RBMO

REVIEW

Characteristics, prevalence and sources of stress in individuals who discontinue assisted reproductive technology treatments: a systematic review

BIOGRAPHY

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KEY MESSAGE

Clinical factors associated with worse prognosis, physical discomfort caused by treatment procedures, family demands, time pressure and economic burden were identified as sources of 'stress' that contributed to assisted reproductive technology discontinuation.

ABSTRACT

By considering the reasons behind discontinuing assisted reproductive technology (ART) treatment, several studies have indicated that 'stress' is an important issue, but the prevalence of stressors and stress responses, either acute or chronic, remains unclear. In this systematic review, we evaluated the characteristics, prevalence and causes of what was perceived and reported as 'stress' by couples who discontinued ART treatment. Electronic databases were systematically searched, and studies were considered eligible if they evaluated stress as a possible reason for ART discontinuation. Twelve studies were included, with 15,264 participants from eight countries. In all studies, 'stress' was assessed through generic questionnaires or medical records, not by validated stress questionnaires or biomarkers. The prevalence of 'stress' ranged from 11–53%. When the results were pooled, 'stress' was cited as a reason for ART discontinuation by 775 out of 2507 participants (30.9%). Clinical factors associated with worse prognosis, physical discomfort due to treatment procedures, family demands, time pressure and economic burden were identified as sources of 'stress' that contributed to ART discontinuation. Precisely knowing the characteristics of the stress associated with infertility is essential to devise preventive or supportive interventions to help patients to cope and endure the treatments. Further studies are necessary to investigate whether the mitigation of stress factors can reduce ART discontinuation rates.

INTRODUCTION

Globally, it is estimated that millions of individuals suffer with infertility (*Cox et al., 2022*). Assisted reproductive technology (ART) offers new hope for infertile persons and couples to become biological parents, particularly when oocytes are collected before ovarian ageing (*Chambers et al., 2021*). As much as 60% of these individuals, however, forego proposed treatments before achieving pregnancy (*Schröder et al., 2004*; *Miller et al., 2021*). Dropout is an important failure cause in ART, as pursuing several treatment cycles can triple the chance of a live birth compared with a single cycle (*Lande et al., 2015*; *Leijdekkers et al., 2019*; *Gu et al., 2021*; *Miller et al., 2021*).

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1472-6483/
Declaration: The authors report no financial or commercial conflicts of interest.

KEYWORDS

In-vitro fertilization
Discontinuation
Assisted reproductive technology
Stress

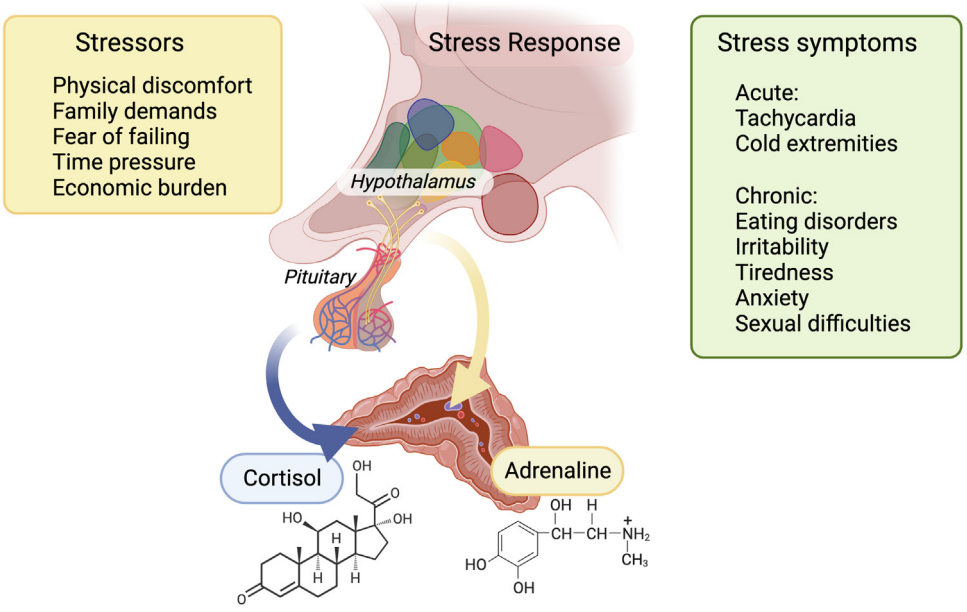

FIGURE 1 Left: examples of stressors (stress factors) cited by women and couples who discontinued assisted reproductive technology treatments; centre: the stress response driven by the hypothalamus–pituitary–adrenal axis; right: acute and chronic stress symptoms that can be assessed through objective questionnaires (adapted from *Tsigos* et al., *2000* and *Nery* et al., *2019*).

By considering the reasons behind ART treatment discontinuation, several studies have indicated that 'stress' is an important cause (*Rooney and Domar, 2018*; *Galhardo et al., 2020*; *Geisler et al., 2020*). Physiologically, stress is defined as an exacerbated, energy-expending response to an environmental event, generated by a threat or by an anticipated threat to organism integrity, whether real or perceived, psychological or physical (*Selye, 1998*). This environmental event is commonly called a stressor or stress factor, whereas reactions to factors are termed stress responses (FIGURE 1). This response is quite complex and induces neurological and metabolic alterations, with central and peripheral repercussions. The stress response starts in the hypothalamus and the brainstem, where specialized neurones produce corticotrophin-releasing hormone and arginine-vasopressin, as well as the locus coeruleus and other central areas that release noradrenaline. The response reaches peripheral organs by endocrine (adrenocorticotropic hormone) and neural (sympathetic) pathways (*Tsigos et al., 2000*). According to its duration, intensity and perception, an individual response can vary widely (*Reis et al., 2020*).

An acute stress factor, such as receiving an infertility diagnosis, activates the sympathetic nervous system and the hypothalamus–pituitary–adrenal axis, which normally prepares individuals for adverse situations (*Stefanaki et al., 2018*). When situations are prolonged, such as years of unsuccessful fertility treatment, an inability to cope may produce a chronic stress state that triggers a catabolic process and causes cell and organ damage (*Lazarus and Folkman, 1984*; *Smeenk et al., 2004*; *Walschaerts et al., 2013*; *Lande et al., 2015*; *Reis et al., 2020*). This state can be distinguished from other psychological phenomena, like anxiety and depression. This is because chronic stress produces a predominantly somatic condition with marked endocrine and autonomic responses (*Lindeberg et al., 2006*; *Stefanaki et al., 2018*).

If stress is an important reason for ART discontinuation, strategies reversing this process can incorporate improved coping mechanisms (*Verkuijlen et al., 2016*; *Sant'Anna et al., 2020*; *Rahimi et al., 2021*) and mitigation of the main stressors. The assessment of chronic stress, however, should ideally include objective scales of physical symptoms and measurement of biomarkers of the stress response (*Tsigos et al., 2000*; *Nery et al., 2019*). Without knowing precisely what people who discontinue ART mean by 'stress', it is difficult to devise preventive or supportive interventions to help them to cope and endure the treatments. In this systematic review, we evaluated the characteristics, prevalence and causes of what was perceived and reported as 'stress' by couples who discontinued ART treatment.

MATERIALS AND METHODS

This study adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (*Page et al., 2021*) and was registered in the International Prospective Register of Systematic Reviews database (PROSPERO, reference CRD42020210932). The electronic bibliographic search was conducted using the databases *PubMed/MEDLINE* and *Scopus*. The search terms used were as follows: ('ART' OR 'in-vitro fertilization' OR 'IVF') AND stress NOT oxidative AND (dropout OR abandon OR discontinuation OR interruption). A comprehensive examination of reference sections in articles was also carried out to identify relevant manuscripts.

The types of study eligible for inclusion were cohort, case-control, cross-sectional and case series. Additional inclusion criteria were as follows: individuals undergoing ART; discontinuation of ART treatment as an outcome; 'stress' as a cause of ART discontinuation; and publication in English. Exclusion criteria were as follows: non-human studies, review articles, case reports and full-text unavailability.

Two research qualified reviewers (ES and SNF) independently read titles and abstracts of retrieved articles using a predefined search strategy and applied study criteria. Selected full texts were read by the same authors and then independently by two other authors (LCT and MC), using the same pre-established criteria. Any disagreements regarding article inclusion or exclusion were discussed until a consensus was reached. Then, data were extracted from selected studies independently by two reviewers. Data extraction included study design and type of questionnaire, participant numbers and characteristics, definition of ART discontinuation, reasons for discontinuing treatment and stress measure.

The methodological quality of selected studies was assessed by two reviewers according to Newcastle–Ottawa Scale (NOS) criteria for case-control, cohort and cross-sectional studies. This scale consisted of three criteria: selection of participants; comparability of study groups; and verification of exposure (for case-control studies) or outcome of interest (for cohort and cross-sectional studies). The score was measured using a star system in which each study could receive 0–9 stars, with a maximum of four stars for the selection category, two for comparability and three for outcome or exposure. The score, or number of stars, was converted to the Agency for Health Care Research and Quality standard, which permitted study classification as poor, fair or good quality (*Shamsrizi et al., 2020*).

RESULTS

Description of studies

Database and manual searches returned 109 non-duplicated articles, of which 97 did not meet inclusion criteria or were excluded for several reasons (FIGURE 2). Finally, 12 articles were selected for this review (*Mao and Wood, 1984*; *Goldfarb et al., 1997*; *Rajkhowa et al., 2006*; *Brandes et al., 2009*; *Moini et al., 2009*; *Domar et al., 2010*; *McDowell and Murray, 2011*; *Khalili et al., 2012*; *Walschaerts et al., 2013*; *Troude et al., 2014*; *Domar et al., 2018*; *Miller et al., 2021*) (FIGURE 2).

Selected studies evaluated 15,264 participants from eight countries. The average age of women was 34 years, mean infertility duration was 5.7 years, and mean number of treatment cycles for each couple was 2.1. Of the 12 articles, eight were cohort studies (seven were retrospective), one was a case-control study and three were cross-sectional studies (TABLE 1). For inclusion criteria, four studies (*Mao and Wood, 1984*; *Goldfarb et al., 1997*; *Domar et al., 2010*; *Troude et al., 2014*) required that participants were starting their first ART cycle, one included only individuals with primary infertility (*Moini et al., 2009*) and another study included only cases of male factor infertility (*Walschaerts et al., 2013*). Three studies (*Khalili et al., 2012*; *Troude et al., 2014*; *Miller et al., 2021*) were multicentric.

In terms of data collection tools, one study used records from a previous survey to evaluate reasons for ART treatment discontinuation (*Troude et al., 2014*), one retrieved information from medical records (*Miller et al., 2021*), whereas the remaining 10 studies used prospective questionnaires completed by participants

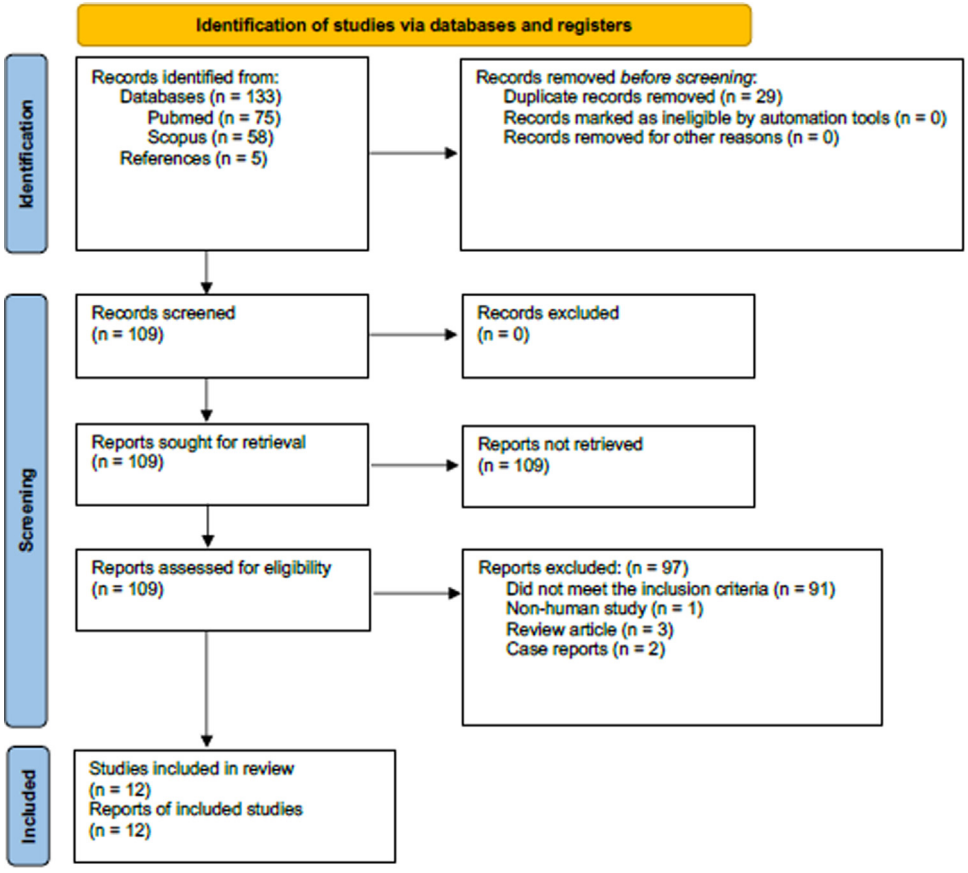

FIGURE 2 Decision flowchart for study selection according to PRISMA 2020 guidelines (*Page et al., 2021*).

TABLE 1 CHARACTERISTICS OF THE INCLUDED STUDIES

Author, year	Country	Design	Participants	Female age (years, mean)	Infertility (years, mean)	ART cycles	Insured ART	Type of questionnaire	Definition of Discontinuation
Mao and Wood, 1984	Australia	Case-control	Couples undergoing the first cycle of IVF.	36	9.0	4	No	Multiple choice	Interrupt ART after the first cycle.
Goldfarb et al., 1997	USA	Retrospective cohort	Women undergoing the first cycle of IVF.	34	6.9	1	No	Likert-type scale with 5 stages	Interrupt ART after the first cycle.
Rajkhowa et al., 2006	Scotland	Retrospective cohort	Couples undergoing ART.	37	10.0	NA	Yes	Multiple choice	Discontinue ART before completing two or three cycles in 6 years.
Brandes et al., 2009	Holland	Retrospective cohort	Couples undergoing ART.	34	2.0	3	Yes	Open	Stop ART up to the time of data analysis.
Moini et al., 2009	Iran	Cross-sectional	Couples with primary infertility.	34	NA	3	No	Open	Interrupt ART after the third cycle.
Domar et al., 2010	USA	Prospective cohort	Women undergoing the first cycle of IVF.	36	3.8	2	Yes	Multiple choice	Discontinue ART before completing the three cycles covered by insurance.
McDowell and Murray, 2011	New Zealand	Retrospective cohort	Couples undergoing IVF treatment.	NA	NA	1	Yes	Likert-type scale with 5 states	Interrupt ART after the first cycle.
Khalili et al., 2012	Iran, Turkey	Cross-sectional	Women who did not get pregnant after embryo transfer.	32	9.0	2	No	Multiple choice	Stop ART.
Walschaerts et al., 2013	France	Retrospective cohort	Couples with male factor infertility.	32	NA	4	NA	Structured interview	Stop ART before getting pregnant.
Troude et al., 2014	France	Retrospective cohort	Couples undergoing the first cycle of IVF.	33	3.0	1	Yes	Multiple choice	Interrupt ART after the first cycle.
Domar et al., 2018	USA	Cross-sectional	Women aged 18–42 years at the time of discontinuation.	35	4.5	1	Yes	Multiple choice	Discontinue ART for 1 year after the first cycle.
Miller et al., 2021	New Zealand	Retrospective cohort	Couples qualifying for publicly funded IVF treatment.	32	3.4	1	Yes	None (only medical records)	Interrupt ART after the first cycle.

ART, assisted reproductive technology; IUI, intrauterine insemination; NA, information not available.

(email, telephone or interview methods). Ten studies used structured questionnaires (multiple choice of Likert-type scale), whereas two asked open questions (TABLE 1).

Results summary

As shown in TABLE 2, 'stress' or some proxy term was cited as a reason for ART discontinuation by 775 out of 2507 participants (pooled prevalence = 30.9, range 11–53%). In all included studies, stress evaluation was subjective and self-reported or based on the retrospective review of annotations in medical records. None of the studies used objective scales to measure stress symptoms or laboratory tests to quantify stress biomarkers (TABLE 2).

In terms of the primary sources of stress during ART treatment, a structured questionnaire answered by 127 women from one IVF centre in the USA highlighted 'infertility taking too much of a toll on our relationship'; 'too anxious or depressed to continue'; 'it was too difficult to get to the IVF centre so often'; 'I had already given IVF my best chance'; and 'could not stand the side-effects of medication' (*Domar et al., 2010*; *Domar et al., 2018*). Clinical factors associated with worse ART prognosis, such as advanced age increased the fear of failing and were reported as important stressors (*Mao and Wood, 1984*; *Troude et al., 2014*). Physical discomfort owing to treatment procedures was also mentioned as a stress factor (*Domar et al., 2010*) and a contributing factor to dropout (*Goldfarb et al., 1997*; *Moini et al., 2009*; *Domar et al., 2010*; *Troude et al., 2014*). Family demands, time pressure and economic burden were also cited as potential stressors (*Mao and Wood, 1984*; *Rajkhowa et al., 2006*; *Brandes et al., 2009*; *Moini et al., 2009*; *Domar et al., 2010*; *Khalili et al., 2012*; *Troude et al., 2014*) (FIGURE 1).

Quality assessment

Newcastle–Ottawa Scale ratings indicated four studies (*Mao and Wood, 1984*; *Goldfarb et al., 1997*; *McDowell and Murray, 2011*; *Walschaerts et al., 2013*) of fair quality and eight of good quality (*Rajkhowa et al., 2006*; *Brandes et al., 2009*; *Moini et al., 2009*; *Domar et al., 2010*; *Khalili et al., 2012*; *Troude et al., 2014*; *Domar et al., 2018*; *Miller et al., 2021*), according to scale conversion thresholds of Agency for Health Care Research and Quality standards (**Supplementary Table**). Consensus was reached on all occasions, and no study was excluded from this review based on the risk of bias.

DISCUSSION

Main findings

In this systematic review, we found that 'stress' was mentioned by a high proportion (>30%) of patients who terminated ART treatments, but quantifiable stress signs, symptoms and biomarkers were not assessed. Clinical factors associated with worse prognosis, physical discomfort caused by treatment

TABLE 2 MAIN RESULTS OF THE INCLUDED STUDIES

Author, year	Selected participants, *n*	Participants with follow-up, *n*	Discontinuation rate, *n* (%)	'Stress' as reason for discontinuation, *n* (%)	Stress measure
Mao and Wood, 1984	228	91	121/228 (53.1)	32/91 (35.2)	Response to questionnaire citing 'disruption of life and strain on marriage'.
Goldfarb et al., 1997	54	28	NA	11/28 (39.3)	Marking 'agree' in a Likert-type scale stating that dropout was due to emotional distress.
Rajkhowa et al., 2006	1510	732	247/732 (33.7)	185/513 (36.1)	Response to questionnaire stating 'psychological stress' as a reason for discontinuation.
Brandes et al., 2009	1391	1347	319/1347 (23.7)	71/319 (22.3)	Self-reported 'emotional distress' in open-ended questionnaire.
Moini et al., 2009	665	338	376/665 (56.5)	169/338 (50.0)	Self-reported 'psychological stress' as a reason for discontinuation.
Domar et al., 2010	390	390	133/390 (34.1)	16/41 (39.0)	Response to questionnaire listing 'causes of treatment stress'.
McDowell and Murray, 2011	1310	526	81/526 (15.4)	43/81 (53.1)	Marking 'agree' or 'strongly agree' in a Likert-type scale for 'stress' as a reason for dropout.
Khalili et al., 2012	621	553	139/553 (25.1)	25/139 (18.0)	Response to questionnaire stating 'psychological stress' as a reason for discontinuation.
Walschaerts et al., 2013	1345	879	407/879 (46.3)	93/407 (22.9)	Response to telephone interview stating 'emotional painfulness of treatment' as a reason for dropout.
Troude et al., 2014	6507	5135	1337/5135 (26.0)	32/299 (10.7)	Medical record stating 'psychological burden of treatment' as a reason for dropout.
Domar et al., 2018	893	312	204/312 (65.4)	82/204 (40.2)	Response to structured questionnaire stating that 'further treatment was too stressful'.
Miller et al., 2021	350	350	47/350 (13.4)	16/47 (34.0)	Medical record stating 'emotional stress' as a reason for dropout.

NA, information not available.

procedures, family demands, time pressure and economic burden were identified as 'stress' factors arising during ART treatment. The included studies had different designs but most used structured questionnaires, whereas two applied open questionnaires in which patients spontaneously reported their reasons behind ART discontinuation.

Interpretation

Woman's age, together with the number of recovered oocytes and the number of viable embryos for transfer, are determining elements of the success or failure of the treatment (*Leijdekkers et al., 2019*). In this context, advanced age *per se* is a source of stress in these patients, which is aggravated in those with diminished ovarian reserve. Fertility preservation through oocyte vitrification is an alternative to 'stop the clock' and reduce time pressure on patients who need to postpone gestation. Female fertility preservation, however, still requires complex, expensive, and sometimes painful procedures, which can be stressful.

Couples with fertility problems may experience a state of mental suffering derived from the uncertainties and demands that come with the clinical condition and treatments (*González-Rodríguez et al., 2020*). Psychological suffering varies according to personal beliefs and social pressure to become parents (*Dancet et al., 2011*). Facing childlessness can be traumatic and challenging, particularly when dealing with feedback from family and friends.

The final decision to terminate treatment may be driven by unrealistic expectations of success and the inability to deal with treatment failure. Many couples enter treatment confidently but end up succumbing to despair after repeated unsuccessful IVF cycles. The realization that live birth rates are typically below 50% per ART cycle, added to the high cost of treatment, contributes to further increase the psychological stress of patients (*McDowell and Murray, 2011*; *Custers et al., 2013*; *Troude et al., 2014*; *Domar et al., 2018*). Financial cost is a relevant stress factor for many individuals because, in many health systems of different countries, ART treatments are not insured (*Rooney and Domar, 2018*; *Oliveira et al., 2021*).

Strengths and limitations

A strength of the present systematic review is that the studies evaluated were fairly homogeneous in objectives, inclusion criteria, discontinuity definitions, data collection tools and outcomes. The overall response rate in studies was high, which provided a broad dataset for analysis. The main limitation of our systematic review is the lack of studies with a robust method to assess and quantify the stress experienced by the participants. Notably, none of the studies evaluated the stress response with objective scales or biomarkers, and all relied on what the participants themselves perceived as 'emotional stress'. The selected studies, although identifying probable associations between stress and ART discontinuation, did not evaluate if stress reduction interventions decreased ART discontinuation rates.

Conclusion and perspectives

In summary, about one-third of the individuals who decide to discontinue ART treatments attribute their decision to the 'stress' associated with treatment failure (or the fear of failing), physical discomfort, family pressure, time constrains and economic burden. As some of these factors cannot be avoided, psychological support may help infertile couples cope with stress and mitigate their psychological suffering (*Domar et al., 2015*). Patients should be well informed, given the opportunity to discuss treatment concerns, and receive guidance on possible negative outcomes. New randomized controlled trials should investigate whether stress-reducing interventions might prevent early dropouts, thereby improving cumulative live birth rates in ART treatments.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2023.01.020.

DATA AVAILABILITY

Data will be made available on request.

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Received 29 December 2022; accepted 24 January 2023.