaluate whether FertiQOL scores differed by the couples' diagnosis (PCOS or UI), whether women and men had consistent differences in their FertiQOL scores in the two cohorts, and whether FertiQOL scores at enrollment had any relation to pregnancy outcomes. We hypothesized that women with PCOS would report overall lower fertility-related QOL than women with UI, that men would report greater fertility-related QOL than women in both cohorts and that fertility-related QOL at baseline would not have a relationship to pregnancy outcomes.

Materials and Methods

Overview of the conduct of RMN trials

The RMN, begun in 1990, carries out large, multicenter clinical trials of diagnostic and therapeutic interventions for male and female infertility and reproductive diseases and disorders. The Network is funded through the National Institute of Child Health and Human Development's Fertility and Infertility (FI) Branch and comprises seven main (primary) research sites, seven ancillary sites and a data coordinating center. Each primary Reproductive Medicine Unit is linked to an associated ancillary site, and these have a broad geographical distribution across the USA. The RMN's structure allows investigators to test hypotheses in large numbers of patients who are enrolled in common protocols at multiple centers. This method produces answers more rapidly than would be possible by individual sites working alone. All RMN clinical trials undergo approval prior to implementation by both a National Institutes of Health–appointed Advisory Board and a Data and Safety Monitoring Board. The Data and Safety Monitoring Board provides oversight during the conduct of the study.

For both trials, couples were recruited from the local practices at each academic center's clinical site, combined with radio and newspaper advertising. Respondents were screened for eligibility with a brief telephone interview that was standardized across all sites. Eligible couples were then invited for a formal screening visit, at which time written informed consent was obtained and study questionnaires were collected. This strategy resulted in samples that are roughly representative of their communities.

Ethical approval

All protocols were approved by the Institutional Review Boards at each clinical site and each participant provided written informed consent for their participation in the study.

Data collection

Data from the screening visits for potential participants were used for this study. Couples were screened for eligibility and provided informed consent for the intended clinical trial after their diagnosis was confirmed using specific study criteria (see below). All questionnaires reported in this study were completed at the time of the screening visit. All eligible participants in both RMN trials (and their male partners) were asked to complete the FertiQOL (Boivin et al., 2011b), the Short Form-36 (SF-36) (Ware et al., 1993) and Primary Care Evaluation of Mental Disorders (PRIME-MD) (Spitzer et al., 1999) questionnaires. Only data from the FertiQOL is reported herein, as addition of these two additional questionnaires did not change any of the major findings (unpublished data). The same clinical sites recruited for each of the two studies using similar methods and thus both sets of participants were sampled from the same clinical population base. We have previously published some of the baseline data from these questionnaires as well as the baseline characteristics of the two study populations (Legro et al., 2012; Diamond et al., 2015b).

Concurrent Trial #1

This trial was limited to women with PCOS and their partners. The trial was designed to test whether letrozole was a superior treatment to clomiphene citrate for ovulation induction and achievement of a live birth in women with PCOS (Legro and Zhand, 2014). Seven hundred fifty female participants and their partners enrolled into the PPCOS II trial. Of these, 733 women (97.7%) and 641 men (85.5%) completed the questionnaires. Enrollment criteria for the PPCOS II trial have been previously reported (Legro et al., 2012). The following inclusions had to be met for enrollment: aged 18–39 years, confirmed diagnosis of PCOS (defined by the modified Rotterdam criteria; Rotterdam, 2004), and exclusion of other disorders that could mimic the syndrome, such as congenital adrenal hyperplasia, hyperprolactinemia or thyroid disease. All participants were required to have a normal uterine cavity and at least one patent fallopian tube. Male partners were required to have at least 14 million sperm per milliliter on screening semen analysis.

Participants in the PPCOS II trial were randomized to five cycles of ovulation induction with timed intercourse using one of two treatments: letrozole or clomiphene citrate. Participation rate was 71.1% (1054 patients provided consent, 750 enrolled and randomized). Participation lasted for ~24 weeks. Patients who conceived were followed through pregnancy for outcomes.

Concurrent Trial #2

This trial was limited to couples with a diagnosis of UI. The trial was designed to test whether letrozole was more effective at producing monofollicular development and therefore fewer multiple pregnancies than either clomiphene citrate or gonadotrophins, while being similarly effective to clomiphene citrate (Diamond et al., 2011, 2015a). The AMIGOS trial enrolled 900 women and their partners; 865 women (96.1%) and 849 (94.3%) men completed the questionnaires. Enrollment criteria for AMIGOS have been previously reported (Diamond et al., 2015b). Couples were required to have a diagnosis of UI as follows: aged18–40 years, one or more years of infertility history with a desire to conceive, regular ovulation (defined as nine or more menses per year), and evidence of a normal uterine cavity and at least one patent fallopian tube. Male partners were required to have at least 5 million total motile sperm in the ejaculate in a semen analysis within 1 year of study initiation.

Participants in the AMIGOS trial were randomized to one of three treatments: letrozole, clomiphene citrate or gonadotrophin treatment for the female partner for up to four treatment cycles. Participation rate was 73.6% (1222 patients provided consent, 900 enrolled and randomized). All treatment cycles were accompanied by timed IUI. Patients who conceived were followed through pregnancy for outcomes.

All couples from both concurrent clinical trials were asked to complete several psychosocial instruments at the time of screening. Because the

questionnaires were administered during enrollment (prior to treatment), only 24 of the 36 original FertiQOL items were used (Boivin *et al.*, 2011b). The complete FertiQOL questionnaire, consists of 36 items scored on a five-point Likert-type scale, is estimated to take 15–20 minutes to complete, and assesses key domains believed to be relevant to the infertility experience. The 36-item FertiQOL assesses core and treatment-related QOL as well as overall life and physical health. Mean scaled scores are available for the validation sample and for a Dutch sample of 583 patients with infertility facing medically assisted reproduction (Aarts *et al.*, 2011). Because the questionnaires were administered during enrollment (prior to treatment), the Treatment-related questions were not used. We included the Emotional, Mind/Body, Relational and Social domains of the instrument. The FertiQOL is scored from 0 to 100, with higher scores indicating better QOL (Boivin *et al.*, 2011b).

Measurements

At screening, visits were standardized across all study sites and each site used identical case report forms prepared by the RMN Data Coordination Center at Yale University. Forms and procedures for data collection were identical for both cohorts. BMI was calculated from height and weight measurements performed as the screening visit. Participants were weighed while dressed in light clothing, without shoes. Height was measured without shoes. Couples were administered a basic demographic questionnaire that collected information about educational attainment in categories (high school education or less; college education or some college; graduate level education) and income (household income $<$ or $>$\$50 000 per year). Hirsutism was assessed in all participants using the Ferriman–Gallwey hirsutism scoring scale (Ferriman and Gallwey, 1961).

Outcomes of the parent studies

The primary outcome for the PPCOS II trial was live birth. The cumulative live birth rate in the PPCOS II trial was 27.5% after letrozole administration and 19.1% for clomiphene citrate. Live birth was a secondary outcome of the AMIGOS study, as its primary outcome was the rate of multiple pregnancies. Cumulative rates of live birth in the AMIGOS study were 32.2% after gonadotrophin administration, 23.3% for clomiphene citrate and 18.7% for letrozole. Participants who conceived in both studies were followed at the clinical site for ultrasound evidence of a viable intrauterine pregnancy (fetal heart motion) and referred for obstetrical care. Information on pregnancy progress and delivery outcomes was obtained by infant and maternal medical record review.

Dropout in the parent studies

The study dropouts in both studies refer to participants who withdrew from the treatment and the trial, and were lost to follow-up in the studies. A total of 158 women (85 of 376 in the clomiphene citrate group [22.6%] and 73 of 374 in the letrozole group [19.5%], $P = 0.30$) dropped out or were excluded from the final analyses in the PPCOS II trial. There were no significant differences between treatment groups in the reason for withdrawal. Study dropout from PPCOS II was evenly distributed across the 5 months of the protocol. Similarly, 154 women dropped out or were excluded from the final analysis in the AMIGOS trial. Similar proportions and reasons for dropout were observed in the three treatment groups. Detailed information on study dropout is provided in the primary publications from both studies (Legro and Zhand, 2014; Diamond *et al.*, 2015a) and in two ancillary publications (Kuang *et al.*, 2015a,b).

Data analysis

FertiQOL scores were grouped by sex and by diagnosis (PCOS or UI). The average of all FertiQOL subsections was taken and multiplied by a raw score of 25 (Boivin *et al.*, 2011b). Means and sample variances were computed. Histograms, QQ plots and the formal test for normality for FertiQOL total and domain scores were performed. Since FertiQol scores were not normally distributed, between-group comparisons were performed using the Wilcoxon Rank-Sum Test and difference in FertiQol scores within couples was tested using Wilcoxon signed-rank method using each couple as a matched pair. Multivariable models were performed to assess the association between FertiQOL scores and key participant characteristics such as age, socioeconomic status, defined as education and reported income level, BMI, hirsutism and race. Polynomial transformations (quadratic and cubic) of the FertiQol scores were considered to achieve a closer normality of the response variable in the regression analysis. Since similar significant levels were obtained using the transformed FertiQol scores when compared with those without using the transformed scores, the results with transformed FertiQol scores were not shown for more straightforward interpretation. Logistic regression was used to assess the relationship between FertiQOL scores and pregnancy outcomes, with adjustment of treatment arms and female age. These regression models used FertiQOL scores from either women or their partners, but not both, as the response. All data were analyzed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA) in Windows 8. A two-tailed *P*-value of <0.05 was considered to be statistically significant.

Results

Characteristics of the study sample are provided in Table I. Participants in each of the two concurrent studies differed on some key variables. For example: (i) PCOS women and men were younger than those with UI, (ii) women with PCOS had a higher BMI than those with UI, (iii) overall educational attainment and household income was higher for participants with UI than for those with PCOS and (iv) PCOS participants were less likely to be White and more likely to be Hispanic than couples with UI.

FertiQOL scores among couples with PCOS (PPCOS II) compared with couples with UI (AMIGOS)

Women with PCOS had significantly lower FertiQOL scores in all domains ($P < 0.001$) except Relational when compared with women with UI (Table II). The largest between-group difference between these two cohorts was in the Emotional domain, where PCOS women scored a mean of 8.7 points lower. In contrast to the women, male partners of women with PCOS had significantly ($P < 0.05$) higher FertiQOL scores than their male counterparts with UI for the total, Emotional and Mind/Body domains (Table II). The largest score difference was found in the Mind/Body domain, where the men with UI reported a mean of three points lower than the male partners of women with PCOS. Figure 1 depicts the unadjusted relationships between QOL measures in women with PCOS and UI and their partners. FertiQOL score was not related to study dropout.

FertiQOL scores in women with PCOS and their partners

A total of 733 women and 641 men completed mean domain scores for the FertiQOL at the time of study enrollment (numbers vary due to incomplete data for some domains; Table II). Mean ($\pm$SD) domain scores for the female cohort ranged from 59.6 $\pm$ 22.4 (Emotional

Table I Subject demographic and key factors by patient group (PCOS patient or partner and UI patient and partner).

	PCOS Female	UI	*P*-value**	PCOS Partner Male	UI Partner	*P*-value**
Age, year	28.9 ± 4.3 (*n* = 733)*	32.2 ± 4.3 (*n* = 865)	<0.001	31.4 ± 5.4 (*n* = 712)	34.3 ± 5.7 (*n* = 858)	<0.001
BMI (kg/m^2)	35.2 ± 9.3 (*n* = 733)	26.8 ± 6.4 (*n* = 865)	<0.001	30.4 ± 6.9 (*n* = 698)	28.9 ± 5.8 (*n* = 841)	<0.001
F-G score	17.0 ± 8.6 (*n* = 733)	7.6 ± 5.8 (*n* = 859)	<0.001			
Level of education						
High school graduate or less	168/733 (22.9)$	68/865 (7.9)	<0.001	277/712 (38.9)	159/856 (18.6)	<0.001
College graduate or some college	480/733 (65.5)	563/865 (65.1)		380/712 (53.4)	538/856 (62.9)	
Graduate degree	85/733 (11.6)	234/865 (27.1)		55/712 (7.7)	159/856 (18.6)	
Annual household income						
<$50 000	295/733 (40.3)	143/865 (16.5)	<0.001			
≥$50 000	339/733 (46.3)	567/865 (66.6)				
Wish to not answer	99/733 (13.5)	146/865 (16.9)				
Race						
White	580/733 (79.1)	705/865 (81.5)	<0.001	555/710 (78.2)	706/857 (82.4)	<0.001
Black	95/733 (13.0)	70/865 (8.1)		114/710 (16.1)	77/857 (9.0)	
Asian	22/733 (3.0)	56/865 (6.5)		18/710 (2.5)	47/857 (5.5)	
Mixed race	27/733 (3.7)	25/865 (2.9)		14/710 (2.0)	18/857 (2.1)	
Hispanic/Latino	127/733 (17.3)	93/865 (10.8)	<0.001	140/712 (19.7)	80/858 (9.3)	<0.001
Patient had prior therapy for infertility	408/733 (55.7)	483/865 (55.8)	0.944			
How long has the patient been attempting conception (months)?	41.8 ± 38.0 (*n* = 699)	34.5 ± 25.0 (*n* = 856)	0.695			

PCOS, polycystic ovary syndrome; UI, unexplained infertility; F-G, Ferriman–Gallwey.
*Mean ± SD (*N*).
$no./total no. (%).
**A Wilcoxon rank-sum test was used for continuous variables; χ^2 or Fisher's exact test was used for categorical variables.

domain) to 80.1 ± 14.6 (Relational domain). Male partners' scores ranged from 79.3 ± 15.1 (Relational domain) to 91.7 ± 11.3 (Mind/Body domain). With the exception of the Relational domain, male partners scored higher on all other domains and in their total FertiQOL score ($P < 0.0001$ for all groups except Relational). The largest difference was observed in the Emotional domain, with women scoring 24.6 points lower than men.

FertiQOL scores among couples with UI

Table II mean domain scores in the 865 women who completed the FertiQOL ranged from 68.3 ± 18.6 (Emotional component) to 81.5 ± 13.7 (Relational component). Male partners' scores ($n = 849$) were significantly higher in every domain except Relational ($P < 0.0001$), in which case they were significantly *lower* than their female partners ($P < 0.0001$). Male scores ranged from 78.9 ± 15.2 (Relational domain) to 88.7 ± 11.9 (Mind/Body domain). As for women with PCOS and their partners, the largest difference between men and women was in the Emotional domain, with women scoring 14.5 points lower than men.

Combined FertiQOL scores between women and men in both concurrent trials

When both cohorts were combined, there were significant differences between men and women in all FertiQOL domains, with men consistently scoring higher than women (data not shown; Table II). Differences between male and female FertiQOL scores in each domain in UI patients (AMIGOS participants) were overall less than that in PCOS patients (PPCOS II participants) except relational; all differences were statistically significant ($P < 0.001$) except for the Relational domain.

Multivariable analysis

For women, the influence of age, BMI, hirsutism score, education, annual household income and race on FertiQOL scores are shown in Table III. After adjustment for these factors the differences in FertiQOL total or domain scores between women with PCOS and those with UI were no longer statistically significant. Older age ($P < 0.001$) and higher income ($P = 0.014$) were related to better QOL scores for the total FertiQOL, whereas higher BMI ($P = 0.017$) and higher Ferriman–Gallwey score ($P = 0.015$) were associated with worse QOL scores. These relationships were generally true across all domains. Educational attainment was not associated with FertiQOL scores. Male partners demonstrated a relationship between age and FertiQOL score that was similar to their female partners ($P < 0.001$) but no other variables were associated with QOL scores. After adjustment of age, the differences in male partner total and domain FertiQOL scores between men whose female partner was diagnosed with PCOS and men in couples with UI remain statistically significant, except for relational domain score (data not shown).

Table II Patient and their partner FertiQol scores for women with PCOS and couples with UI.

Variables	PCOS patient	PCOS partner	Difference (%95 CI) between patient and partner	P-value**	UI patient	UI partner	Difference (%95 CI) between patient and partner	P-value**	Difference (95% CI) between UI and PCOS patient	P-value***	Difference (95% CI) between UI and PCOS partner	P-value***
FertiQol total score	72.3 ± 14.8 (733)*	84.9 ± 10.2 (641)	−12.3 (−13.4, −11.2)	<0.0001	77.1 ± 12.8 (865)	83.3 ± 10.8 (849)	−6.3 (−29.2, 13.5)	<0.0001	4.7 (3.3, 6.1)	<0.001	−1.5 (−2.6, −0.5)	0.003
Emotional	59.6 ± 22.4 (731)	84.3 ± 15.2 (636)	−24.6 (−26.4, −22.7)	<0.0001	68.3 ± 18.6 (864)	82.7 ± 15.2 (845)	−14.5 (−45.8, −12.5)	<0.0001	8.7 (6.7, 10.7)	<0.001	−1.6 (−3.2, −0.1)	0.013
Mind/body	74.4 ± 18.5 (732)	91.7 ± 11.3 (640)	−16.8 (−18.3, −15.4)	<0.0001	80.0 ± 15.1 (864)	88.7 ± 11.9 (848)	−8.7 (−37.5, 15.0)	<0.0001	5.7 (4.0, 7.3)	<0.001	−3.0 (−4.2, −1.8)	<0.001
Relational	80.1 ± 14.6 (733)	79.3 ± 15.1 (636)	1.1 (−0.3, 2.4)	0.095	81.5 ± 13.7 (865)	78.9 ± 15.2 (847)	2.6 (−20.8, 29.2)	<0.0001	1.4 (0, 4.2)	0.113	−0.4 (−2.0, 1.1)	0.582
Social	75.3 ± 17.6 (731)	84.2 ± 13.0 (633)	−8.8 (−10.2, −7.3)	<0.0001	78.4 ± 16.1 (864)	83.0 ± 13.6 (844)	−4.7 (−33.3, 20.8)	<0.0001	3.1 (1.5, 4.8)	<0.001	−1.2 (−2.6, 0.1)	0.093

FertiQol, fertility-specific quality of life survey.
*Mean ± SD (N).
**A Wilcoxon signed-rank test was used.
***A Wilcoxon rank-sum test was used.

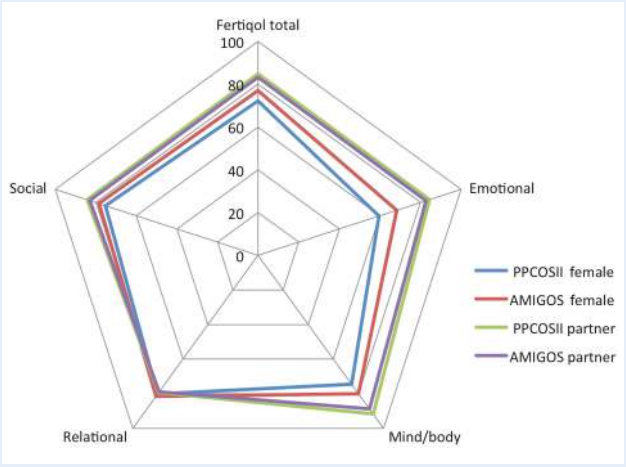

Figure 1 Polar plot of FertiQOL scores by cohort and by sex. Women with PCOS and their partners were enrolled in the PPCOS II trial. Couples with UI were enrolled in in the AMIGOS trial. Higher scores indicate better quality of life. Blue line: PPCOS II/PCOS female; red line: UI/AMIGOS female; green line: PPCOS II/PCOS partner; purple line: AMIGOS/UI partner.

FertiQOL scores in relation to duration of infertility

Associations between duration of infertility and FertiQOL scores were present only for women with PCOS (Table IV), who demonstrated a consistent, negative relationship of FertiQOL scores to length of infertility; both total FertiQOL and all domains except Relational were significantly lower in women with PCOS having a longer duration of infertility (Table IV).

FertiQOL scores in relation to pregnancy outcomes

Associations between FertiQOL scores and pregnancy outcomes with adjustment of treatment and female age differed by cohort (Table V). In women with PCOS, female Emotional FertiQOL score was positively related to both conception and singleton live birth (odds ratio (OR) for singleton live birth = 1.28, 95% CI = 1.09–1.51, $P = 0.003$; OR for conception = 1.21, 95% CI = 1.05–1.40, $P = 0.009$). In the UI cohort, female Mind/body domain score was negatively associated with singleton live birth (OR = 0.78, 95% CI = 0.63–0.97, $P = 0.022$). No other significant association was observed between FertiQOL scores and singleton live birth or conception. When patients with PCOS or UI were combined, no significant associations were found between any FertiQol scores and singleton live birth or conception.

Discussion

We have observed QOL measures in two concurrently collected cohorts, totaling over 3000 US-based patients suffering from infertility due to different diagnoses and have found that oligo-ovulatory women with PCOS had lower scores than women with UI, which were largely explained by the differences in demographics and hirsutism between the groups. Males with UI had lower scores than males partnered with

Table III Association between patient FertiQol scores and patient group, patient demographic and key factors (multivariable model analysis).*

Variables	FertiQol total		Emotional		Mind/body		Relational		Social	
	Beta (95% CI)	*P*-value	Beta (95% CI)	*P*-value	Beta (95% CI)	*P*-value	Beta (95% CI)	*P*-value	Beta (95% CI)	*P*-value
Patient group										
UI	Reference		Reference		Reference		Reference		Reference	
PCOS	−1.3 (−3.1, 0.6)	0.178	−1.8 (−4.4, 0.9)	0.200	−0.6 (−2.9, 1.6)	0.564	−1.7 (−3.6, 0.2)	0.073	−0.9 (−3.2, 1.3)	0.417
Age	0.4 (0.3, 0.6)	<0.001	0.9 (0.7, 1.1)	<0.001	0.6 (0.4, 0.8)	<0.001	−0.2 (−0.4, −0.04)	0.018	0.4 (0.2, 0.6)	<0.001
BMI	−0.1 (−0.2, −0.02)	0.019	−0.2 (−0.4, −0.1)	<0.001	−0.1 (−0.2, −0.02)	0.019	−0.02 (−0.1, 0.1)	0.665	−0.1 (−0.2, 0.1)	0.337
F-G Score	−0.1 (−0.2, −0.03)	0.012	−0.2 (−0.3, −0.06)	0.005	−0.2 (−0.3, −0.1)	0.002	0.01 (−0.1, 0.1)	0.835	−0.1 (−0.2, 0.004)	0.051
Education										
High school graduate or less	Reference		Reference		Reference		Reference		Reference	
College graduate or some college	−0.03 (−2.0, 2.0)	0.975	−0.3 (−3.3, 2.7)	0.845	−0.2 (−2.7, 2.2)	0.854	1.9 (−0.2, 3.9)	0.079	−1.3 (−3.8, 1.1)	0.289
Graduate degree	−1.8 (−4.4, 0.7)	0.151	−2.5 (−6.2, 1.2)	0.187	−0.4 (−3.4, 2.7)	0.812	0.2 (−2.4, 2.8)	0.885	−4.6 (−7.7, −1.5)	0.004
Annual household income										
<$50 000	Reference		Reference		Reference		Reference		Reference	
≥$50 000	2.1 (0.4, 3.8)	0.014	2.7 (0.1, 5.2)	0.038	3.0 (0.9, 5.0)	0.005	1.6 (−0.1, 3.4)	0.069	1.2 (−0.9, 3.3)	0.276
Wish to not answer	−0.3 (−2.5, 1.9)	0.769	0.5 (−2.7, 3.7)	0.756	0.5 (−2.1, 3.1)	0.718	−0.7 (−3.0, 1.5)	0.521	−1.7 (−4.4, 0.9)	0.206
Race										
White	Reference		Reference		Reference		Reference		Reference	
Black	−0.5 (−2.8, 1.7)	0.661	0.5 (−2.8, 3.9)	0.748	1.2 (−1.5, 4.0)	0.371	−2.4 (−4.7, −0.1)	0.043	−1.3 (−4.0, 1.5)	0.360
Asian	−2.8 (−6.0, 0.3)	0.080	0.6 (−4.0, 5.3)	0.786	−4.5 (−8.3, −0.6)	0.022	−4.9 (−8.2, −1.6)	0.003	−2.7 (−6.6, 1.2)	0.173
Others	0.2 (−3.1, 3.5)	0.906	3.0 (−1.9, 7.8)	0.231	1.5 (−2.5, 5.5)	0.462	−2.7 (−6.1, 0.7)	0.119	−1.0 (−5.0, 3.1)	0.642

*General linear regression was used. Similar results were obtained with a cubic transformation for FertiQol scores.

women who had PCOS. Although women and men were found to have dissimilar perceptions of fertility-related QOL, with men having better QOL scores on multiple psychosocial instruments, the attribution of the cause of infertility may have affected these scores in the males. It is possible that QOL is impaired in the partner who is perceived to be responsible for infertility.

Table IV Spearman correlation coefficients (r_s) between female FertQol scores and length of infertility (months) for women with PCOS and UI*.

Variables	r_s for PCOS patients	*P*-value	r_s for UI patients	*P*-value
FertiQOL total score	−0.14	<0.001	0.01	0.823
Emotional score	−0.16	<0.001	0.01	0.774
Mind/Body score	−0.08	0.039	0.03	0.399
Relational score	−0.05	0.156	0.05	0.116
Social score	−0.15	<0.001	−0.02	0.518

*Unadjusted for covariates and multiple comparisons.

Our finding of lower QOL scores in women with PCOS than women with UI is not surprising. Firstly, women with PCOS were younger, had a much higher BMI, and were more hirsute than women with UI. Both hirsutism and elevated BMI (Hahn *et al.*, 2005; Coffey *et al.*, 2006; Jones *et al.*, 2011; Khomami *et al.*, 2015) are diagnostic aspects of PCOS that are associated with a lower QOL in many studies and were associated with lower QOL in the multivariable analysis. Thus, while these demographic features covary with both a diagnosis of PCOS and with a lower QOL, they are in many cases not separable from the diagnosis. Women with PCOS are oligo-ovulatory and therefore likely to present for infertility treatment at a younger age than women with UI. Obesity, while not a diagnostic feature of PCOS, is a common feature, especially in US cohorts of women with the disorder. Hirsutism is a clinical feature that is often used to diagnose the condition.

In addition to these physical attributes, women with PCOS were less educated, reported lower household income, and were more likely to be Black or Hispanic compared with women with UI. The prevalence of PCOS does not appear to vary by race/ethnicity (Azziz *et al.*, 2004). Some of the differences in educational attainment and household income that we observed in women with PCOS compared with those with UI may be related to race/ethnicity. Blacks and Hispanics are less likely than Whites to have a high school degree in the USA (9.9, 11

Table V Association between pregnancy outcome and FertiQol scores, with adjustment of treatment and female age^.

Variables	Singleton live birth		Conception	
	OR (95% CI)*	*P*-value#	OR (95% CI)*	*P*-value#
PCOS patients				
FertiQol total patient	1.24 (0.97, 1.58)	0.084	1.16 (0.94, 1.44)	0.164
Emotional	1.28 (1.09, 1.51)	0.003	1.21 (1.05, 1.40)	0.009
Mind/body	1.15 (0.95, 1.40)	0.158	1.12 (0.94, 1.33)	0.200
Relational	0.97 (0.77, 1.23)	0.806	0.98 (0.80, 1.22)	0.884
Social	1.09 (0.89, 1.33)	0.421	1.02 (0.85, 1.22)	0.824
FertiQol total partner	1.16 (0.79, 1.69)	0.461	1.18 (0.84, 1.64)	0.342
Emotional	1.08 (0.84, 1.40)	0.554	1.08 (0.87, 1.35)	0.491
Mind/body	1.01 (0.72, 1.41)	0.976	1.05 (0.78, 1.41)	0.770
Relational	1.10 (0.85, 1.42)	0.475	1.08 (0.87, 1.35)	0.488
Social	1.16 (0.85, 1.57)	0.348	1.17 (0.90, 1.52)	0.246
UI patients				
FertiQol total patient	0.85 (0.66, 1.10)	0.210	0.96 (0.77, 1.19)	0.678
Emotional	0.93 (0.78, 1.11)	0.403	0.97 (0.83, 1.13)	0.677
Mind/body	0.78 (0.63, 0.97)	0.022	0.88 (0.73, 1.06)	0.172
Relational	0.96 (0.76, 1.23)	0.767	0.97 (0.79, 1.19)	0.770
Social	0.93 (0.76, 1.14)	0.494	1.06 (0.89, 1.26)	0.537
FertiQol total partner	0.97 (0.71, 1.31)	0.818	1.14 (0.88, 1.49)	0.327
Emotional	0.99 (0.80, 1.24)	0.937	1.13 (0.94, 1.37)	0.200
Mind/body	0.98 (0.74, 1.29)	0.860	1.17 (0.92, 1.49)	0.209
Relational	0.94 (0.75, 1.17)	0.567	0.98 (0.82, 1.19)	0.868
Social	0.99 (0.77, 1.27)	0.945	1.06 (0.86, 1.31)	0.564

^Singleton live birth was defined by the delivery of a single live born infant. Conception was defined by a serum level of hCG of more than 10 mIU per milliliter for PCOS patients (PPCOS II study), and as having a rising serum level of hCG for two consecutive tests for UI patients (AMIGOS study).
*OR (95% CI) is for a change of 20 units.
#Logistic regression was used.

and 56%, respectively; http://www.census.gov/hhes/socdemo/education/data/cps/2014/tables.html). Individuals with a higher educational level may be more likely to seek assistance for their infertility. This may account for the higher prevalence of Whites in the UI sample compared with the PCOS sample. Since both RMN studies provided all study medications at no cost to the participants, we would not expect household income to play a large factor in participant recruitment for these studies.

The typical symptoms of PCOS (irregular menstruation, hyperandrogenism, obesity, infertility and acne) have all been considered to be reasons for their significant reduction in health-related quality of life (HRQol) in multiple studies and meta-analyses. A Danish study found that the prevalence of depression in women with PCOS is 4-fold higher than those without PCOS and that hyperandrogenemia was associated with an increase in antidepressant prescriptions, suggesting that hirsutism impacts a woman's emotional equilibrium (Altinok *et al.*, 2014). A recent meta-analysis of 28 studies indicated that depression, anxiety and emotional distress are higher in PCOS women, and that increased BMI and clinical hyperandrogenism partly but not completely explained this relationship (Veltman-Verhulst *et al.*, 2012). In agreement with this finding, we observed a negative association of FertiQOL score with the Ferriman–Gallwey hirsutism score ($\beta = -0.16$, 95% CI, -0.29 to -0.04, $P = 0.011$ in women with PCOS but not in those with UI). We also found a negative relationship between BMI and Ferriman–Gallwey score and QOL in the multivariable models. These features of PCOS therefore may contribute to the lower QOL in this group overall. Because the PCOS participants were younger than those in AMIGOS, their QOL scores may also have been lower because of the age effect observed in the multivariable models. Indeed, when statistical adjustments were made for these key differences between the two samples, the significance of the association with QOL was no longer present.

The higher BMI of women with PCOS compared with women with UI may have contributed to their lower FertiQOL scores. One recent study compared 173 women aged 18–44 years with PCOS who completed the SF-36 to age- and sex-matched Australian population norms ($n = 5620$) and found that HRQol was significantly poorer in the PCOS population in several domains, and this correlated significantly with higher BMI. However, the SF-36 scores remained significantly lower, even when compared with a subset of age- and sex-matched overweight and obese Australian women ($n = 1466–1481$), implying that BMI alone provides only a partial explanation. Others (Hahn *et al.*, 2005; Elsenbruch *et al.*, 2006) have observed lower QOL scores in PCOS patients compared with age-matched healthy controls using the SF-36 as well. Coffey *et al.* compared women with PCOS ($n = 22$) recruited from an outpatient clinic to a control group ($n = 96$) presenting to a family planning clinic. Although PCOS patients scored lower on both the SF-36 and the PCOS questionnaire compared with controls, this difference was no longer evident after controlling for BMI (Coffey *et al.*, 2006).

Of the four subscales of the FertiQOL, PCOS patients scored statistically lower on the Emotional, Mind/Body, and Social subscales but not statistically differently on the Relational subscale when compared with women with UI. This finding implies that couples with either diagnosis for their infertility seem to adjust within their marital relationship in ways that maintain QOL similarly. Alternatively, couples seeking treatment for infertility may have an overall high-quality relationship, which enables them to support each other successfully through the vicissitudes of the diagnostic workup and treatment of their infertility. Studies from the early 1990s support the notion that infertility can bring a couple closer together (Greil, 1991). The FertiQoL relational domain scores were relatively high in all the participants of this study, ranging from means of 81.5 ± 14.6 in women with UI and 80.1 ± 14.6 in women with PCOS, to 79.3 ± 15.1 in male partners of women with PCOS and 78.9 ± 15.2 in male partners of couples with UI. It is notable that the relational domain score of the FertiQol was the highest of all the subscales among both the women with PCOS and UI. In contrast, the relational domain score of the FertiQol was the lowest domain subscale among the male partners of both women with PCOS and UI. The explanation for these gender differences in perception of relational quality is beyond the scope of this study.

Psychosocial aspects of infertility have been studied in other countries using FertiQOL. Males have been found to have higher FertiQOL scores compared with females in other studies from China (Hsu *et al.*, 2013) and the Netherlands, as well as a number of other studies, some of which predated the FertiQOL (Wright *et al.*, 1991; Andrews *et al.*, 1992; Abbey *et al.*, 1995; El Kissi *et al.*, 2013; Huppelschoten *et al.*, 2013) with only one study (Berg and Wilson, 1995) demonstrating that 18% of distressed men were paired with a non-distressed wife. The investigators concluded that women have greater risk for developing emotional problems during and after fertility treatment compared with their male partners (Huppelschoten *et al.*, 2013).

In our study, the differences between male and female partners' perceptions of fertility-related QOL varied by diagnosis, with men in couples with UI having lower FertiQOL scores than those in couples in which the female partner was diagnosed with PCOS. Men who perceive themselves as the sole contributor of a couple's infertility demonstrate an increased negative sexual and personal impact when diagnosed with isolated male factor infertility (Nachtigall *et al.*, 1992; Abbey *et al.*, 1995). However, in the few studies that have compared men with UI to normally fertile men and men with a clear-cut male factor infertility diagnosis, men with UI and men without infertility did not differ from each other on measures of self-esteem and perception of loss (Nachtigall *et al.*, 1992; Dhillon *et al.*, 2000; Smith *et al.*, 2009). These latter studies all had smaller sample sizes than the present work, ranging from 36 to 357 men. In our sample of 1570 men, male partners in couples with UI reported an overall lower QOL than did men whose partners had PCOS, suggesting that the impact of an unknown infertility problem on the couple has a negative effect on male QOL. These findings persisted after adjustment for sociodemographic factors, which is not surprising, given that the overall sociodemographic pattern of the UI sample would favor a better QOL in patients with this diagnosis. Given the discordance in the direction of the male and female FertiQOL scores by infertility diagnosis, we may have underestimated the true impact of a UI diagnosis on FertiQOL scores in males in this study.

The relation of psychological stress to fertility and pregnancy outcomes is a topic of intense interest in the field. A recent meta-analysis of 39 studies, incorporating over 2700 patients, supported psychosocial interventions for infertility-related stress because of their efficacy in reducing short-term stress; the authors also observed a possible positive effect of intervention on pregnancy rates (Frederiksen *et al.*, 2015). An earlier meta-analysis of 31 studies found a small but significant effect of stress on live birth rates, and an effect of stress and anxiety on clinical pregnancy rates (but no relationship between state or trait anxiety and live birth) (Matthiesen *et al.*, 2011). These authors concluded that

while there might be an effect of stress and distress on ART outcomes, it was limited. A third meta-analysis of 14 studies encompassing 3583 infertile women did not find any relationship between emotional distress and pregnancy (Boivin *et al.*, 2011a). Stress may mediate adverse physiologic responses leading to impaired fertility in males, as lower serum total testosterone, higher LH/FSH levels and altered semen quality have been observed under stressful circumstances (Bhongade *et al.*, 2015). Biomarkers of stress, such as salivary alpha-amylase in females, have been negatively associated with fecundity (Louis *et al.*, 2011). In other studies, lower anxiety levels and fewer negative life events were predictive of pregnancy (Csemiczky *et al.*, 2000; Ebbesen *et al.*, 2009). In contrast to these findings, others have not found a significant association between pregnancy outcomes and psychological stress, depression or anxiety (Anderheim *et al.*, 2005; Lynch *et al.*, 2012; Pasch *et al.*, 2012). Our findings indicate that QOL at baseline (i.e. prior to treatment) is likely not an important factor in predicting pregnancy outcomes, at least among couples undergoing medically managed fertility treatments (i.e. not involving IVF). Our finding that higher FertiQOL emotional scores were associated with a higher chance of live birth and conception in PCOS patients but not in patients with UI is of unclear significance, since it is not consistent across the two diagnoses. Our examination of multiple cycles of treatment may have made our study more sensitive, similar to those used in the meta-analysis that found an association between stress and outcomes (Matthiesen *et al.*, 2011), but due to a small effect size, we only detected the association in our PCOS and not our UI sample. Because lower QOL was associated with higher BMI, and higher BMI was related to a reduced probability of pregnancy in the primary trial (Legro and Zhand, 2014), confounding may account for the apparent relation of the emotional FertiQOL score to pregnancy.

Similar to other studies, we found several additional factors related to baseline QOL. Older age was related to better QOL in both men and women, and higher female BMI and Ferriman–Gallwey score were related to lower QOL. Interestingly, a longer duration of infertility was related to lower QOL only among PCOS women. Prior studies indicate that duration of infertility is a significant factor contributing to fertility-related QOL (Karabulut *et al.*, 2013; Kahyaoglu Sut and Balkanli Kaplan, 2015), yet despite similar durations of infertility, we only observed this relationship in women with PCOS. Perhaps the attribution of the infertility solely to the female partner with PCOS becomes more wearying as time passes without pregnancy and thus further reduces QOL. Alternatively, worse hirsutism is associated with lower QOL as well as reduced fecundity, so this association of lower QOL with increased duration of infertility may be confounded by the degree of hirsutism in the women with PCOS.

This study has several strengths and weaknesses. Among the strengths is the large sample size, which represents the largest US-based cohort of infertile couples studied to date. The standardized timing of administration of the FertiQOL and other measures, except pregnancy outcome, used in this study and excellent follow-up of all participants for outcomes is another strength. Weaknesses of our study include less comprehensive survey completion in the male partners of women with PCOS, and the use of multiple tests of association, some of which may have resulted in spurious statistically significant findings. The significant differences in educational attainment and household income between the two concurrent cohorts also influenced our findings. However, it may not be possible to separate the physical features of PCOS from these sociodemographics. Our study evaluated baseline QOL prior to treatment and therefore does not assess if changes in QOL affected pregnancy outcome. Finally, participants for both studies were drawn from the areas surrounding the RMN clinical sites, which were distributed throughout the USA. Although they likely represent their local communities, they are not a population-based sample and thus firm conclusions about how representative these couples are to the general population must be made with caution.

Our results have some implications for clinical practice. Similar to prior studies, we find that women have overall lower fertility-associated QOL and the clinician should be sensitive to the need for emotional support of infertile couples in general, especially women. Moreover, women with PCOS who share some of the features that we found to be associated with lower QOL (high BMI, hirsutism, lower educational and income levels and younger age) may be in particular need of emotional support as they navigate diagnostic and treatment regimens. Men with UI may also require more emotional support than those whose partners are infertile. Thus, our findings may help clinicians target support to the patients who may need it the most.

In summary, we used a new instrument, devised to assess specifically the fertility-related QOL (FertiQOL), to test the largest US-based cohort to date and found that QOL is reduced for women with PCOS compared with those with UI. Men have overall less compromise of QOL in association with an infertility diagnosis, but men with UI had lower QOL than men whose partners had PCOS. Finally, QOL did not overall predict conception or live birth in this study.

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Authors' roles

N.S. was the primary author and Chair of the Reproductive Medicine Network Steering Committee at the time the study was designed and carried out, contributed to the design of the study and drafted the manuscript. E.E. was the NIH Project Scientist for the Reproductive Medicine Network and contributed to the design of the study, revised the manuscript critically for important intellectual content and provided final approval. J.C.T., L.B.C. and C.G. contributed to the conception and design of the manuscript, revised the manuscript critically for important intellectual content and provided final approval. R.A., P.C., G.C., C.C., M.D., R.S.L., R.D.R. and W.D.S. were site Principal Investigators and contributed to the design and data acquisition, revised the manuscript critically for important intellectual content and provided final approval. S.J., H.H. and H.Z. performed analysis and interpretation of data (H.Z. also provided substantial contribution to the study and manuscript conception and design), revised the manuscript critically for important intellectual content and provided final approval.

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Conflict of interest

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