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Measurement and evaluation of quality of life and well-being in individuals having or having had fertility problems: a systematic review

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ABSTRACT

Objectives: The aims of this study were: (1) to identify which measurement instruments are used in practice to assess the quality of life or well-being of individuals with and without (sub)fertility; (2) to describe the design and outcomes of studies comparing quality of life or well-being of individuals with and without fertility problems; and (3) to determine which of the outcomes of the identified studies could be used in cost-utility studies.

Methods: A systematic literature review was performed of studies published before July 2018, using multiple databases. Included studies investigated (health-related) quality of life or well-being of individuals with fertility problems. The applied instruments were assessed, as were the outcomes and suitability for use in cost-utility studies.

Results: Twenty-six studies met the inclusion criteria. Twelve distinct instruments of measurement were applied: two generic quality-of-life instruments, five generic well-being instruments and five disease-specific instruments. Most studies found negative associations in one or more domains assessing fertility problems and quality of life or well-being. However, two studies found the opposite. None of the studies reported outcomes relevant for cost-utility studies.

Conclusion: Quality of life and well-being related to having fertility problems are regularly studied. However, the reported information is not suitable for use in cost-utility studies. There is a clear need for studies investigating the impact of fertility problems on quality of life in a way that outcomes can be compared across studies and disease areas.

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Introduction

Up to 15% of reproductive-aged couples worldwide experience infertility [1]. In absolute numbers, 48.5 million couples are unable to fulfil their desire for a child (defined as not having been able to conceive over a period of 5 years). Of these, 19.2 million couples do not succeed in having a first child and 29.3 million do not succeed in having a second child [2]. About half of couples with infertility seek medical help [3]. Fertility problems affect individuals in high-income countries, as well as those in middle- and low-income countries [2].

A study among the general Dutch population showed that as many as 91% of those questioned considered having mild fertility problems to be an unacceptable health condition for women aged 30, and 93% felt that infertility was unacceptable [4]. In other words, fertility seems an important aspect of a normal healthy life. Be that as it may, not being fertile, or being less fertile, may not result in directly visible health problems. Fertility care may therefore sometimes be seen as unnecessary or of low priority. In practice, in many countries this has resulted in policies limiting access to fertility care in health insurance schemes or in national health service systems. In the Netherlands, couples currently get a maximum of three *in vitro* fertilisation (IVF) or intra-cytoplasmic sperm injection attempts

reimbursed through the basic benefits package of the mandatory health insurance system. In Austria, 70% of treatment and drug costs are reimbursed under certain circumstances, while in the USA a large proportion of women pay for their own treatment [5]. These limitations in access to fertility-related care may contribute to the burden of disease of women with fertility problems.

Although, obviously, the most important outcome of fertility treatment may be considered the birth of a baby, this outcome may not be the primary outcome considered in policy-makers' reimbursement decisions. In many countries, cost-effectiveness outcomes play an important role in these decisions. In other words, does a treatment (e.g. IVF) offer value for money? Effectiveness in cost-effectiveness studies is preferentially expressed in costs per quality-adjusted life year (QALY). Cost-effectiveness studies expressing outcomes in QALYs are commonly referred to as cost-utility studies. The QALY is a composite measure of length of life and quality of life of the individual. However, most health economic studies with regard to fertility treatment examine the costs of fertility treatment per live birth, rather than the costs per QALY gained. The difficulty for policy-makers is that costs per live birth cannot be compared with cost-effectiveness outcomes of other medical interventions treating other diseases. Consequently, it is not possible to determine whether fertility treatments offer value for

money compared with treatments for other diseases. In order to be able to conduct cost-utility studies it is necessary to have insights into the effects of subfertility and infertility on quality of life.

The effect of fertility problems on the quality of life of individuals has often been studied. Outcomes show that infertility can cause tremendous psychological distress in women and men. Disease severity may sometimes be as profound as that of life-threatening diseases such as cancer and heart disease [6]. Still, such evidence may not always reach policy-makers, or be adequately included in reimbursement decisions, since the quality-of-life studies were not designed to feed cost-utility studies. Most available evidence is collected in studies within social sciences covering a single domain of health or well-being rather than general quality of life. In order for evidence to be able to be included in cost-utility studies, quality of life needs to be measured and valued in such a way that the outcomes are comparable across diseases. Commonly, this implies using preference-based generic quality-of-life or well-being instruments.

The extent to which evidence is available regarding the effects of fertility problems on quality of life suitable for use in cost-utility studies is unclear. To gain insights into the impact of infertility on quality of life, it is especially interesting to examine studies comparing the quality of life or well-being of women with fertility problems with that of people without fertility problems.

The aims of this study were: (1) to identify which measurement instruments are used in practice to assess the quality of life or well-being of individuals with and without (sub)fertility; (2) to describe the design and outcomes of studies comparing quality of life or well-being of individuals with and without fertility problems; and (3) to determine which of the outcomes of the identified studies could be used in cost-utility studies.

In order to meet these objectives an extensive systematic review was conducted using multiple databases.

Methods

The systematic review was set up to identify a wide scope of scientific studies investigating either disease-specific or generic quality of life and/or well-being of individuals with fertility problems now or in the past, with or without (ever) receiving treatment, with or without children.

The review included the following databases: Medline (OvidSP), Web of Science, PsycINFO (OvidSP), Embase, Cochrane, PubMed and Google Scholar. The searches were conducted to include all studies published before 9 July 2018. Words included in the search strategy were related to: (1) fertility (such as 'fertility', 'subfertility' and 'infertility'); (2) quality-of-life aspects (including 'well-being', 'quality of life' and 'distress'); and (3) measurement instruments (including 'questionnaire', 'scale' and 'score'). Different search strategies were explored to determine the most eligible one, thus including the most relevant studies. The specific search queries may be found in the appendix.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were as follows: (1) studies had to specifically assess generic or disease-specific

quality of life or well-being of humans with (past) infertility/subfertility; (2) studies had to be of a quantitative nature (e.g. studies applying open interviews were excluded); (3) studies had to be original scientific research (i.e. comments, editorials and reviews were excluded); (4) studies were excluded if they were primarily aimed at the evaluation of a specific fertility-related treatment; (5) studies were excluded when they focussed on fertility-related problems or causes of infertility, when they studied the relationship between quality of life or well-being and factors other than fertility, or when they investigated an indirect effect of fertility on quality of life or well-being (e.g. the role of coping styles in the effect of infertility on quality of life); (6) studies were excluded when they focused on many conditions of which subfertility or infertility was one; (7) studies had to compare quality of life or well-being of individuals with and without fertility problems; and (8) instrument development studies were excluded.

Identification of published studies and instruments

To identify the relevant published papers from the initial search, the following procedure was undertaken. First, titles and abstracts were examined and independently coded by two researchers (KH and MK) as irrelevant, likely to be relevant, or unclear. Differences were discussed until consensus was reached. In case of doubt, studies were included in the full-text investigation. Studies that were coded as irrelevant received an additional code to describe which of the inclusion criteria were not met or which exclusion criteria applied.

After the title and abstract search, full-text papers were examined to determine whether all inclusion criteria were indeed met and the exclusion criteria did not apply. Full-text examinations were conducted in close collaboration between KH and MK.

After relevant studies had been identified, it was assessed what the studies aimed to measure specifically and what type of instrument was used to measure quality of life or well-being: generic, disease or domain specific. Generic instruments are designed to measure quality of life over the complete spectrum of diseases in various populations and can be used to compare changes across different patient groups. Disease-specific instruments are designed to measure the most relevant domains of quality of life specific to a particular disease, while domain-specific instruments focus on a single domain of health (e.g. social well-being). After identifying the instruments, the content of the applied instruments was examined and summarised.

An overview table was constructed summarising the main characteristics of the studies comparing quality of life or well-being of people with and without fertility problems, such as the study aim, the sample size, the instruments used and the main outcomes. Finally, it was investigated whether the applied instruments and the presented outcomes in the studies were suitable for use in cost-utility studies.

Compliance with ethical standards

As this article does not contain any studies with human participants or animals performed by any of the authors, no ethics approval was required.

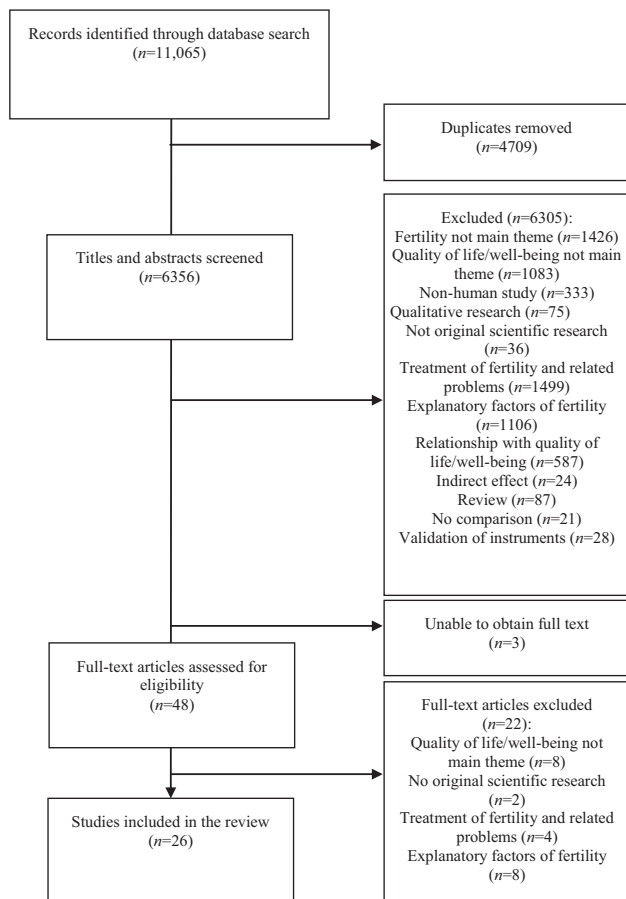


Figure 1. Flow diagram.

Results

Review process

As shown in Figure 1, the initial database searches identified 11,065 potentially relevant papers, of which 4695 duplicate studies were detected and excluded by means of EndNote X7 (<https://endnote.com>). A further 14 duplicates were detected and manually removed. Title and abstract searches resulted in the exclusion of 6305 studies: 1426 were not primarily aimed at fertility, 1083 did not consider quality of life or well-being as a main theme, 333 explored non-human subjects, 75 were qualitative studies, 36 did not report original scientific research, 1499 were about treatment of fertility and fertility-related problems, 1106 investigated causes of infertility, 587 were about the relationship between quality of life or well-being and other factors than fertility, 24 studied an indirect effect of fertility on quality of life or well-being, 87 were reviews of previous literature, 21 did not compare quality of life/well-being of individuals with and without fertility problems, and 28 aimed to validate rather than apply instruments. The initial similarity percentage between the coding of the researchers in the title and abstract examination was high (91.8%).

A total of 51 studies were intended to be included in the full-text examinations. However, we were not able to obtain the full-text paper of three studies; 22 studies were excluded based on the full-text examination. This left a total of 26 studies included in the analyses.

A short description of the design of the studies, an overview of the quality-of-life and/or well-being instruments used and a summary of the studies' outcomes are presented in Table 1. In most countries only one or two

studies were conducted, with the exception of Iran (six studies) [8–10,13,23,27], Germany (three studies) [22,28,31] and Turkey (three studies) [25,26,29]. Most studies had similar aims and objectives (to compare quality of life/well-being of individuals with fertility problems with quality of life/well-being of individuals without fertility problems). However, study populations differed. For instance, some studies investigated quality of life of individuals during IVF treatment and some of individuals after IVF treatment. Some only studied women's quality of life, while others investigated quality of life in couples. Diverse quality-of-life and well-being instruments were used.

Quality-of-life and well-being instruments

We identified 12 instruments used in the 26 studies, of which three were generic instruments measuring quality of life, five were generic instrument measuring well-being and four were disease-specific instruments. A short description of the applied instruments is provided in Table 2. The study outcomes are discussed below. When a difference in outcomes is described as significantly different, it is statistically different according to the outcomes reported in the specific study. Note that the distinction between quality-of-life instruments and well-being instruments was not always evident. We categorised the instruments based on labelling of the instrument in the instruments' modes of instruction.

Generic quality-of-life instruments and their outcomes

Sixteen of the 26 identified studies applied a generic health status or quality-of-life instrument. Three different (types of) generic instruments were used: the Short Form 36 (SF-36), two versions of World Health Organization (WHO) quality-of-life measures – the abbreviated version, WHOQOL-BREF, and the WHOQOL-100 – and one self-constructed rating scale.

The SF-36 was used in nine of the included empirical studies [8–10,12–16,29]. De Pascalis et al. [12] found that couples who underwent successful assisted reproductive technology (ART) reported lower quality of life in the SF-36 physical summary score. Ashraf et al. [10] reported significantly worse scores in quality of life of infertile or subfertile women compared with fertile women in the domains of physical functioning, role limitations due to physical problems, general health, vitality, social functioning, role limitations due to emotional problems and mental health. Ahmadi et al. [8] reported that during pregnancy, women who conceived naturally had better physical functioning and less role limitation due to physical problems, less bodily pain and better social functioning, while women who conceived by ART reported better general health, vitality, role limitation due to emotional problems and mental health. After childbirth, women who had conceived by ART scored better compared with the natural conception group on all but one dimension. Drosdzol and Skrzypulec [14] showed significantly worse scores on the SF-36 among infertile women compared with fertile controls in five out of nine domains, while the other indices were slightly but insignificantly better. Infertile males were found to have no significantly different values compared with fertile controls, although vitality was slightly decreased. El Kissi et al. [15] found a lower summary score in the mental dimension of

Table 1. Summary of identified studies' designs and outcomes.

Study and country	Aims	Sample	Assessment	Results	Association between infertility and QoL/well-being ^a
Aduloju et al. [7] Nigeria	To examine QoL in women of reproductive age by comparing QoL scores between infertile and fertile women attending gynaecology or postnatal clinics	361 infertile women and 722 fertile women	Generic QoL: WHOQOL-BREF	QoL was significantly lower among infertile women compared with fertile women	Negative
Ahmadi et al. [8] Iran	To assess QoL of women who conceived by ART and had successful childbirth for the first time and compare it with QoL in women who become pregnant naturally and similarly had successful childbirth for the first time	86 women with successful ART and 76 women with natural conception	Generic QoL: SF-36	During pregnancy, women who naturally conceived scored better on physical functioning, role limitation due to physical problems, bodily pain and social functioning, while the ART group scored better on general health, vitality, role limitation due to emotional problems, and mental health; after childbirth, the ART group scored higher than the naturally conceived group on all but one dimension	Unclear
Amiri et al. [9] Iran	To compare QoL among fertile and infertile women and the factors affecting it	511 infertile women and 1017 fertile women	Generic QoL: SF-36	Fertile women's QoL score was not significantly different from that of infertile women	No association
Ashraf et al. [10] Iran	To compare QoL in fertile and infertile women	111 infertile women and 339 fertile women	Generic QoL: SF-36	Infertile women scored significantly lower than fertile women in 7/8 domains of the SF-36	Negative
Caillan [11] Australia	To examine the psychological well-being and marital happiness of three groups of women: mothers of younger children, voluntarily childless wives, and a group of long-term infertile women currently attempting to have a child on an IVF programme	53 infertile women, 32 voluntarily childless women and 50 mothers	Generic well-being: self-constructed rating scale	Infertile women were less satisfied with their lives compared with voluntarily childless women; no difference was found between mothers and either of the two other groups	Negative
De Pascalis et al. [12] Italy	To compare levels of and changes in QoL during pregnancy between couples who conceived spontaneously and couples who underwent successful ART treatment	57 couples with successful ART and 58 couples who spontaneously conceived	Generic QoL: SF-36	ART couples reported a lower QoL compared with non-ART couples in the physical summary score; little difference was found in the mental summary score	Mixed results
Direkvand-Moghadam et al. [13] Iran	To compare QoL in fertile and infertile women	339 fertile women and 111 infertile women	Generic QoL: SF-36	The major dimension QoL of infertile women was lower than that of fertile women	Negative
Drosdzol and Skrzypulec [14] Poland	To evaluate the influence of infertility on QoL and sexual functioning of infertile couples	206 infertile couples and 190 fertile couples	Generic QoL: SF-36	Infertile women had significantly lower QoL compared with controls in 5/9 domains of the SF-36; infertile males were not found to have significantly different QoL from that of the fertile control group	Negative for women, no association in men
El Kissi et al. [15] Tunisia	To compare QoL gender differences in infertile couples and between infertile couples and controls	100 infertile couples and 100 control couples	Generic QoL: SF-36	Infertile men scored lower in the mental dimension of the SF-36 compared with men in the control group, and they had lower social functioning and role-emotion; infertile women compared with controls scored lower on both summary scores of the mental and physical dimensions, vitality, social functioning, role-emotion, and mental health	Negative

(continued)

Table 1. Continued.

Study and country	Aims	Sample	Assessment	Results	Association between infertility and QoL/well-being ^a
Graham [16] Australia	To examine the association between motherhood status and general physical and mental health and well-being over a 10 year period	4139 mothers and 1939 childless women	Generic QoL: SF-36	Childless women experienced significantly better scores on the mental and physical component summary measures compared with mothers	Positive
Hassanin et al. [17] Egypt	To assess the effect of infertility on health-related QoL and sexual function of infertile women	116 women with primary infertility and 116 fertile controls	Disease-specific QoL: QLQ-C30	Infertile women had significantly lower QoL compared with fertile women; women with infertility duration of 4–6 years had even lower mean QoL	Negative
Jeffries and Konnert [18] Canada	To compare voluntarily childless women, involuntarily childless women and mothers on measures of regret and present-ideal self-evaluations	23 voluntarily childless women, 24 involuntarily childless women and 25 mothers	Generic well-being: SPWB-SF	No significant differences were found in overall psychological well-being between involuntarily childless women, voluntarily childless women and mothers	No association
Johansson et al. [19] Sweden	To describe QoL in men and women who had terminated IVF in the public health system 4.0–5.5 years previously, and for whom treatment did not result in childbirth	149 women with unsuccessful IVF, 121 men with unsuccessful IVF, 126 female controls and 99 male controls	Generic well-being: PGWB	Compared with the control group, men with unsuccessful IVF scored lower in the PGWB domains of depression and positive well-being; men with successful IVF had better vitality; women with unsuccessful IVF scored lower on depression; and women with successful IVF showed no differences in total or domain scores	Unclear
Johansson et al. [20] Sweden	To describe and compare QoL in men and women who had IVF in the Swedish public health system 4.0–5.5 years previously, either unsuccessfully and subsequently living without children or successfully and having children aged 4.0–5.5 years	26 men with unsuccessful IVF, 135 men with successful IVF, 37 women with unsuccessful IVF, 154 women with successful IVF, 93 male controls and 118 female controls	Generic well-being: PGWB	Total PGWB scores and domain scores except anxiety were lower among men with unsuccessful IVF compared with men with successful IVF; men with unsuccessful IVF showed lower scores on depression and positive well-being than men in the control group; no difference in total PGWB scores was found when comparing either successful IVF men or women with the control group	Unclear
Klemetti et al. [21] Finland	To examine mental disorders, depression, psychological distress, perceived health and QoL among women and men who had experienced infertility	239 infertile women, 99 infertile men and 1953 fertile men and women	Generic QoL: self-constructed rating scale	QoL was only significantly lower among infertile childless men compared with men without infertility	Negative for men; no association in women
Kowalcek et al. [22] Germany	To investigate the following about subjective well-being: do involuntarily childless women and men differ in the extent of their subjective well-being from healthy individuals and other women? Do women and men in infertile couples differ in their subjective impairment according to the cause of infertility?	110 infertile couples	Generic well-being: Von Zerssen symptom checklist	No difference between infertile couples and healthy comparators	No association
Masoumi et al. [23] Iran	To compare the QoL and marital and sexual satisfaction between fertile and infertile couples	125 infertile couples and 125 fertile couples	Generic QoL: WHOQOL-BREF	Fertile couples had significantly higher QoL compared with infertile couples	Negative
Monga et al. [24] USA	To evaluate the hypothesis that infertility may result in a decrease in QoL and an increase in marital discord and sexual dysfunction	18 infertile couples and 12 control couples	Generic well-being: QWB	Women in couples seeking infertility treatment showed lower health-related QoL compared with women in couples seeking elective sterilisation; there was no difference in men from the same couples	Negative for women; no association in men

(continued)

Table 1. Continued.

Study and country	Aims	Sample	Assessment	Results	Association between infertility and QoL/well-being ^a
Onat and Beji [25] Turkey	To investigate the effects of infertility on marital relations and QoL	58 infertile couples and 51 fertile couples	Generic QoL: WHOQOL-BREF	Infertile couples had significantly higher scores in all subdomains of the WHOQOL-BREF compared with fertile controls	Positive
Pinar and Zeyneloglu [26] Turkey	To evaluate QoL and anxiety/depression levels of women prior to receiving ART	80 infertile men, 80 infertile women, 160 controls	Generic QoL: WHOQOL-BREF	The infertile group scored significantly lower in all subdomains of QoL compared with fertile controls	Negative
Sani et al. [27] Iran	To evaluate and compare QoL, self-efficacy and resiliency in infertile and fertile women	60 infertile women and 60 fertile women	Generic QoL: WHOQOL-BREF	QoL in infertile women was lower than that in fertile women	Negative
Schanz et al. [28] Germany	To measure QoL of infertile men at baseline and after 5 years with a specific QoL instrument for involuntarily childless men	101 involuntarily childless men	Fertility-specific QoL: TLMK	Scores over 5 years in the domains of desire for a child and gender identity improved; no differences were found in QoL between those who had become fathers and those who remained childless	No association
Sezgin et al. [29] Turkey	To compare the level of psychiatric symptoms, disability and QoL in fertile and infertile urban women	100 infertile women and 100 fertile women	Generic QoL: SF-36	Urban married women seeking treatment for infertility had poorer QoL compared with fertile married controls	Negative
Valsangkar et al. [30] India	To measure and compare the impact of infertility on marital adjustment, sexual functioning, QoL and acceptability of various infertility treatment modalities	106 infertile women and 212 fertile women	Fertility-specific QoL: FertiQoL	Infertile women had decreased QoL compared with reference data	Negative
Wischmann et al. [31] Germany	To find out in a large sample whether, in comparison with parents, involuntarily childless couples had a different subjective perception of overall and specific QoL over a period of > 10 years	148 couples with previous infertility treatment	Fertility-specific QoL: self-constructed rating scale	Childless couples and parents had increased QoL, but it was not significantly different between groups	Unclear
Xiaoli et al. [32] China	To assess QoL of infertile Chinese women and determine the specific factors adversely affecting QoL for improving care and treatment compliance of infertile women	81 infertile women and 81 fertile women	Generic QoL: WHOQOL-100	Married infertile Chinese women had significantly lower overall and comprehensive QoL scores compared with fertile controls	Negative

^aPositive: infertility is associated with higher QoL/well-being; negative: infertility is associated with lower QoL/well-being. QoL, quality of life.

Table 2. Applied quality-of-life and well-being instruments.

Instrument	Description	Availability of preference-based utility weights	Study
Generic QoL instruments			
SF-36	The SF-36 is a generic instrument used to measure health status in 8 dimensions: physical function, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health; these domains can be used to compose the Physical Component Summary and the Mental Component Summary [33]	Yes (convert to SF-6D)	Ahmadi et al. [8] Amiri et al. [9] Ashraf et al. [10] De Pascalis et al. [12] Direkvand-Moghadam et al. [13] Drosdzol and Skrzypulec [14] El Kissi et al. [15] Graham [16] Sezgin et al. [29] Xiaoli et al. [32]
WHOQOL-100	The WHOQOL-100 is a QoL instrument developed by the WHO; it contains 100 items scored on a 5 point Likert scale [32]	No	
WHOQOL-BREF	The WHOQOL-BREF is a QoL instrument developed by the WHO; it is an abbreviated version of the WHOQOL-100 and contains 27 items divided over four subdomains: physical, emotional, environmental and social [26]	No	Aduloju et al. [7] Masoumi et al. [23] Onat and Beji [25] Pinar and Zeyneloglu [26] Sani et al. [27]
Generic well-being instruments			
QWB	The QWB is a preference-based instrument designed to classify health status from which health-state values can be calculated; outcomes are presented on a scale between 0 and 1, where higher values indicate better health-related QoL [24]	Yes	Monga et al. [24]
PGWB	The PGWB is a generic instrument used to measure psychological general well-being, indicating subjective well-being and distress in six domains: anxiety, depressed mood, positive well-being, self-control, general health, and vitality; a higher score indicates better well-being [19]	No	Johansson et al. [19] Johansson et al. [20]
SPWB-SF	The SPWB-SF is used to assess overall psychological well-being and has subscales on well-being of autonomy, environmental mastery, personal growth, positive relations with others, purpose in life and self-acceptance [18]	No	Jeffries and Konnert [18]
Von Zerssen symptom checklist	The Von Zerssen symptom checklist is applied to determine subjective well-being, consisting of 24 items including somatic, general and psychological symptoms; the total score indicates the extent of subjective impairment [22]	No	Kowalcek et al. [22]
Disease-specific QoL and well-being instruments			
FertiQoL	FertiQoL is a fertility-specific self-report questionnaire designed to assess QoL of infertile individuals [34]	No	Valsangkar et al. [30]
TLMK	The TLMK is a fertility-specific instrument originally used to assess QoL in men with a desire for a child; it consists of items covering four areas: desire for a child and associated stress, gender identity, marital relationship and psychological well-being [35]	No	Schanz et al. [28]
QLQ-C30	The QLQ-C30 is designed to collect information on function, global health, QoL and symptoms in cancer patients; a higher global score indicates better QoL [17]	Yes	Hassanin et al. [17]

QoL: quality of life.

the SF-36 among infertile men compared with controls. Infertile women compared with controls scored worse on both summary scores. Amiri et al. [9] found that the total quality-of-life score was not significantly different between fertile and infertile women. Direkvand-Moghadam et al. [13] found that infertile women scored worse in the domains of physical function, role limitations due to physical problems, general health, vitality, social functioning, role limitations due to emotional problems and mental health. Graham [16] found that childless women experienced significantly better scores on the mental and physical component summary measures compared with mothers. Sezgin et al. [29] found that infertile women reported poorer quality of life compared with fertile control women.

The WHOQOL-BREF was used in five studies [7,23,25–27]. Masoumi et al. [23] found that fertile couples had significantly higher quality of life compared with infertile couples. Sani and Tamannaefar [27] found the quality of life of infertile women to be lower than that of fertile women. Onat and Beji [25] reported a significantly higher

quality-of-life score among the infertile group compared with the fertile group in all subdomains of the WHOQOL-BREF. By contrast, Pinar and Zeyneloglu [26] reported scores in all subdomains of quality of life to be significantly lower in the infertile group. Aduloju et al. [7] found that quality of life was significantly lower among infertile women compared with fertile women. The WHOQOL-100 was used in one study, by Xiaoli et al. [32], who concluded that infertile women had significantly lower overall quality of life compared with fertile women.

Klemetti et al. [21] measured quality of life on a single-item scale from 0 to 10 and concluded that quality of life was significantly lower among infertile childless men compared with fertile men, but no difference was found among women.

Generic well-being instruments and their outcomes

Six of the 26 identified studies applied five different well-being instruments: the Psychological General Well-Being

Index (PGWB), the Scales of Psychological Well-Being–Short Form (SPWB-SF), the Von Zerssen symptom checklist, a self-constructed rating scale on global well-being and the Quality of Well-Being Scale (QWB). A description of the instruments is provided in [Table 2](#).

The PGWB was applied in two separate studies [19,20]. Johansson et al. [20] found that total PGWB scores and domain scores, except anxiety, were worse among men with unsuccessful IVF than among men with successful IVF. Additionally, compared with controls, men with unsuccessful IVF reported worse scores in the domains of depression and positive well-being. Women who had undergone unsuccessful IVF scored worse on depression compared with a control group. However, no difference in total PGWB scores was found when comparing successful IVF treatments in men or women with a control group. Johansson et al. [19] found that compared with control groups, men with unsuccessful IVF scored worse in the PGWB domains of depression and positive well-being, men with successful IVF had better vitality, and women with unsuccessful IVF had significantly worse well-being scores in anxiety and depression.

The SPWB-SF was used in one cross-sectional study by Jeffries and Konnert [18] which reported no significant differences in overall psychological well-being between involuntarily childless women, voluntarily childless women and mothers.

Kowalcek et al. [22] applied the generic Von Zerssen symptom checklist to investigate the well-being of infertile couples. These authors found no notable difference between the symptom scores of infertile couples and the applied reference data of healthy comparators.

In a study by Callan [11] a self-constructed rating scale was used to measure global well-being. Well-being was assessed by posing a question on life satisfaction on a 1–9 scale, where 1 indicated being not very satisfied and 9 very satisfied. Comparing mothers, infertile women and voluntarily childless women, infertile women were less satisfied with their life compared with voluntarily childless women.

The QWB was used in one study. Monga et al. [24] found that women in couples seeking infertility treatment showed lower health-related quality of life compared with women in couples seeking elective sterilisation. Additionally, no difference was found in men in the same couples.

Disease-specific quality-of-life and well-being instruments and their outcomes

Four of the 26 studies included in our review applied disease-specific instruments. Four different instruments were applied: the Fertility Quality-of-Life Questionnaire (FertiQoL), the Tübinger Lebensqualitätsfragebogen für Männer mit Kinderwunsch (TLMK), the Quality-of-Life Questionnaire C30 (QLQ-C30) and one self-constructed rating scale.

Valsangkar et al. [30] applied the FertiQoL instrument and found that infertile women had a lower fertility-related quality of life compared with reference data.

Applying the TLMK, Schanz et al. [28] found that the quality-of-life scores over 5 years of involuntarily childless men had improved in the domains of desire for a child and

gender identity, indicating that the negative impact of these domains had decreased. However, no differences in quality of life were found among those who had become fathers and those who remained childless.

The QLQ-C30 was used in a case–control study by Hassanin et al. [17], who reported that infertile women had a significantly lower quality of life compared with fertile women.

Wischmann et al. [31] applied a generic rating system comparing subjective change in quality of life on a single scale of 1–5 (1 indicating being much worse after termination of infertility treatment and 5 being much better). They found that childless men and women and parents reported increased quality of life after termination of infertility treatment, but this increase was not significantly different between childless partners and parents.

Quality-of-life and well-being outcomes

The majority of the included studies reported decreased quality of life or well-being in one or more domains due to infertility/subfertility. Sixteen out of the 26 studies showed evidence of significantly deprived health status in men, women and couples in one or more domains [7,10–15,17,21,23,24,26,27,29,30,32]. Two studies found the opposite for either women or couples [16,25]. Eight studies found no overall evident relationship between infertility/subfertility and quality of life or well-being [8,9,18–20,22,28,31].

Suitability for use in cost-utility studies

Preference-based utility weights were available for three of the 12 applied instruments in the studies included in this review. Such utility weights are important since these can be used to construct QALYs to allow for comparison of outcomes across diseases. The three instruments for which preference-based utility weights were available (and therefore suitable for use in cost-utility studies) are the SF-36, the QWB and the QLQ-C30. As shown in [Table 2](#), these instruments were applied in 11 studies. This means that in those studies it would have been possible to report utilities that could be applied in cost-utility studies. However, none of the studies reported outcomes in utilities.

Discussion

The impact of having fertility problems on quality of life and well-being of individuals is regularly studied. Our study reviewed the available evidence regarding the impact of having fertility problems on quality of life and well-being.

Findings and interpretation

The outcomes of this systematic review indicated that the relationship between fertility and quality of life is not always clear. Although in most studies people with fertility problems scored lower in one or more domains of quality of life/well-being, not all did. Moreover, the association between having fertility problems and different domains of quality of life was not consistent between studies. There can be various reasons for these differences. For instance,

the 26 studies were conducted in 15 different countries; cultural differences in these countries, such as social acceptability of infertility, are likely to have influenced the association between fertility problems and quality of life. Moreover, the differences in reported outcomes may be related to other aspects of the study design, such as the sample size and, obviously, the applied instruments. The 26 studies reported a total of 12 distinct instruments, making comparisons between studies difficult. In addition, the study population of interest differed between studies. Of course, having insight into the effect of fertility problems on quality of life in different subgroups is in itself important.

Almost half of the studies applied instruments that enable the outcomes to be presented in terms of utilities. Remarkably, however, none of the studies reported quality-of-life outcomes expressed in utilities (which is necessary to be able to include outcomes in cost-utility studies). This implies that in order to be able to properly include the available quality-of-life evidence related to (in)fertility in comparative health economic analyses it is necessary to reanalyse the available data to calculate the outcomes in terms of utilities. This could also allow interesting comparisons of outcomes between the available studies.

Limitations and strengths of the study

A potential limitation of this review deserves attention. Although the search strategy was quite extensive, we might have missed some relevant quality-of-life evidence as a result of methodological choices made, such as excluding multi-disease studies and studies primarily aimed at the evaluation of a specific treatment.

Despite this limitation, some findings are important. Although outcomes were not consistent, evidence seems to indicate that there is a negative association between having fertility problems and quality of life/well-being.

Unanswered questions and future research

How the impact of fertility problems on quality of life relates to other health problems is far from clear. Therefore, it is necessary to better quantify the impact of fertility problems on quality of life and well-being to determine the relative impact compared with that of having other health problems. It is advised that future studies (additionally) include generic quality-of-life/well-being instruments and subsequently report the outcomes in terms of comparable measures. Suitable instruments are, for instance, the EuroQoL 5D, the Health Utility Index and the Short Form 6D. Disease-specific instruments such as FertiQoL may be used to provide additional relevant disease-specific information.

Note that using cost-utility studies to determine the value for money of treating fertility problems is not without dispute. Fertility treatments may be argued to be one of the very few parts of health care not primarily aimed at increasing or maintaining people's health or welfare. For instance, the value of creating new life may be difficult to grasp in our current economic evaluations, as the future QALYs gained (and the economic value) of the baby born as a result of fertility treatment are commonly not included

in cost-effectiveness studies. Another challenging factor is that parenthood (the result of successful fertility treatment) may also have negative effects on quality of life [36]. These aspects are important to consider in fertility-related quality-of-life research.

Conclusions

Quality of life and well-being related to having fertility problems is regularly studied. However, the reported quality-of-life information is not suitable for use in cost-utility studies. There is a clear need for studies investigating the impact of fertility problems on quality of life in a way that outcomes can be compared across studies and disease areas.

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