


BMJ Open Identifying, synthesising and appraising existing evidence relating to myalgic encephalomyelitis/chronic fatigue syndrome and pregnancy: a mixed-methods systematic review

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ABSTRACT

Objectives To identify, synthesise and appraise evidence relating to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and pregnancy.

Design Mixed-methods systematic review, using convergent segregated design.

Data sources MEDLINE, EMBASE, Scopus, PsycINFO, CINAHL, MedRxiv, PROSPERO and grey literature sources through 6 August 2023.

Eligibility criteria We included original research studies, expert opinion and grey literature reporting on ME/CFS and pregnancy/post partum (up to 2 years), risk of pregnancy outcomes with ME/CFS or experiences during pregnancy for mother, partner or health and social care professionals following ME/CFS during pregnancy, all where the evidence was relevant to a confirmed ME/CFS diagnosis prior to pregnancy.

Data extraction and synthesis Three independent reviewers completed all screening, data extraction and quality assessment. Risk of bias was assessed using the mixed-methods appraisal tool V.2018. Qualitative and quantitative literature was analysed separately using thematic and descriptive syntheses. Findings were integrated through configuration.

Results Searches identified 3675 articles, 16 met the inclusion criteria: 4 quantitative (1 grey), 11 qualitative (9 grey) and 1 grey mixed-methods study. Of the four quantitative studies that reported on ME/CFS severity during pregnancy, two suggested pregnancy negatively impacted on ME/CFS, one found most women had no change in ME/CFS symptoms and one found ME/CFS improved; this difference in symptom severity across studies was supported by the qualitative evidence. The qualitative literature also highlighted the importance of individualised care throughout pregnancy and birth, and the need for additional support during family planning, pregnancy and with childcare. Only one quantitative study reported on pregnancy outcomes, finding decreased vaginal births and higher rates of spontaneous abortions and developmental and learning delays associated with pregnancies in those with ME/CFS.

Conclusions Current evidence on ME/CFS in pregnancy is limited and findings inconclusive. More high-quality

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Thorough and systematic search for both peer-reviewed and grey literature relating to myalgic encephalomyelitis/chronic fatigue syndrome and pregnancy that was not limited by date of publication.
- ⇒ Inclusion of both qualitative and quantitative evidence from both peer-reviewed and grey literature sources allowed us to explore different aspects of a complex research question.
- ⇒ Limited evidence was available, particularly peer-reviewed literature, which restricted the conclusions we were able to make in this study.

research is urgently needed to support the development of evidence-based guidelines on ME/CFS and pregnancy.

INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a fluctuating and complex condition involving physical, mental and emotional fatigue.^{1 2} Prior to the COVID-19 epidemic, prevalence was estimated to be between 0.2% and 0.4% in the UK general population, meaning that a general practice with 10 000 patients would have between 20 and 40 patients with ME/CFS.^{2 3} Following the emergence of the COVID-19 pandemic, it is anticipated that rates of ME/CFS may rise, with Long COVID sharing many of the same symptoms as ME/CFS.⁴ ME/CFS is more common, with higher levels of functional disability, in women (Please note that we use the term ‘women’ where this term has been used in the original reference. Our research is relevant to all birthing people and their partners.) than men^{5 6} and tends to develop between mid-20s and mid-40s; this age range includes



people who are of childbearing age (15–45 years).⁷ A meta-analysis of studies from 13 countries suggests that in women with a mean age of 40.0±9.8 years, the prevalence of ME/CFS was 1.4% (0.9–2.0).⁸ Primary research has found that women with ME/CFS who are of childbearing age are concerned about the effects that pregnancy might have on themselves and their infant.^{9 10}

Summary evidence that did not use systematic review methodology, describes clinical and anecdotal evidence suggesting a possible improvement of ME/CFS symptoms during pregnancy,^{10 11} but a relapse of symptoms in the postpartum period.¹⁰ To date, there are no systematic reviews considering the evidence relating to ME/CFS and pregnancy. The lack of quality assessed, and systematic summary evidence relating to ME/CFS and pregnancy, childbirth and the postpartum period makes it harder for people with ME/CFS to make informed decisions about pregnancy, and harder for healthcare professionals to offer evidence-based care and guidance. Based on the prevalence estimate of 1.4%,⁸ and using conception rates for 2020 in the UK (817 515),¹² approximately 11 445 people in the UK and their healthcare providers made decisions about their pregnancies without adequate information. A further unknown number of people would have made a decision to delay or avoid pregnancy, possibly due the lack of information available. A systematic review is required to summarise existing evidence relating to ME/CFS and pregnancy to date and highlight gaps in the evidence.

METHODS

Convergent segregated mixed-methods systematic review methodology was used^{13–16} to address four key research questions shown in [box 1](#), within the overarching aim of assessing and summarising evidence relating to ME/CFS and pregnancy.

Identification of literature

Standard review and reporting relevant to mixed-methods systematic review methods were followed,¹⁷ Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist attached as online supplemental information 1. The search strategy was developed with support from an Information Scientist at

Newcastle University, and for each evidence type consisted of keywords and Medical Subject Headings (dependent on the database) combining the keywords for the population (pregnant and postpartum women), exposure (ME/CFS) and outcomes (pregnancy outcomes, including mental health or experience and attitudes) incorporating elements of the PICOS (Population/Patient Intervention Comparison Outcome Setting) framework for quantitative studies and SPICE (Setting, Perspective, Intervention or exposure, Comparator group and Evaluation) for qualitative studies into our search strategy.

We searched the following electronic bibliographical databases between inception and 6 August 2023: MEDLINE, EMBASE, Scopus, PsycINFO and Cumulative Index to Nursing and Allied Health Literature (CINAHL), MedRxiv and PROSPERO. We also searched relevant grey literature using the National Grey Literature Collection and relevant websites including WHO, Centers for Disease Control and Prevention, Royal College of Obstetricians and Gynaecologists, Royal College of Midwives, American College of Obstetricians and Gynecologists (ACOG), Institute of Health Visiting, ME Association, Action for M.E. and ME Research UK. (The full search strategy is attached as online supplemental information 2).

We searched reference lists of included full papers. We also searched papers that had cited the included papers (citation searching) using Google Scholar. Citation searching, and reference list screening was completed by 6 August 2023. Where there was not enough information in the study or where only a published abstract was available, study authors were contacted for further information. There were no language limitations applied to the search and Google Translate was used to translate relevant articles (one relevant summary article identified and reference list screened¹⁸).

Inclusion criteria

All original research studies, expert opinion articles, commentaries or grey literature that report on ME/CFS and pregnancy/post partum (up to 2 years), risk of pregnancy outcomes with ME/CFS or experiences during pregnancy for mother, partner or health and social care professionals following ME/CFS during pregnancy, all where the evidence was relevant to a confirmed ME/CFS diagnosis prior to pregnancy, were eligible for inclusion. No restrictions were placed on year of publication or language.

Exclusion criteria

Non-human studies and studies including patients with a symptom of fatigue, but not with a diagnosis of ME/CFS were excluded. Abstract only citations were to be excluded; however, this was not required. Relevant reviews were excluded, but reference lists were scanned for relevant studies.

All relevant studies were downloaded to EndNote and duplicates removed. All studies identified by the search strategy were then screened by two reviewers. First, initial

Box 1 Key research questions

1. What is the effect of pregnancy on myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) severity and symptoms during pregnancy and post partum (up to 2 years)?
2. What is the risk of adverse pregnancy outcomes associated with ME/CFS for birthing person and child?
3. What are experiences of, and attitudes towards, pregnancy in people with ME/CFS and their partners?
4. What are health professional's knowledge and attitudes towards pregnancy and ME/CFS?

screening of titles and abstracts was carried out against the predetermined inclusion criteria to identify potentially relevant studies. Exclusion at this stage occurred if both reviewers independently excluded based on inclusion criteria. We then screened the full studies identified as potentially relevant in the initial screening; all full studies were independently screened and then agreed by two reviewers. References were managed and recorded in EndNote V.X9.

Risk of bias and quality assessment

Quality of included studies was assessed independently by two reviewers using the mixed-methods appraisal tool.¹⁹ All studies were included regardless of quality. Based on the user advice given in the Mixed Methods Appraisal Tool,¹⁹ no quality scores were assigned to the studies, rather a more detailed presentation and discussion of the quality has been used.

Quantitative data extraction and synthesis

Quantitative data extraction was carried out independently by two reviewers using an adapted version of the standardised Cochrane Collaboration data extraction tool for non-intervention studies (online supplemental information 3), previously used in a systematic review relating to women's health.²⁰ This was piloted and deemed appropriate by two reviewers. The form included information on study details (study period, study location, etc), study methodology, case ascertainment, statistical analysis (where relevant), and pregnancy outcomes.

Owing to the limited evidence, heterogeneity of pregnancy outcomes and reporting of results in the primary studies, pooling of data was not appropriate, and meta-analysis was not possible. A descriptive synthesis has been used to provide a narrative summary of pregnancy outcomes by the four key research questions of interest (box 1).

Qualitative data extraction and synthesis

Qualitative data extraction was done independently by two reviewers, and informed by the purpose of the review using a specifically developed extraction template²¹ (template available as online supplemental information 4). Primarily, descriptive information was extracted for each study including country, aims of study, study setting, theoretical background of the study, participant characteristics (including diagnosis of ME/CFS), data collection methods and data analysis approach. The next phase of data extraction formed part of the thematic synthesis described below, where relevant quotes were highlighted and recorded in Microsoft Excel. Thematic synthesis was carried out in three stages.²² These were:

1. Coding of text 'line by line': two reviewers independently coded each line of text relevant to ME/CFS and pregnancy according to its content and meaning.
2. Development of 'descriptive themes': two reviewers looked for similarities and differences between codes

Box 2 Questions from Stern *et al*¹³ used to guide integration process

1. Are the findings from the individual quantitative and qualitative synthesis supportive or contradictory?
2. Which aspects of the quantitative evidence are not explored in the qualitative studies?
3. Which aspects of the qualitative studies are not tested in the quantitative studies?

to start grouping them into descriptive themes to capture the meaning of the initial codes.

3. Generation of 'analytical themes': unlike the previous two stages, which keep close to the findings of the primary included studies, this stage is thought to go beyond this to generate additional concepts, understanding or hypotheses²² which we did by reflecting back on our four key research questions that we temporarily put aside at the beginning of the thematic synthesis process. First, this was done by two reviewers and then reviewed by the research team; this review was continued until all descriptive themes were explained within analytical themes.

Integration

Results from quantitative and qualitative syntheses were compared, in relation to the review research questions, to allow integration through configuration. Here, a conceptual model diagram has been developed to arrange and summarise key findings from both the quantitative and qualitative evidence. Questions from Stern *et al*¹³ were used as a guide for the configuration process (box 2).

Patient and public involvement

Patients and the public were not involved in any way in this systematic review.

RESULTS

A total of 3675 articles were identified by the searches, of which 16 met the inclusion criteria.^{9–11 23–35} A PRISMA flow diagram¹⁷ is presented in figure 1. Of these 16, 3 were peer-reviewed quantitative studies^{9 23 25} and 2 were peer-reviewed qualitative articles^{11 28} and 11 were pieces of grey literature.^{24 26 27 29–35} There was one additional quantitative article that could have potentially been included in the review.³⁶ However, following contact with the author, we were unable to clarify whether ME/CFS diagnosis occurred prior to pregnancy and so the article did not meet our inclusion criteria and was excluded from the review.

Quantitative synthesis

Four quantitative studies and one mixed method study were included in the quantitative synthesis and are summarised in table 1. These were two cross-sectional studies, only one of which was peer-reviewed²⁵ with the

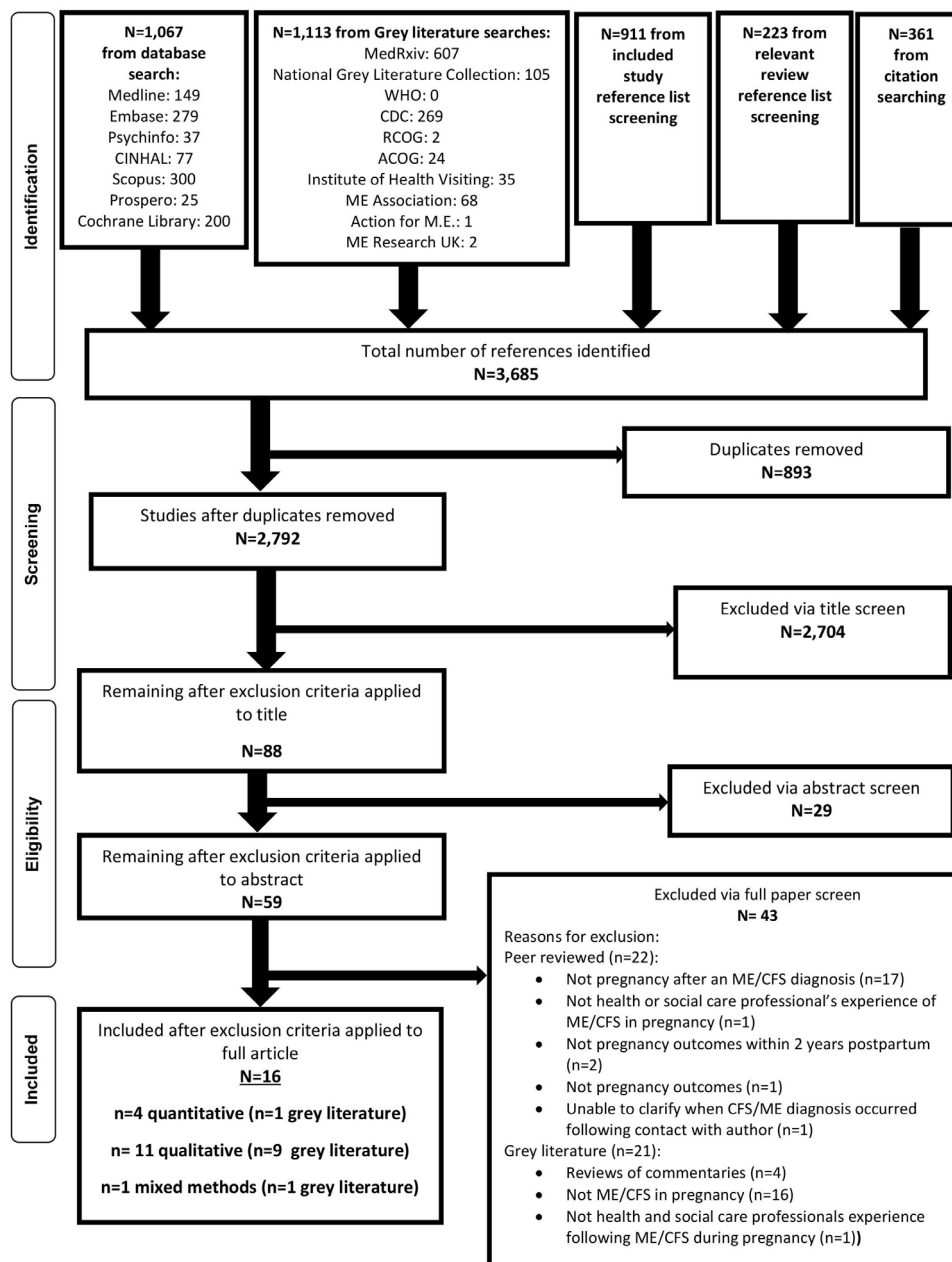


Figure 1 PRISMA flowchart of searches, screening, and inclusion and exclusion of studies. ACOG, American College of Obstetricians and Gynecologists; CDC, Centers for Disease Control and Prevention; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCOG, Royal College of Obstetricians and Gynaecologists.

other being a cross sectional pilot study in the grey literature,²⁴ one observational study of no specified design,⁹ one case-report²³ and one piece of mixed-methods grey literature which included a cross-sectional social media poll on a UK ME/CFS parenting social media group (Facebook).²⁶ Of the included quantitative studies, five (three peer-reviewed^{9 23 25} and two pieces of grey literature^{24 26}) reported on the influence of pregnancy on ME/CFS severity and symptoms during pregnancy and post partum; two reported on the risk of adverse pregnancy outcomes associated with ME/CFS for parent or child,^{9 23} one reported results relating to experiences of, and attitudes towards, pregnancy in parents with ME/CFS and

their partners.⁹ No quantitative studies reported results relating to health professional's knowledge and attitudes towards pregnancy and ME/CFS.

The effect of pregnancy on ME/CFS severity and symptoms both during pregnancy and post partum

Three peer-reviewed studies^{9 23 25} and two pieces of grey literature^{24 26} reported on the effect of pregnancy on ME/CFS severity. Of the three peer-reviewed studies, one observational study from the USA, found that, in pregnancies after the onset of ME/CFS, self-reported ME/CFS symptoms during pregnancy were worse for 20 (29%) women, there was an improvement of symptoms for 21 (30%)

Table 1 Table of included quantitative studies (both grey literature and peer-reviewed)

Author, year of publication, location of study	Type of study	Sample size	Data collection time period	Diagnosis of ME/CFS in study	Pregnancy outcome studied including how measured (self-report/clinician)
Chu <i>et al</i> , 2019, San Francisco Bay area, USA ²⁵	Peer-reviewed: cross-sectional survey	N=200; 121 female (n=26 had ever been pregnant)	January to July 2013	Participants were included if they fitted 'Fukuda 1994 CFS criteria'	Self-reported: Impact of pregnancy on ME/CFS severity
Clark, 2006, Adelaide, Australia ²⁴	Grey literature: cross-sectional pilot study	N=75 (n=12 pregnant during the illness)	2005–2006	Patients meeting the 'Canadian ME/CFS criteria (2003)' were selected to participate in the pilot study	Self-reported: Impact of pregnancy on ME/CFS severity
Pears, 2021, UK ²⁶	Grey literature: mixed methods-quantitative aspect cross-sectional social media poll	N=95	Not specified	Self-reported (members of a ME/CFS support group)	Self-reported: Impact of pregnancy on ME/CFS
Schacterle and Komaroff, 2004, ⁹ Brigham and Women's Hospital, Boston, USA	Peer-reviewed: observational study	N=86 subjects with 252 pregnancies; most pregnancies n=176 (70%), occurred prior to the patient's onset of CFS, n=76 (30%), occurred following CFS onset	Not specified	Participants met the '1994 Centers for Disease Control and Prevention case definition for CFS'	Self-reported: Reasons given for not having children after CFS onset. Severity of symptoms of CFS during and after pregnancy. Maternal outcomes (gestational diabetes, pregnancy induced hypertension or pre-eclampsia, toxæmia and/or eclampsia, vaginal bleeding in the first trimester, vaginal bleeding in the second trimester, severe nausea or vomiting, premature rupture of membranes, premature labour with bed rest and/or hospitalisation, difficult or prolonged labour, placental insufficiency)
Schacterle and Komaroff, 2004, continued. ⁹					Pregnancy outcomes: (live birth, vaginal delivery, live birth caesarean delivery, spontaneous abortion, ectopic pregnancy, induced abortion, stillbirth) Outcomes in the offspring: (birth weight, female sex, premature birth (3 weeks before due date) low birth weight (<2495g), breech presentation, birth defects (they include conditions such as down syndrome or muscular dystrophy), developmental delays, learning disabilities (they include such conditions as dyslexia))
Jha <i>et al</i> , 1999, UK ²³	Peer-reviewed: case report	N=1 female patient with CFS	Not specified	Method of ME/CFS diagnosis not specified.	Self-reported: Weekly sleep quantity Well-being score in pregnancy Clinician reported: Blood pressure urinalysis

Note that the ME/CFS terms in italics are those used by the authors in the original literature source. Quotation marks are used to show where the ME/CFS terms are used in an ME/CFS diagnostic criteria. ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome.

and there was no change in symptoms for 29 (41%).⁹ Self-reported ME/CFS symptoms after pregnancy were worse for 35 (50%) women, there was an improvement of symptoms for 14 (20%) and there was no change in symptoms for 21 (30%).⁹ The other peer-reviewed study was a cross-sectional survey in the USA which included 121 women, 26 of whom had been pregnant.²⁵ Of the 26 women, 8 (31%) experienced no change in ME/CFS symptoms, 11 (42%) experienced worsening fatigue or ME/CFS symptoms and 7 (27%) experienced improved fatigue or ME/CFS symptoms.²⁵ Additionally, there was a case-report from the UK which used a self-reported well-being score to comment on ME/CFS symptoms during and after pregnancy, reporting that during the first and second trimesters, well-being score remained low, and the participant remained bedbound most of the time with the exception of two episodes of higher energy levels.²³ As pregnancy progressed, ME/CFS improved and despite the energy required to care for a newborn baby and breast feeding, the participant continued to improve.²³

Of the two pieces of grey literature, one reported results of a poll posted to a private Facebook group based in the UK.²⁶ The poll asked: 'Did you find it (pregnancy) lessened your ME symptoms? Or made them worse?'.²⁶ Contact with the author confirmed options for responses were; 'Generally, a positive experience-fatigue better', 'Negative experience-fatigue much worse during pregnancy' and 'No change'.²⁶ Of the 95 members of the group who responded to the poll; 55 (58%) stated that they had a positive experience, 12 (13%) stated that they had a negative experience and 28 (29%) stated that they had no change in ME/CFS symptoms.²⁶ The other piece of grey literature was an Australian cross-sectional pilot study of 75 patients with ME/CFS (both men and women), 12 (9%) of whom had been pregnant during the illness; of these, 10 (86%) reported that they were 'made worse by the illness',²⁴ although there was no clarification of exactly what this referred to.

Risk of adverse pregnancy outcomes associated with ME/CFS for parent or child

Two peer-reviewed studies reported on adverse pregnancy outcomes associated with ME/CFS for parent or child.^{9 23} One study was a case-report (n=1) from the UK which reported self-reported weekly sleep quantity; this was found to generally decline as the pregnancy progressed and after delivery and corresponded to well-being scores (well-being scores reflected ME/CFS severity during pregnancy and are reported in the previous section).²³

The second peer-reviewed study was an observational study including pregnancies after the onset of ME/CFS (n=76) and those prior to the onset of ME/CFS (n=176).⁹ There was a significantly increased proportion of spontaneous abortions in the pregnancies occurring after the onset of ME/CFS compared with pregnancies before the onset of ME/CFS (before onset n=13 (8%), after onset n=22 (30%), $p \leq 0.001$). There was also a significantly increased proportion of developmental delays and

learning disabilities (which was defined as 'including conditions such as dyslexia') in offspring of women who became pregnant after the onset of ME/CFS compared with those before the onset of ME/CFS (before onset n=11 (8%), after onset n=9 (21%), $p=0.01$).⁹ The proportion of live birth via vaginal delivery was found to be significantly higher for pregnancies before the onset of ME/CFS (before onset n=116 (68%), after onset n=33 (45%), $p=0.002$), as was the proportion of breech presentation (before onset n=14 (10%), after onset n=0 (0%), $p=0.03$).⁹ There was no significant difference for other outcomes investigated; gestational diabetes, pregnancy-induced hypertension or pre-eclampsia, toxæmia and/or eclampsia, vaginal bleeding in the first or second trimester, severe nausea or vomiting, premature rupture of membranes, premature labour with bed rest and/or hospitalisation, difficult or prolonged labour, placental insufficiency, live birth via caesarean section, ectopic pregnancy, induced abortion, stillbirth, birth weight, sex of baby, premature birth (3 weeks before due date), low birth weight (<2495 g), or 'birth defects' (including conditions such as Down syndrome or muscular dystrophy).⁹

Experiences of, and attitudes towards, pregnancy in parents with ME/CFS and their partners in the form of reasons given for not having children after ME/CFS onset

One study reported results relating to the experiences of, and attitudes towards, pregnancy in parents with ME/CFS and their partners in the form of reasons given for not having children after ME/CFS onset.⁹ This was a peer-reviewed study of 176 pregnancies before the onset of ME/CFS and 76 pregnancies after the onset of ME/CFS from the USA.⁹ Of the 18 (21%) patients reporting that they decided not to have children (or more children) because of the illness, 17 (94%) the most common responses, in relation to their ME/CFS, were that it may impact on their ability to raise small children (17 (94%)) that their children would not be healthy (10 (56%)) and that pregnancy may make their ME/CFS symptoms worse (9 (50%)).⁹

Health professional's knowledge and attitudes towards pregnancy and ME/CFS

No included quantitative studies reported results relating to health professional's knowledge and attitudes towards pregnancy and ME/CFS.

Qualitative synthesis

Twelve pieces of literature were included in the qualitative synthesis (table 2); 2 were peer-reviewed articles: 1 peer-reviewed report on ME/CFS in pregnancy including a pregnant clients experience of unspecified location²⁸ and 1 article which, although included a literature review, also presented opinions of 'CFS experts' in relation to pregnancy and childbirth (please note that the literature review itself is not summarised here, only the relevant quotes from 'CFS experts' and patient reports),¹¹ and 10 were grey literature^{10 26 27 29-35}; 1 section from a book

Table 2 Table of included qualitative articles (both grey literature and peer-reviewed)

Author, year of publication, location of study	Type of study	Aims of study or description of focus of article	Theoretical background of the study	Sampling approach	Participant characteristics including diagnosis of ME/CFS in study	Data collection methods
Allen, 2008, location not specified ¹¹	Peer-reviewed: report including quotes from 'CFS experts' and reports of pregnant patients with CFS	Quotes from medical professionals	N/A	Personal communication	Expert opinion through personal communication. Experience of one 27-year-old pregnant person who had been ill with CFS since the age of 18.	Personal communication
Dvorjetz, 2021, location not specified ²⁹	Grey literature; qualitative report of one women's experience of ME and pregnancy	Several stories from people with ME/CFS describing how they managed to cope with intimacy	N/A	One women's experience of ME and pregnancy	Participant stated to have suffered with ME for 26 years and, for the last 17 years, to have been mainly housebound. Participant married. Method of ME/CFS diagnosis not specified.	Not specified
Hart and Grace, 2000, ²⁷ Canterbury and Wellington, New Zealand	Grey literature; qualitative phenomenological examination	To provide a comprehensive phenomenological examination of n=30 New Zealand women's experiences of CFS	Enaction as a theory of embodied action	n=30 women with CFS or had recovered from CFS. These women were recruited from GP practices in Canterbury and Wellington, and the Christchurch and Wellington ME support groups.	n=10 participants had recovered from CFS at the time of interviews. Method of ME/CFS diagnosis not specified.	60 first-person psycho-phenomenological interviews
Lapp, 2000, location not specified ³⁴	Grey literature; commentary on 'Childbearing and CFIDS' with one women's experience of ME and pregnancy	"This article aims to provide some general advice"	N/A	N/A	Dr Lapp is head of the Hunter-Hopkins Center in Charlotte, North Carolina, USA, and Clinical Associate Professor of Family and Community Medicine at Duke University. One woman who had been ill with 'ME or CFIDS' for 8 years.	N/A
ME Association, 2022, (interview with Dr Charles Shepherd) UK-based charity publication ³³	Grey literature: published transcript of a radio interview with the medical advisor to the 'ME Association'	Woman's Hour discusses ME/CFS	N/A	N/A	Medical advisor to the 'ME Association'	N/A
Pears, 2021, UK ²⁶	Grey literature: mixed-methods-qualitative aspect is authors own experience	Author's reflection of how they navigated their journey while living with ME/CFS	N/A	Author's experience (also includes reflection of a friend's experience of ME/CFS in pregnancy)	Married, 37 weeks pregnant at the time of writing article. Also discusses a friend's experience of ME/CFS in pregnancy Method of ME/CFS diagnosis not specified.	Author's own reflection and reflection of a friend's experience of ME/CFS in pregnancy

Continued

Table 2 Continued

Author, year of publication, location of study	Type of study	Aims of study or description of focus of article	Theoretical background of the study	Sampling approach	Participant characteristics including diagnosis of ME/CFS in study	Data collection methods
Peachey, 2001, not specified ²⁸	Peer-reviewed: report including one pregnant client's qualitative experience	The relevant section presents one pregnant clients experience of pregnancy	Not stated	One pregnant client's experience of ME	Method of ME/CFS diagnosis not specified.	Not specified
Redshaw, 2019, not specified in the article, but author in UK ³⁰	Grey literature: qualitative report of authors own experience	A description of personal experience of the emotional impact of a long-term physical illness (ME)	N/A	Author's experience	Author states they have been unwell every single day since September 2010 (article published in 2019). Method of ME/CFS diagnosis not specified.	Author's own reflection
Shepherd, 2020, UK based charity publication ³¹	Grey literature: commentary on ME/CFS and pregnancy	Commentary on ME/CFS and pregnancy by the medical advisor to the 'ME Association'	N/A	Commentary from a medical professional	Medical advisor to the 'ME Association'	N/A
Shepherd, 1999, UK ³²	Grey literature: case history (self-reported reflection) and author's note	Not stated but a reflection on experience of ME/CFS in pregnancy by one person and a note from the author of the book who is a medical professional	N/A	Experience of a person living with ME/CFS and note from the author (medical professional)	Self-reported case history of a 37-year-old female with ME/CFS in pregnancy; method of ME/CFS diagnosis not specified. Medical doctor with expertise in ME/CFS.	N/A
Underhill, 2009, location not specified but published by 'New Jersey Chronic Fatigue Syndrome Association' ³⁵	Grey literature: commentary on ME/CFS and pregnancy	Commentary on 'Pregnancy in Women with Chronic Fatigue Syndrome (ME/CFS)' by a surgeon and obstetrician/gynaecologist	N/A	Commentary from a medical professional	Surgeon and obstetrician/gynaecologist who was consultant and member of the board of Trustees of the 'New Jersey ME/CFS Association'	N/A
Young, 2005, location not specified but published by a US charity ¹⁰	Grey literature: quotes from medical professionals	Quotes from medical professionals included within an article published by the 'CFIDS Association of America'	N/A	Article by the Director of Publications of the "CFIDS Association of America"	Various medical professionals including one endocrinologist and gynaecologist from Amsterdam and four Doctors of Medicine with special interests and expertise in CFS.	N/A

Note that the ME/CFS terms in italics are those used by the authors in the original literature source. Quotation marks are used to show where the ME/CFS terms are used in the name of an organisation.

CFIDS, chronic fatigue syndrome and immune function disorder; CFS, chronic fatigue syndrome; GP, General Practitioner; ME, myalgic encephalomyelitis.

which included an experience of pregnancy with ME/CFS and the author's comments as a medical professional from the UK,³² 1 qualitative thesis from New Zealand²⁷ and 8 articles published by ME/CFS charities^{10 26 29–31 33–35}; 1 published transcript from a radio interview with the medical advisor to the 'ME Association',³³ 1 commentary on pregnancy, childbirth and ME/CFS from the medical advisor to the 'ME Association',³¹ 1 piece that presented experiences of ME/CFS in pregnancy from the UK,²⁶ 1 piece presenting a personal experience around childlessness from the UK,³⁰ 2 pieces from a US charity relating to reproductive issues in those with ME/CFS,¹⁰ and child-bearing in ME/CFS,³⁴ 1 piece from another US charity relating to pregnancy in women with ME/CFS,³⁵ and 1 piece relating to personal relationships and intimacy that included a personal experience relating to pregnancy which did not specify location.²⁹

From these, five main analytical themes emerged; (1) a difficult decision, (2) the impact of pregnancy and childcare on ME/CFS severity is very individual, (3) the importance of individualised care and healthcare professionals acknowledging the impact of ME/CFS, (4) additional support and (5) pregnancy outcomes and fertility in those with ME/CFS.

A difficult decision

This theme was identified within eight included articles.^{10 26 29–32 34 35} It related to factors in general life, but was also specific to ME/CFS, and how these different factors make any decision about trying to start a family a very difficult one with 'careful thought and planning' required.^{31 34} Evidence from medical professionals highlighted particular factors to consider in the decision-making process including current status of, and stability of health, need for medication and dietary changes, maternal age, ability to cope with childcare and the level of support you would need.^{31 32 34 35} Current state of health was highlighted as the 'most important' factor by one medical professional,³¹ and it was recommended that if age allowed, it would be best to wait until symptoms had improved and stabilised to contemplate pregnancy.^{31 32 35} While another medical professional stated that 'coping with childcare is the largest factor in deciding whether or not to have a baby'.³⁴

Quotes from those living with ME/CFS referred to there being 'a lot to consider'²⁶ when making the decision, including 'the impact on your M.E./CFS symptoms'²⁶ and how 'making an informed decision is difficult due to the lack of research and the huge variation in pregnancy experiences'.²⁶ There were also aspects of ME/CFS severity impacting on the decision with some quotes referring to how the severity of the author's ME/CFS had meant that they had concluded not to have children.³⁰ This author also discussed how coming to 'this devastating conclusion'³⁰ had impacted on them, referring to an 'internal conflict'³⁰ whenever a friend announced a pregnancy. Others living with ME/CFS stated that their current status of health made it a 'very difficult decision'.³²

The impact of pregnancy and childcare on ME/CFS severity and management is very individual

This theme was identified within eight included articles.^{10 11 26 28 31 32 34 35} Information from those living with ME/CFS in pregnancy demonstrated that the impact of pregnancy on ME/CFS severity was different for different people with one article commenting 'pregnancy was really tough'²⁶, while another stated 'during my pregnancy my ME was much improved'.²⁸ Evidence from medical professionals also highlighted this difference.^{11 31 34} There was also discussion around the management of ME/CFS in pregnancy, and how it is important to 'listen to your body'²⁶; with evidence highlighting that that even within the same person with ME/CFS, the experience and outcome of pregnancy could be different depending on the stage of pregnancy^{26 35} and between pregnancies in the same person.³⁵ Evidence from medical professionals also highlighted the possibility of relapse of ME/CFS symptoms in the postpartum period^{11 34 35} which they stated may due to 'physiologic reduction in red cell mass and blood volume that increased in pregnancy, and/or to the cumulative stress of interrupted sleep and demands of caring for an infant'¹¹ and 'the loss of the elevated pregnancy hormones'.³⁵

The importance of individualised care and healthcare professionals acknowledging the impact of ME/CFS

This theme was identified within seven included articles.^{11 26 28 31 32 34 35} Articles discussed both medical care pathways and practicalities. This related to how those with ME/CFS should be under consultant-led care rather than midwife-led care only, and how decisions around pain management and birth options should be the right options 'for you',²⁶ and discussed with healthcare professionals 'well in advance of the baby's due date'.³⁴ Accessibility of appointments was also discussed; evidence from someone with ME/CFS highlighted that attending antenatal appointments in person led to relapses in symptoms of ME/CFS due to 'travelling to the hospital and sitting in a hot room for extended periods of time'.³⁴ This person also reflected on how having a private room after the birth helped as it 'kept me apart from the noise and let me get better rest'.³⁴

Evidence from a medical professional highlighted that general pregnancy management is still applicable to those with ME/CFS,³¹ for example, any medication and supplement usage should also be discussed with healthcare professionals, and any 'potentially dangerous' drugs stopped.³⁵ Evidence from both medical professionals and from an experience of a patient with ME/CFS in pregnancy noted the lack of knowledge of ME/CFS among healthcare professionals.³² One article reflecting the experiences of a patient with ME/CFS in pregnancy not only highlighted the negative impact of midwives not acknowledging their ME/CFS, but also, how having a midwife who was willing to listen and learn about how ME/CFS made a huge difference and impacted positively on the patient experience.²⁸

Additional support is needed

This theme was identified within seven included articles,^{26 29–32 34 35} and referred to different types of support needed during pregnancy, and with childcare. Evidence from medical professionals and someone living with ME/CFS^{29 34} highlighted that additional support from partner, family and friends is ‘vital’³¹ during pregnancy and the postpartum period. Another article stated that where this support is not available, additional support may need to be hired.³⁴ Evidence from both those living with ME/CFS²⁶ and medical professionals,^{31 34 35} also underlined the importance of talking to, and getting advice from other people with ME/CFS. Talking to others was also seen to be beneficial for the author who had concluded they would not be able to have children due to the severity of their ME/CFS, but in this case the support came from a healthcare professional ‘further removed than my own support network’.³⁰

Pregnancy, fertility, labour and birth outcomes in those with ME/CFS

This theme was identified within seven of the articles.^{11 26 27 29 32 34 35} The information related to specific pregnancy outcomes experienced by people with ME/CFS, and outcomes that have been observed in those living with ME/CFS in pregnancy by medical professionals. Evidence from medical professionals highlighted that there may be a higher risk of postpartum depression in those with ME/CFS,³⁵ and hormone-related changes in fatigue during pregnancy may be worse in those living with ME/CFS, especially if they have a history of depression.³² In addition, there was said to be no evidence for the risk of miscarriage being higher in those with ME/CFS,^{32 34} and that there may be an increased length of hospital stay following birth due to ME/CFS symptoms.³⁴ These anecdotal reports also stated that ‘if ME/CFS is caused by a virus’,³⁴ there is a small theoretical possibility of viral transfer across the placenta,³² via the birth canal or through breast milk.³⁴

Evidence from those living with ME/CFS described experience of outcomes from conception to the postnatal period. A decline in mental health in pregnancy was experienced by some people with ME/CFS, for example, one person noted that they ‘became very anxious about whether our decision had been wise’³² after pregnancy confirmation. In addition, one person living with ME/CFS described how they ‘...could cope with the first stage of labour, but by the second stage were completely exhausted...had no urge to push and no strength to push either’³² leading to a forceps delivery. Breast feeding was also mentioned by three of the articles; one person found breastfeeding ‘worked well’,³² another experienced not being able to produce breast milk following either of her pregnancies and ‘put this down to the body just being too exhausted to make any’,²⁹ and the third was a ‘CFS

expert’s’ report of a patient who ‘breastfed her infant until 2 weeks postpartum, at which time she weaned because of a concern that the rigours of night-time feedings would trigger a CFS relapse’.¹¹

Integration of qualitative and quantitative synthesis

Overall, findings from individual quantitative and qualitative syntheses are supportive. Evidence from the quantitative synthesis related mainly to pregnancy outcomes in those with ME/CFS, severity of ME/CFS in pregnancy and reasons for not having children after ME/CFS onset. It also related to the impact of pregnancy on ME/CFS severity and how this could be very different for different people, which again was also seen in the quantitative evidence both during pregnancy and in the postpartum period. Qualitative evidence highlighted that there was a difficult decision around whether or not to have children, alongside the factors affecting this decision; this theme was found to be supported by the quantitative evidence. The evidence from the qualitative synthesis is also related to pregnancy outcomes in those with ME/CFS; with discussion of outcomes experienced by those with ME/CFS or outcomes seen in the literature. One area of conflict was around miscarriage (or ‘spontaneous abortion’), with the qualitative evidence suggesting that people with ME/CFS have no increased risk of miscarriage, while the quantitative evidence suggested that there was an increase in the rate of spontaneous abortion. However, this difference may be explained by the dates of publication; 1999³² and 2000³⁴ for the qualitative articles, and 2004 for the quantitative study,⁹ additional factors such as maternal age not being adjusted for, or the limited evidence available.

Some aspects of the qualitative evidence were not identified in the quantitative studies; while the impact of not having children due to ME/CFS was discussed within the qualitative literature, this was not explored or highlighted by the quantitative evidence. In addition, while the qualitative evidence highlighted the importance of individualised care and of healthcare professionals acknowledging the impact of ME/CFS, this was not captured in the quantitative evidence. The qualitative evidence also highlighted the importance of additional support both from friends and family during pregnancy and with childcare, and additional support regarding the impact of the conclusion not to have children from outside the social network, from healthcare professionals. This concept of additional support was not captured in the quantitative evidence. There was also very limited included evidence (qualitative or quantitative) that captured knowledge of, and attitudes towards ME/CFS and pregnancy among healthcare professionals. While qualitative evidence did include commentaries and opinions from medical professionals, these were more related to advice for patients and healthcare professionals, rather than detailed experiences in clinical practice, insight into attitudes or information on existing knowledge.

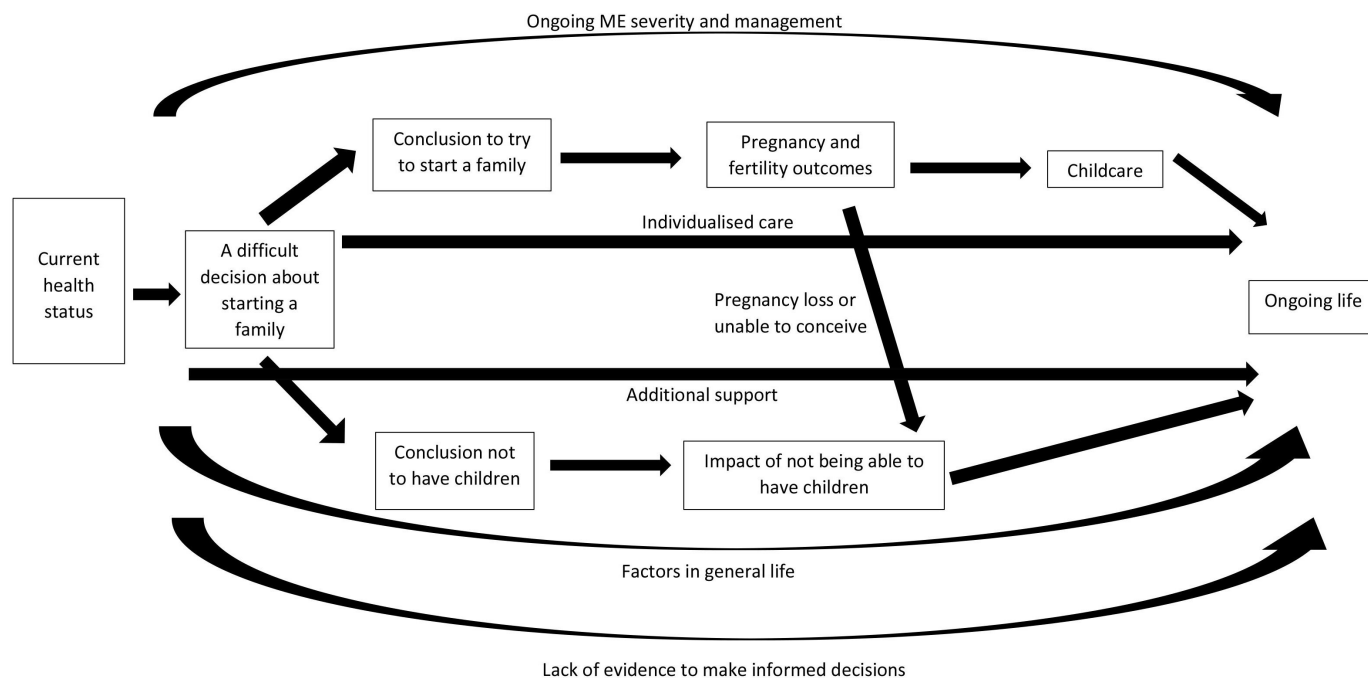


Figure 2 Conceptual model generated through integration phase of review. Note: Key findings have been presented starting with current health status impacting on a difficult decision regarding whether or not to have children. This moves to either the impact of coming to the conclusion not to have children due to ME/CFS or deciding to try to start a family. If the decision is taken to try to start a family, evidence from this review discussed pregnancy (there was no evidence relating to other methods of starting a family, eg, adoption) and then to childcare, or pregnancy loss. Overarching arrows also represent how ongoing ME/CFS severity and management, factors in general life and lack of evidence to make informed decisions impact on every phase of the process. Arrows also highlight the importance of individualised care, and additional support. ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome.

Results from the qualitative and quantitative synthesis have been combined to develop a conceptual model diagram shown in figure 2.

Quality assessment

Results from the quality assessment (QA) are shown in table 3. For 2 of the quantitative^{23 26} and 10 of the qualitative articles^{10 11 26 27 29–35} (note: 1 grey literature article contained both qualitative and quantitative evidence so has been assessed as both²⁶), there was no clear research question. The main issues in the quantitative literature related to not being able to tell if the included population was representative of people with ME/CFS who could become or had been pregnant, and a potentially high risk of non-response bias in at least three of the studies as the response rate was <80%.^{9 24 25} In the qualitative literature, the main issue related to the articles not providing details to answer the QA questions, mostly because they were from the grey literature and not peer-reviewed research studies. The one study that did provide sufficient details appeared to be of high quality, however, the aims of the research did not relate directly to ME/CFS in pregnancy.²⁷

DISCUSSION

This systematic review set out to assess and summarise evidence relating to ME/CFS and pregnancy. Despite thorough searches of the literature, we found very limited

evidence relating to ME/CFS and pregnancy with only 16 articles relevant for inclusion. The impact of pregnancy on ME/CFS severity was found to vary within and between studies, and this was consistent across quantitative and qualitative literature. Qualitative evidence suggested that the experience is different from person to person, and quantitative evidence showed differences in rates of participants with no change in symptoms, worsening symptoms and improved symptoms both during pregnancy and post partum. The risk of adverse pregnancy outcomes was also considered in both the qualitative and quantitative evidence, although evidence was again very limited. For those with ME/CFS, increased spontaneous abortions and developmental and learning delays alongside decreased vaginal births were reported in the quantitative literature. The need for forceps delivery, decreased mental health and issues with breast feeding were also discussed in the qualitative literature. Experiences of, and attitudes towards, pregnancy in people with ME/CFS were presented predominantly in the qualitative literature, although the quantitative literature did explore reasons for not having children, there was no evidence directly presenting experiences of partners of those with ME/CFS. There was limited evidence relating to experiences of healthcare professionals themselves identified in this review, although the importance of individualised care, healthcare professionals being knowledgeable or willing

Table 3 Quality assessment of included studies

Quantitative evidence										
Author, year	Screening questions			Quantitative study quality assessment questions						
	Are there clear research questions or objectives?	Do the collected data allow to address the research questions?	Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of non-response bias low? (Is response rate >80%)	Is the statistical analysis appropriate to answer the research question?			
Chu <i>et al</i> , 2019 ²⁵	Yes	Yes	Yes	Cannot tell	Yes	No	Yes			
Clark, 2006 ²⁴	Yes	Yes	Yes	Cannot tell	Yes	No	Yes			
Jha <i>et al</i> , 1999 ²³	No	Cannot tell	Cannot tell	Cannot tell	No	Yes	Cannot tell			
Schacterle and Komaroff, 2004 ⁹	Yes	Yes	Yes	Yes	Yes	No	Yes			
Pears, 2021 ²⁶	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Allen, 2008 ¹¹	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Hart and Grace, 2000 ²⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Lapp, 2000 ³⁴	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
ME Association, 2022 ³³	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Peachey, 2001 ²⁸	Yes	Yes	Yes	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Pears, 2021 ²⁶	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Redshaw, 2019 ³⁰	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Dvorjetz, 2021 ²⁹	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Shepherd, 2020 ³¹	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Shepherd, 1999 ³²	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Underhill, 2006 ³⁵	No	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			
Young, 2005 ¹⁰	ON	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell			

to learn about ME/CFS and acknowledging the impact of ME/CFS on pregnancy, emerged from the qualitative literature relating to experiences of people with ME/CFS themselves.

The evidence included in this review was limited by quality; only 5 of the 16 included studies provided peer-reviewed evidence.^{9 11 23 25 28} The quantitative evidence was limited by small sample size, lack of a healthy control group and the fact that no studies considered the impact of potential confounders or effect modifiers such as maternal age or additional pre-existing health conditions in their analysis. This may mean that the observed results could be explained by other factors; for example, Schacterle and Komaroff highlight in their discussion of results that the higher rate of miscarriage could be explained by increased maternal age.⁹ Qualitative evidence was also limited in quality, and where quality was higher, the research question was not directly related to pregnancy and only one quote was applicable to this review.²⁷ Evidence was also limited by a lack of consistency in the terminology used for ME/CFS, and in how ME/CFS was diagnosed and defined. This further impedes comparisons between studies and limits the conclusions that can be drawn.

Although literature reviews relating to pregnancy and ME/CFS have been published,^{11 37 38} ours is the first review using systematic review methodology to explore ME/CFS and pregnancy. Despite the limited evidence available, included studies did allow separate quantitative and qualitative syntheses to be carried out, followed by an integration phase. Evidence was most limited reflecting experiences of healthcare professionals in practice; although we identified evidence written by, or including opinions of medical professionals, these tended to provide practical advice around planning for and management of pregnancy for those with ME/CFS, or thoughts on existing research, rather than detailed experience of care provision and current practice.

Due to the limited evidence available in this review, it was not possible to consider either the experience of pregnancy, or pregnancy outcomes by level of ME/CFS severity, or to investigate the effect of pregnancy on ME/CFS severity by specific stage of pregnancy, or in birth and labour. In addition, while both the qualitative and quantitative evidence included in this review highlighted that there was a difficult decision to be made for those with ME/CFS and their partners around whether to start a family, there was no evidence relating to those who may be too unwell for this to be a 'decision'; where their health may take away any process of contemplation around becoming a parent. Those with severe and very severe ME/CFS are under-represented in research, in part because the significant health burdens experienced make participation difficult.³⁹ This means that the evidence available to date, and so the results from this review, may be limited to those with ME/CFS whose health status allows them to be in a position to make a decision around whether or not to have children. We also identified no

evidence that considered the partner's experience of supporting someone with ME/CFS through pregnancy and around related decision-making, and no evidence relating to the option and process of adoption for those living with ME/CFS.

This review has underlined the importance of both individualised care, and of healthcare professionals learning about ME/CFS in relation to family planning and pregnancy. It has also highlighted the lack of evidence available relating to ME/CFS and pregnancy. This lack of evidence means that there are currently no evidence-based guidelines for management of ME/CFS and pregnancy, and that those with ME/CFS, their partners and healthcare professionals are unable to make informed, evidence-based decisions around family planning, pregnancy, labour and birth. More research is urgently needed, considering all aspects of pregnancy and ME/CFS for patients and healthcare professionals. In particular, research should explore what would constitute high-quality care for those with ME/CFS relating to pregnancy and family planning. Quantitative research with larger sample sizes, healthy control groups and clearly defined research questions is required; this should consider ME/CFS severity in pregnancy, labour, birth and post partum; pregnancy outcomes in those with ME/CFS; and how prepregnancy ME/CFS severity impacts on these. Research into ME/CFS, pregnancy and related topics, should work towards the use of a standard diagnostic criteria for ME/CFS, with all studies being clear and transparent about the diagnostic criteria, and definitions used.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This is a systematic review study and does not involve human or animal participants therefore no ethical approval was required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data extraction form templates can be found as Supplementary Information 3 and 4. Data extracted from included studies is available from the authors upon reasonable request. No statistical code or analysis was used for this systematic review. The protocol for this review was registered in PROSPERO under CRD42022303774 and is available at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=303774. Amendments were made to add an additional review team member (KAP), and to update the exclusion criteria following protocol publication.⁴⁰



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Supplementary Information 1: PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg.1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg. 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg.5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pgs.5-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg.5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary information 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pgs.6-7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pgs.6-7 and supplementary material 3+4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pgs.6-7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pgs.6-7 and supplementary material 3+4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg.6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pgs. 6-8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pgs. 7-8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pgs. 7-8

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pgs. 7-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pgs. 7-8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n/a
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	n/a
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	n/a
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pg. 8, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pg. 8-9
Study characteristics	17	Cite each included study and present its characteristics.	Tables 1 and 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 3, pg. 20
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Summarised in tables 1 and 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Tables 1,2+3, Pgs. 20-24
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	n/a
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n/a
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pgs. 27-28
	23b	Discuss any limitations of the evidence included in the review.	Pgs. 27-28

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Pgs. 27-28
	23d	Discuss implications of the results for practice, policy, and future research.	Pgs. 27-28
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg. 29
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg. 29
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Pg.29
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg. 29
Competing interests	26	Declare any competing interests of review authors.	Pg. 29
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pg. 29 and supplementary material 3 and 4

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Information 2: Electronic bibliographical database searches**Medline (run 03.08.22)**

Ovid MEDLINE(R) 1946 to July week 4 2023

#	Searches	Results
1	exp pregnancy/	1007163
2	(pregnan* or birth* or parturition or gestation).ti,ab,kw,kf.	854214
3	(preconception or pre-conception).ti,ab,kw,kf.	5342
4	gravid*.ti,ab,kw,kf.	14554
5	Fatigue Syndrome, Chronic/	6172
6	(chronic fatigue or CFS).ti,ab,kw,kf.	11402
7	Myalgic encephalomyelitis.ti,ab,kw,kf.	1164
8	or/1-4	1296825
9	or/5-7	12450
10	8 and 9	180
11	exp animals/ not exp humans/	5140329
12	10 not 11	149

Embase (search run 03/8/23)

Database(s): Embase 1974 to 2023 August 02

#	Searches	Results
1	exp Pregnancy/ or birth/	784771
2	(pregnan* or birth* or parturition or gestation).ti,ab,kw,kf.	1184071
3	(preconception or pre-conception).ti,ab,kw,kf.	9231
4	gravid*.ti,ab,kw,kf.	21653
5	chronic fatigue syndrome/	11965
6	(chronic fatigue or CFS).ti,ab,kw,kf.	18950
7	Myalgic encephalomyelitis.ti,ab,kw,kf.	1766
8	or/1-4	1419492
9	or/5-7	22381
10	8 and 9	318
11	exp animal/ not exp human/	5118579
12	10 not 11	279

PSYCHINFO (run 03.08.23)

Database(s): APA PsycInfo 1806 to October Week 5 2022

#	Searches	Results
1	exp pregnancy/ or exp birth/	48863
2	(pregnan* or birth* or parturition or gestation).ti,ab,id.	115735
3	(preconception or pre-conception).ti,ab,id.	1097
4	gravid*.ti,ab,id.	788
5	Chronic Fatigue Syndrome/	2136
6	(chronic fatigue or CFS).ti,ab,id.	3740
7	Myalgic encephalomyelitis.ti,ab,id.	356
8	or/1-4	123275
9	or/5-7	3801
10	8 and 9	37

Scopus (run 03.08.23)

TITLE-ABS-KEY (pregnan* OR birth* OR parturition OR gestation OR preconception OR pre-conception OR gravid*) AND TITLE-ABS-KEY ("chronic fatigue" OR cfs OR "Myalgic encephalomyelitis") AND (EXCLUDE (SUBJAREA , "AGRI") OR EXCLUDE (SUBJAREA , "VETE"))

300 results**CINAHL via EbscoHost (run 03.08.23)**

S1	(MH "Pregnancy+")	240,762
S2	(MH "Childbirth+")	34,743
S3	TI (pregnan* or birth* or parturition or gestation) OR AB (pregnan* or birth* or parturition or gestation)	261,155
S4	TI (preconception or pre-conception) OR AB (preconception or pre-conception)	3,450
S5	TI gravid* OR AB gravid*	4,226
S6	S1 OR S2 OR S3 OR S4 OR S5	358,322
S7	MH ("Fatigue Syndrome, Chronic")	3,371
S8	TI (chronic fatigue or CFS) OR AB (chronic fatigue or CFS)	5,428
S9	TI Myalgic encephalomyelitis OR AB Myalgic encephalomyelitis	611
S10	S7 OR S8 OR S9	6,206
S11	S6 AND S10	77

Prospero (run 10.11.22)

- 1) Pregnancy OR Pregnant OR Maternal OR Gestation OR parent OR birth OR Preconception OR postconception OR prenatal OR neonatal OR neonatology 30843
- 2) chronic fatigue syndrome 299
- 3) Myalgic encephalomyelitis 88
- 4) 2 or 3 299
- 5) 1 and 4 25

Cochrane library (run 06.08.23)

ID	Search	Hits
#1	MeSH descriptor: [Pregnancy] explode all trees	31338
#2	MeSH descriptor: [Parturition] explode all trees	734
#3	(pregnan* or birth* or parturition or gestation):ti,ab,kw	107573
#4	(preconception or pre-conception):ti,ab,kw	739
#5	(gravid*.):ti,ab,kw	1416
#6	MeSH descriptor: [Fatigue Syndrome, Chronic] explode all trees	499
#7	(chronic fatigue or CFS):ti,ab,kw	8398
#8	(Myalgic encephalomyelitis):ti,ab,kw	113
#9	{OR #1-#5}	108262
#10	{OR #6-#8}	8401
#11	#9 AND #10	200

Grey and unpublished literature searches**MedRxiv 06.08.23**

Chronic fatigue and pregnancy	555
Myalgic encephalomyelitis and pregnancy	52

National Grey Literature Collection (<https://allcatsrgrey.org.uk/wp/>) 06.08.23

Chronic fatigue and pregnancy	92 (5 full text screen not relevant)
Myalgic encephalomyelitis and pregnancy	13 (0 relevant)

WHO 06.08.23

Chronic fatigue and pregnancy	0
Myalgic encephalomyelitis and pregnancy	0

CDC 06.08.23

“Chronic fatigue” and pregnancy	208
“Myalgic encephalomyelitis” and pregnancy	61

RCOG 06.08.23

Chronic fatigue	2
Myalgic encephalomyelitis	0

Royal college of Midwives 06.08.23

Chronic fatigue	0
Myalgic encephalomyelitis	0

ACOG 06.08.23

Chronic fatigue	24
Myalgic encephalomyelitis	0

Institute of Health Visiting 06.08.23

Chronic fatigue	35
Myalgic encephalomyelitis	0

ME Association 06.08.23

Pregnancy	68
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Action for M.E. 06.08.23

Pregnancy	1
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ME Research UK 06.08.23

Pregnancy	2
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Supplementary Information 3: Quantitative data extraction template**Data Extraction Form adapted from the Cochrane Collaboration**

Title of the systematic review: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and pregnancy: a mixed-methods systematic review

Notes on using data extraction form:

- Be consistent in the order and style you use to describe the information for each report.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s), not that you forgot to extract it.
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.

General Information

Date form completed (<i>dd/mm/yyyy</i>)	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type (<i>e.g. full report, abstract, letter</i>)	
Year of publication	
Notes:	

Study eligibility

Study Characteristics	Eligibility criteria	Location in text or source (<i>pg & ¶/fig/table/other</i>)
Type of study		
Population description		
Diagnosis of ME/CFS prior to pregnancy?		
Types of outcome measures		
Decision (with reasons for either inclusion or exclusion)		

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Population and setting

	Description <i>Include comparative information for each intervention or comparison group if available</i>	Location in text or source (pg & ¶/fig/table/other)
Population description <i>(from which study participants are drawn)</i>		
Dates of recruitment		
Setting <i>(including location i.e. country and city and social context)</i>		
Inclusion criteria		
Exclusion criteria		
Method of recruitment of participants <i>(e.g. phone, mail, clinic patients)</i>		
Withdrawals and exclusions <i>(if not provided below by outcome)</i>		
Notes:		

Methods

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Aim of the study		
Study design		
Study start date		
Study end date		

Notes:

Participants

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Total number of participants/sample size		
ME/CFS status		
Self-report or clinician diagnosis		
Information on length of diagnosis		
Information on severity of ME/CFS		
Age (mean, range, groups etc)		
Sex		
Ethnicity		
Co-morbidities		
Other relevant sociodemographics		
Any subgroups reported		
Notes:		

Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Outcome name		
Outcome definition (<i>with diagnostic criteria if relevant</i>)		
How outcome measured (<i>e.g. self report, clinician defined or not specified</i>)		
Notes:		

Results and findings

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Outcome		
Results		
Statistical analysis method used		
Response/non-response rate		
Notes:		

Other

Study funding sources (<i>including role of funders</i>)		
Possible conflicts of interest (<i>for study authors</i>)		
Notes:		

Other information

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Key conclusions of study authors		
Correspondence required for further study information (<i>from whom, what and when</i>)		
Notes:		

Supplementary Information 4: Qualitative data extraction template

Reference	Country	Aims of study	Study setting	Theoretical background of study	Sampling approach	Participant characteristics including details of diagnosis of ME/CFS	Data collection methods	Data analysis approach