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REVIEW

A critical systematic review and meta-analyses of risk factors for fertility problems in a globalized world

BIOGRAPHY

Bayoumi is Associate Prof. of Psychology and Head of Research at University of Birmingham, Dubai. She has experience in research, clinical practice and teaching. She worked for the WHO and was Takemi Fellow at Harvard School of Public Health. Her research interests include reproductive health, infertility and gender-based violence.

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KEY MESSAGE

Systematic reviews on risk factors for fertility problems disproportionately affecting the Global South uncovered several preventable risk factors: bacterial vaginosis; genital tuberculosis; female genital mutilation/cutting; consanguinity in parents; and dilatation and curettage. The results can inform future research, practice, advocacy and policy change, improving overall health and safety of women.

ABSTRACT

Globally, fertility awareness efforts include well-established risk factors for fertility problems. Risks disproportionately affecting women in the Global South, however, are neglected. To address this gap, we conducted a systematic review and meta-analyses of relevant risk factors to examine the association between risk factors and fertility problems. *MEDLINE*, *Embase*, *Cochrane Library*, regional databases and key organizational websites were used. Three authors screened and extracted data independently. Studies assessing exposure to risk (clinical, community-based samples) were included, and studies without control groups were excluded. Outcome of interest was fertility problems, e.g. inability to achieve pregnancy, live birth, neonatal death depending on study. The Newcastle–Ottawa Scale was used to assess study quality. A total of 3843 studies were identified, and 62 were included (58 in meta-analyses; $n = 111{,}977$). Results revealed the following: a ninefold risk of inability to become pregnant in genital tuberculosis (OR 8.91, 95% CI 1.89 to 42.12); an almost threefold risk in human immunodeficiency virus (OR 2.93, 95% CI 1.95 to 4.42) and bacterial vaginosis (OR 2.81, 95% CI 1.85 to 4.27); a twofold risk of tubal-factor infertility in female genital mutilation/cutting–Type II/III (OR 2.06, 95% CI 1.03 to 4.15); and postnatal mortality in consanguinity (stillbirth, OR 1.28, 95% CI 1.04 to 1.57; neonatal death, OR 1.57, 95% CI 1.22 to 2.02). It seems that risk factors affected reproductive processes through multiple pathways. Health promotion encompassing relevant health indicators could enhance prevention and early detection of fertility problems in the Global South and disproportionately affected populations. The multifactorial risk profile reinforces the need to place fertility within global health initiatives.

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KEYWORDS
Female infertility
Global south
Risk factors

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*Corresponding author. E-mail address: boivin@cardiff.ac.uk (J. Boivin). https://doi.org/10.1016/j.rbmo.2023.04.008 1472-6483/© 2023 The Author(s). Published by Elsevier Ltd on behalf of Reproductive Healthcare Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)
Declaration: The authors report no financial or commercial conflicts of interest.

INTRODUCTION

Background

'Improved reproductive health and reproductive rights via universal access to sexual and reproductive health care services. . .' was established as a Millennium Developmental Goal and continues as a target (3.7) within the Sustainable Development Goals (*United Nations General Assembly, 2015*). A World Health Organization (WHO) policy paper identified fertility care as a critical reproductive health service (*WHO, 2017*), and a recent WHO fact sheet on infertility emphasizes the importance of prevention of infertility as a key component of fertility care (*WHO, 2020*).

Fertility care is defined as 'interventions that include fertility awareness, support and fertility management with an intention to assist individuals and couples to realize their desires associated with reproduction and/or to build a family' (*Zegers-Hochschild et al., 2017*). Within this context, fertility awareness has been the least-addressed component of fertility care (*van der Poel, 2012*; *Harper et al., 2017*). Awareness is becoming an integral aspect of preventative healthcare (*Macaluso et al., 2010*; *Hammarberg et al., 2017*). Current patterns of fertility in the Global South, declining fertility rates, higher contraceptive use, lower maternal and child mortality, achieved through sustained progress on millennium goals suggest there now is space for a broader reproductive agenda that incorporates fertility care (*Fauser et al., 2023*).

The impact of reducing burden of disease by targeting distal and proximal risk factors through tailored prevention programmes and recommendations applied to communicable and non-communicable disease could potentially be applied to fertility problems (*Angell et al., 2012*). These recommendations include the continued development of tools for effective community-based education and referral (*WHO, 2005*), contextualization (*Miranda et al., 2008*) with integration and adaptation that is responsive to the variation in socio-cultural, environmental, institutional, and economic determinants of health (*Huynen et al., 2005*), with special focus on integration of female health (*WHO, 2009*). Additionally, the WHO highlights the need for understanding and addressing exposures to risks, emphasizing that health promotion and communicating accurate information about risks are critical precursors to adoption of healthier behaviours and lifestyle choices (*WHO, 2002*). Targeting the risk factors for fertility problems could reduce its burden. Tools to support fertility awareness have been developed. For example, the fertility status awareness tool (FertiSTAT) was designed as a self-administered tool to provide guidance to help women make informed decisions about their lifestyle, seek timely medical advice when needed, or both (and if desired), based on their own risk profile. It comprises 22 risk factors for reduced fertility related to age, lifestyle risk, e.g. smoking, and reproductive conditions associated with reduced fertility, such as irregular periods and severe period pain, that have demonstrated high ability to discriminate between people with medically confirmed fertility or infertility (*Bunting and Boivin, 2010*). The tool has been translated (*Blanchet et al., 2019*) and adapted for various fertility assessment contexts (*Hvidman et al., 2015*).

Fertility problems occur globally, but often can present a more complex case in the Global South. Evidence from narrative reviews of risk profiles from the sub-Sahara, the Indian subcontinent and the Middle East suggest that socioeconomic and cultural factors affect the risk profile for female fertility problems (*Leke et al., 1993*; *Bosdou et al., 2016*; *Serour and Serour, 2021*). Reproductive health experts suggest that because of geographic variation in prevalence and quality of reproductive health services, women in certain socioeconomic or cultural religious settings could be differently exposed to risks (*Bayoumi et al., 2018*). Complex multifactorial risk profile for fertility problems in the Global South, in addition to global risks, such as smoking, as shown in tools such as FertiSTAT, includes exposure to communicable disorders, i.e. tuberculosis, human immunodeficiency virus (HIV), poorly managed infections, such as bacterial vaginosis, or reproductive events, i.e. birth, consequences of cultural practices, such as consanguineous marriages, female genital mutilation/cutting [FGM/C]) or dubious use of procedures, i.e. dilatation and curettage [D&C]) (*Bayoumi et al., 2018*). One or many of these risks could affect fertility with higher co-occurrence in the Global South. These risk factors could influence female fertility directly by compromising integrity or function of reproductive organs, e.g. genital tuberculosis [GTB] or bacterial vaginosis, or indirectly through variations in patterns of help-seeking or healthcare provision, e.g. availability of screening programmes for GTB or HIV detection (*WHO, 2015b*; *2016*) and any social stigmatization associated with seeking treatment for sexually transmitted infections (STI) (*Bayoumi et al., 2018*) or infertility (*Boivin et al., 2020*).

A multifactorial risk profile associated with reduced fertility should, therefore, include global, e.g. age and smoking, as well as non-global risk factors that are bounded by geography, healthcare resources or culture, e.g. HIV and FGM/C. For this review, risk factors were limited to those affecting female fertility in low- and middle-income countries and were selected based on literature searches, a survey of international fertility-care experts as reported in *Bayoumi et al. (2018)* and commonly used considerations for selection of risk factors (*Ezzati et al., 2002*; *WHO, 2002*). Systematic reviews of these risk factors are now possible owing to the emergence of evidence from primary research studies. A systematic review of these selected risk factors (SRF) would allow an in-depth understanding of the risk profile of more diverse communities and translation into fertility education and awareness tools, a necessary step to reduce the burden of fertility problems globally.

Aims

The aim of this review was to systematically identify and critically appraise the evidence on the association between SRF and female fertility. Most SRF selected were previously identified in a preliminary literature search (*Bayoumi et al., 2018*), and application of criteria for plausibility of being causal factor according to *Ezzati et al. (2002)* (Supplementary Table 1). For each SRF, published research and any suggested plausible causal mechanisms for effects on fertility based on reported reproductive outcomes were reviewed. The eight SRF identified were as follows: GTB, HIV, bacterial vaginosis, consanguinity (CSG), FGM/C, D&C, vitamin D deficiency and water-pipe smoking. If SRF demonstrated an association with fertility, then the new risk factors identified would be recommended for inclusion in the fertility status awareness tool (FertiSTAT), and other awareness tools to make such tools more inclusive.

A generic template of how SRF could potentially be associated with fertility outcomes is presented in FIGURE 1. In this

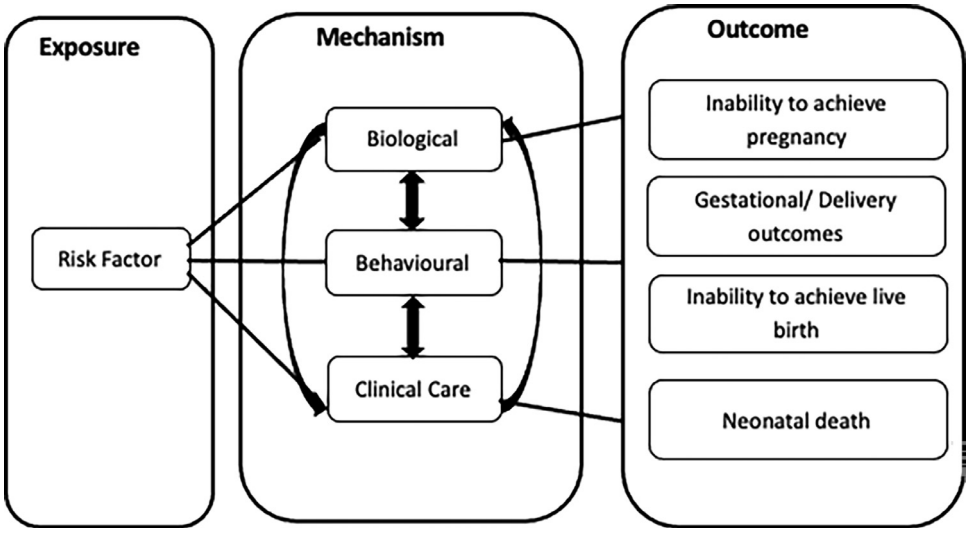

FIGURE 1 Proposed pathways describing the potential effect of selected risk factors on fertility.

figure, the 'exposure' column represents different SRF; the 'mechanism' column, the potential pathways via which exposure is potentially associated with fertility outcomes; and the 'outcome' column represents consequences from exposure. More distal risk factors, such as education or socioeconomic status, are not presented in FIGURE 1, as the overarching aim of the set of reviews was to examine the effects of the SRF identified. The potential mechanisms shown in FIGURE 1 are informed by an aggregation of information available in the best quality published reviews. Biological mechanisms refer to changes or effects to physiology or anatomy, e.g. contracting an infection or the formation of scar tissue. Behavioural mechanisms refer to an effect on the actions people take because of the exposure, e.g. abstaining from sex after exposure to HIV. Clinical care mechanisms refer to the clinical care required as a result of the exposure, e.g. obstetric care will change for a woman with FGM/C. Outcomes are markers of fertility problems as presented in available studies and can include an inability to achieve pregnancy, gestational or delivery problems and an inability to achieve live birth or neonatal death.

MATERIALS AND METHODS

The review was registered with PROSPERO (registration number CRD42016048497, 29 September 2016 'Systematic reviews and meta-analyses of cultural and regional risk factors for female fertility problems in low and middle income countries'), and is reported in accordance with the Meta-analysis Of Observational Studies in Epidemiology checklist (*Stroup et al., 2000*).

Selection of risk factors

Risk factors were selected based on a preliminary literature search, an online survey of international infertility experts, face-to-face consultations with a regional panel of infertility experts in the Middle East (*Bayoumi et al., 2018*) and other generic research on global risk factors of relevance to low- and middle-income countries (*Angell et al., 2012*; *WHO, 2017*). Of these risk factors, the following were considered: whether the risk factor was likely to be among the primary causes of infertility globally and regionally; and whether the risk factor was prevalent or hazardous or highly prevalent amongst specific sub-populations; whether there was a likely causal association based on interdisciplinary scientific knowledge; whether the data on risk levels and exposure were available or could be extrapolated; and whether the risk was potentially modifiable. Only risk factors meeting these criteria were SRF and examined further.

Eligibility criteria: topic of interest

Population, Exposure/Risk Factor, Comparison, Outcome questions were developed for each SRF. The population of interest was females of reproductive age, and study populations could consist of clinical (clinics, hospitals) or community samples in all countries. Studies that included outcomes in females with an SRF were compared with studies that included outcomes in females without the SRF. To reflect the wide range of outcomes in fertility research, a broad definition of 'fertility problems' was used: an inability to achieve a pregnancy; a live birth; or living children. This means that studies that examined primary or secondary infertility, specific causes of infertility, such as tubal infertility, amenorrhoea, defined as per study, childlessness (including due to neonatal death) and cumulative number of pregnancies, were included. Infertility, primary infertility and secondary infertility were defined as per Zegers-Hochschild et al.'s international glossary (2017).

Exclusion criteria were studies that used animal data only; male data only; did not report a fertility-related outcome; did not report the association between the SRF and fertility outcome; time to birth or duration of childlessness was (on average) less than 21 months because that would imply that pregnancy had occurred within the presumed fertile period of 12 months, i.e. 12 months trying plus 9 months gestation; and used secondary or qualitative data or a duplicate record of an included study.

Eligibility criteria: types of studies

All quantitative study designs were included. Published studies were included, and conference abstracts and unpublished PhD or master's theses were excluded. No limits on language or date were applied.

Search strategy

Ovid MEDLINE was searched from 1946 to July 2016, with updates conducted in January 2018, July, August, September and

October 2021, January 2022 and December 2022.

The MeSH terms 'female fertility', 'female infertility', 'fertility' and 'infertility' were used to identify studies examining the outcome and combined using 'OR'. MeSH terms relating to the potential SRF, e.g consanguinity, were identified and combined with 'OR'. Search terms for the SRF were combined with search terms for fertility problems using 'AND' (Appendix A–F). To ensure that the search terms were comprehensive, supplementary searches were conducted for all SRF using MeSH terms for specific indicators of fertility problems, e.g. tubal occlusion and amenorrhoea. These searches did not identify any additional eligible studies.

The search strategy was adapted for *Embase*, the *Cochrane Library*, *LILACS*, *INDMED*, *Africana Periodical Literature* and *African Index Medicus*. Key organizational websites were searched, including the WHO, and the United Nations Population Fund, as well as regional sites of these organizations, such as the Eastern Mediterranean Regional Office and African Regional Office of the WHO. The reference lists of included articles were searched, and authors were contacted for missing information. The steps taken in the review process are presented in Supplementary Figure 1.

Searches from each database were imported into excel, after duplicates were removed. The studies were selected based on eligibility criteria. Screening of titles, abstracts and full text was conducted independently by RRB, NZ and YJL. Disagreements at all stages were resolved by discussion among the reviewers.

Data extraction and quality assessment

A standard form was used to extract information on study design and population, definition and measurement of SRF, definition and measurement of fertility outcome(s), confounders, data relevant to effect size calculation and information required for quality assessment. Data from each paper were extracted in duplicate by two reviewers. Two reviewers completed the Newcastle–Ottawa Scale assessment independently for each included paper. A third reviewer evaluated all discrepancies, and these were resolved in consultation with others in the review group. Authors of studies with missing information were contacted, and, if information was not forthcoming, the study effect was omitted for the relevant analysis. Duplicate data were omitted, and the data from the study reporting the most complete data were used.

Data synthesis and analysis

RevMan Version 5.4 (*Cochrane Collaboration, 2020*) was used to calculate effect sizes, conduct meta-analyses and generate forest plots. The primary outcome measure of association was the odds ratio (*Higgins et al., 2023*), either as presented in the papers or calculated from raw data. In all included analyses and in forest plots an odds ratios of one implied no difference between the exposed (SRF) and non-exposed (no-SRF) groups, an odds ratio greater than one indicated that the exposed group were more likely to have fertility problems than the non-exposed group on the variable being examined, and an odds ratio less than one indicated that the exposed group were less likely to have fertility problems than the non-exposed group. Therefore, higher values mean a higher likelihood of the exposed group having a fertility problem.

When means and SDs were presented in the primary studies, the primary outcome measure was the mean difference (*Higgins et al., 2023*) between exposed and non-exposed groups, and original units of measurement were used.

Random effects meta-analyses were used to obtain pooled estimates of the SRF effects for different outcomes. Heterogeneity between estimates was assessed using the Cochrane Q test and the I^2 statistic. Where heterogeneity was statistically significant ($P < 0.05$), subgroup/sensitivity analysis were conducted. The subgroup analyses were based on differences in methodological characteristics of the study, e.g. type of control group or subcategories of infertility (tubal factor versus ovulatory). When primary studies were insufficient to calculate pooled estimates, a narrative synthesis was conducted.

Assessment of bias and publication bias

Study quality was assessed using the Newcastle–Ottawa Scale (*Wells et al., 2000*). Studies were classified as high (7–10 points), average (4–6 points) or low quality (0–3 points). Funnel plot (≥10 or more studies) Egger's test were used to evaluate publication bias. Where relevant, the trim and fill procedure was used to impute the number of 'missing' studies in the meta-analysis, and calculate the adjusted pooled effect estimate with the 'missing' studies using Comprehensive Meta-Analysis Version 3.

Assessment of potential for causality

The Bradford–Hill criteria were used to evaluate the potential causal nature of the relationship between SRF and 'fertility problems' (*Hill, 1965*; *Fedak et al., 2015*). The criteria are considered a valid and useful aid in making causal inferences from epidemiological research by exploring the strength and consistency of reviewed evidence using nine criteria: associative strength; consistency; specificity; temporality; biological gradient/dose-response; plausibility; coherence; experimental manipulation; and analogy across conditions (*Fedak et al., 2015*). The updated evaluation of the criteria (*Fedak et al., 2015*) determined that the original criteria (*Hill, 1965*) were still applicable.

RESULTS

Search outcome and identified studies

Eight SRF were identified for inclusion in the review (Supplementary Table 1). FIGURE 2 (overall Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] Flowchart) shows that 3354 articles were screened, and, of these, 190 full-text articles were assessed for eligibility. Sixty-one primary studies looking at each risk factor (GTB, HIV, bacterial vaginosis, FGM and D&C), and then one systematic review (for vitamin D) (references given in each risk factor section below). Of these, 58 were included in the meta-analyses and four were reviewed narratively. The 58 studies included in the meta-analyses encompassed a total patient sample of 111,977 (GTB [n = 1210]; HIV [n = 13,290]; bacterial vaginosis [n = 6018]; CSG [n = 66,462]; FGM/C [n = 24,457]; and D&C [n = 1109]), taking into account that 569 participants in the study by *Dhont et al. (2010)* were included in the HIV and bacterial vaginosis analyses. Data were available for meta-analysis for five of the eight new SRF.

Results for each risk factor are presented in TABLE 1, and individually in the next sections. Each individual presentation comprises supplementary figures, namely the PRISMA flow diagram for the risk factor, tables of sample and study design characteristics, Newcastle–Ottawa Quality Assessment, and results of meta-

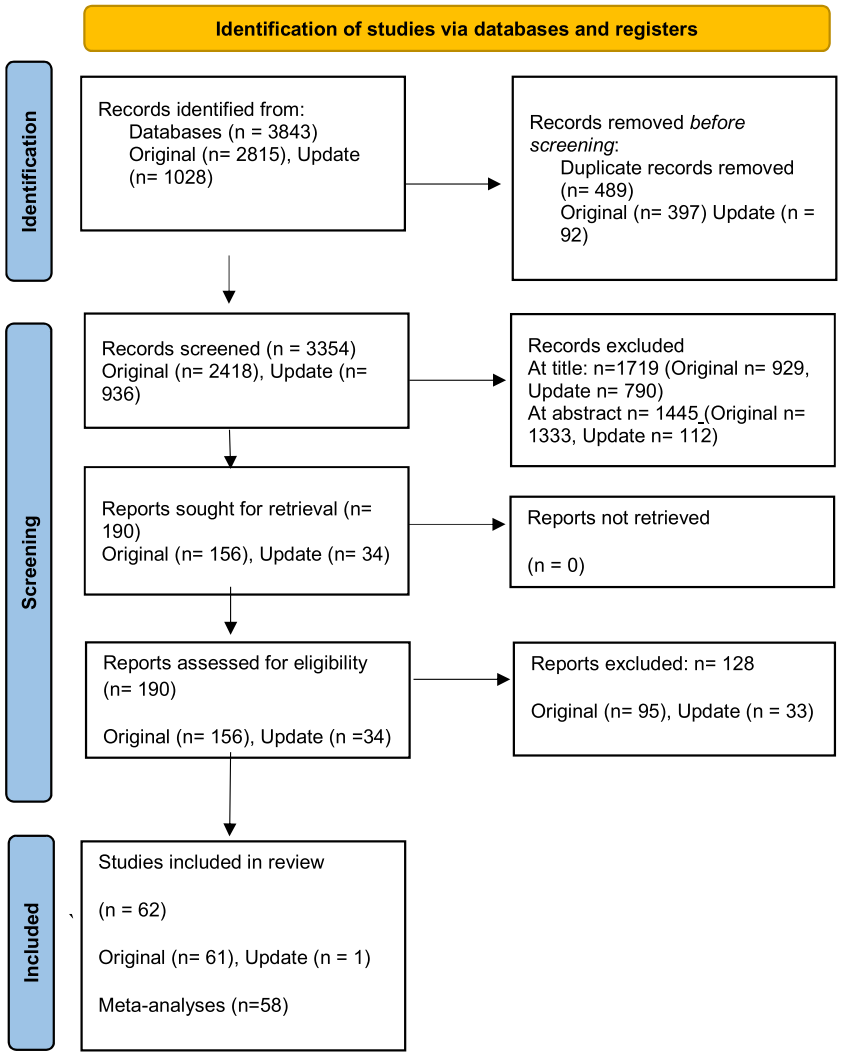

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the selection of all studies for systematic review. Of the 58 studies included in meta-analyses, five were included in genital tuberculosis, 25 in consanguinity, seven in female genital mutilation/cutting, 10 in human immunodeficiency virus and 11 in bacterial vaginosis analyses. The four reviewed narratively were for dilatation and curettage. Reasons for exclusion at all levels are indicated in PRISMA diagrams for each selected risk factor in supplementary materials.

analysis and publication bias (where applicable, or, if not, narrative review).

Genital tuberculosis

Five cross-sectional studies (*Kitilla, 2002*; *Sharma et al., 2011*; *Ali and Abdallah, 2012*; *Malhotra et al., 2012*; *Bhanothu et al., 2014*) met inclusion criteria for GTB (see PRISMA flowchart (Supplementary Figure 2), sample size across studies (n = 1210) women (Supplementary Table 2). The outcomes reported were infertility, amenorrhoea and primary versus secondary infertility (Supplementary Table 3). Quality assessment showed that four studies were average quality and one high quality (Supplementary Table 4). Three meta-analyses, each including two studies, were conducted (TABLE 1). In the first, females with GTB were more likely to be infertile (>12 months) than females without GTB (OR 8.91, 95% CI 1.89 to 42.12) (Supplementary Figure 3). In the second, females with GTB were equally likely to report amenorrhoea as females without GTB (OR 4.24, 95% CI 0.23 to 78.14) (Supplementary Figure 4). In the third, females with GTB were more likely to have primary infertility than secondary infertility compared with females without GTB (OR 2.94, 95% CI 1.89 to 4.57) (Supplementary Figure 5).

Human immunodeficiency virus

Ten studies met inclusion criteria for HIV (see PRISMA flowchart) (Supplementary Figure 6), across studies 13,290 (Supplementary Table 5). Of these, two were case-control studies (*De Muylder et al., 1990*; *Dhont et al., 2010*), two cohort studies (*Ross et al., 2003*; *Linas et al., 2011*), three cross-sectional studies (*Yaro et al., 2001*; *Ezechi et al., 2010*; *Willems et al., 2013*) and three using cross-sectional data embedded within cohort studies (*Chirgwin et al., 1996*; *Gray et al., 1998*; *Cejtin et al., 2006*) (Supplementary Table 6). The outcomes reported were cumulative pregnancy rate, amenorrhoea, level of FSH greater than 25 IU/l (indicative of low ovarian reserve), rate of miscarriage and rate of HIV in infertile and fertile controls (Supplementary Table 6). Quality assessment was high for seven out of 10 studies (Supplementary Table 7). Five meta-analyses were conducted (TABLE 1). In the first, two studies were included; HIV positive females had fewer cumulative pregnancies than HIV negative females (OR 0.36, 95% CI 0.15 to 0.89) (Supplementary Figure 7). In the second, two studies were included; the HIV-positive groups were equally likely to report miscarriages as the HIV-negative groups (OR 1.35, 95% CI 0.77 to 2.35) (Supplementary Figure 8). Three studies were included in the third analysis; the HIV-positive groups were more likely to have amenorrhoea than the HIV-negative groups (OR 2.44, 95% CI 1.56 to 3.81) (Supplementary Figure 9). Two studies were included in the fourth analysis; the HIV-positive groups were equally likely to have FSH over 25 IU/l (indicative of premature ovarian insufficiency) as the HIV-negative groups (OR 1.51, 95% CI 0.77 to 2.94) (Supplementary Figure 10). Two studies were included in the fifth analysis; the HIV-positive groups were more likely to be infertile than the HIV-negative groups (OR 2.93, 95% CI 1.95 to 4.42) (Supplementary Figure 11).

Bacterial vaginosis

Eleven studies were included (see PRISMA flowchart) (Supplementary Figure 12), with sample size across studies (n = 6018) (Supplementary Table 8). Of these, 10 were case-control studies (*Morgan et al., 1997*; *Aboul Enien and El Metwally, 2005*; *Mania-Pramanik et al., 2009*; *Dhont et al., 2010*; *2011*; *Adamson et al., 2011*; *Almanza et al., 2011*; *Salah et al., 2013*; *Tomusiak et al., 2013*; *Durugbo et al., 2015*) and one cross-sectional study (*Kildea and Bowden, 2000*) (Supplementary Table 9). Results are presented in TABLE 1. Eight out of 11 studies were average quality, two high quality and one low quality (Supplementary

TABLE 1 RESULTS OF META-ANALYSIS FOR THE FIVE SELECTED RISK FACTORS FOR WHICH IT WAS POSSIBLE TO CALCULATE POOLED ESTIMATES

Selected risk factor	Evidence reviewed	Outcome reported	Number of studies in the meta-analysis	Number of events/total exposed group	Number of events/total non-exposed group	Heterogeneity I^2 %, *P*- value	Pooled effect estimates (random effects)		
							Crude OR (95% CI)	Adjusted OR (95% CI)	Mean difference (95% CI)
GTB	582 full-text articles screened, five included in meta-analysis (all LMIC)	Infertile (>12 months no pregnancy)	2	102/124	127/308	72, 0.06	8.91 (1.89 to 42.12)		
		Amenorrhoea	2	24/301	12/389	75, 0.05	4.24 (0.23 to 78.14)		
		Primary infertility	2	133/171	149/305	0, 0.71	2.94 (1.89 to 4.57)		
HIV	1134 full-text articles screened, nine included in meta-analysis (seven LMIC)	Cumulative pregnancy rate	2	532/1894	1120/4015	97, <0.00001	0.36 (0.15 to 0.89)	0.32 (0.17 to 0.62)	
		Miscarriage	2	26/155	99/948	0, 0.55	1.35 (0.77 to 2.35)		
		Amenorrhoea	3	173/3942	22/1292	0, 0.46	2.44 (1.56 to 3.81)	2.44 (1.81 to 3.98)	
		FSH >25 IU/l	2	60/1194	10/317	0, 0.39	1.51 (0.77 to 2.94)	2.67 (0.8 to 8.9)	
		Infertile (>12 months no pregnancy)[a]	2	107/146	432/780	0, 0.43	2.93 (1.95 to 4.42)	3.55 (1.85 to 6.79)	
Bacterial vaginosis	267 full-text articles screened, 11 included in meta-analysis (eight LMIC)	Infertile (>12 months no pregnancy)[a]	11	846/1421	1443/4597	83, <0.00001	2.81 (1.85 to 4.27)	2.97 (2.03 to 4.35)	
CSG	585 full-text articles screened, 25 studies included in meta-analysis (12 LMIC)	Time to first birth	2	7011	2608	0, 0.96			+0.24 (−0.39 to 0.87)
		Miscarriage	5	1069/3372	1030/3485	50, 0.09	1.1 (0.93 to 1.30)		
		Never pregnant	3	92/3241	186/4120	49, 0.14	0.66 (0.45 to 0.98)		
		Childlessness	2	380/6651	717/10240	60, 0.04	0.83 (0.67 to 1.03)		
		Mean number of pregnancies	6	3668	5023	59, 0.03			+0.40 (0.16 to 0.63)
		Mean number of live births	8	8366	10730	76, <0.0001			+0.25 (0.08 to 0.41)
		Stillbirth	5	243/3372	211/3485	7, 0.36	1.28 (1.04 to 1.57)		
		Neonatal death	4	151/2072	144/2232	0, 0.46	1.57 (1.22-2.02)		
FGM/C	274 full-text articles screened, seven studies included in meta-analysis (all LMIC)	Infertile (>12 months no pregnancy)	2	117/1090	61/655	0, 0.52	1.17 (0.84 to 1.63)	1.26 (0.89 to 1.78)	
		Childlessness	3	352/9903	251/7760	3, 0.36	1.22 (0.99 to 1.52)	1.20 (1.0 to 1.46)	
		Infertile 2 years (TFI)[a]	2	72/276	15/76	0, 0.68	2.06 (1.03t o 4.15)	2.75[b] (1.15 to 6.57)	

See **Supplementary materials** for the forest plots.

[a] Original study case-control design; odds ratio calculated to reflect infertile in exposed versus non-exposed,

[b] One study tubal factor infertility (TFI) only; one study all infertile. For adjusted odds ratios, studies adjusted for different factors in analyses. The confounders differed between selective risk factor (SRF), e.g. confounders for female genital mutilation/cutting (FGM/C) different from those for consanguinity (CSG).

D&C, dilatation and curettage; GTB, genital tuberculosis; HIV, human immunodeficiency virus; LMIC, low- and middle-income countries; OR, odds ratio.

Table 10). The outcomes reported were cases of bacterial vaginosis in infertile and fertile females (Supplementary Table 9). Females with bacterial vaginosis were more likely to be infertile than females without bacterial vaginosis (OR 2.81, 95% CI 1.85 to 4.27) (Supplementary Figure 13), and sensitivity analysis omitting study on childlessness (Supplementary Figure 14). For this SRF, there were sufficient studies to also conduct pre-specified subgroup analysis, to determine association with tubal factor infertility (TFI). The higher the likelihood of infertility in females with bacterial vaginosis remained significant in the subgroup analysis comprising females with TFI only (OR 5.11, 95% CI 3.27 to 7.99) and that comprising females with multiple types of infertility (OR 2.42, 95% CI 1.53 to 3.84) (for both see Supplementary Figure 15). Egger's test conducted for the meta-analysis was not significant ($P > 0.05$) indicating lack of publication bias (funnel plot not shown). Data were not available to enable a subgroup analysis of women with STI and those without. Only a summary of percentages of women with STI in the bacterial vaginosis and no-bacterial vaginosis groups was possible. Of the 11 studies included in the current meta-analysis, eight reported on STI (Supplementary Table 11). More STI were found in the infertile women in all eight studies, except for more chlamydia found in the fertile group in one study (*Tomusiak et al., 2013*).

Consanguinity

Twenty-five studies were included (see PRISMA flowchart) (Supplementary Figure 16) (sample size $n = 53{,}925$women, 12,537 couples, marriages or families) (Supplementary Table 12). Of these, 21 were cross-sectional studies (*Rao and Inbaraj, 1979*; *Radha Rama Devi et al., 1981*; *Hann, 1985*; *Khlat, 1988*; *Luna and Fuster, 1990*; *Saha et al., 1990*; *Shami et al., 1990*; *Verma et al., 1992*; *Bittles et al., 1993*; *Abdulrazzaq et al., 1997*; *Khoury and Massad, 2000*; *Fuster, 2003*; *Bener and Hussain, 2006*; *Blanco Villegas and Fuster, 2006*; *Al Husain and Al Bunyan, 1997*; *Al Kandari, 2007*; *Yüksel et al., 2009*; *Çiçeklioğlu et al., 2013*; *Islam, 2013*; *Ghrayeb et al., 2014*; *Nawaz et al., 2021*) and four cohort studies (*Yamaguchi et al., 1975*; *Tanaka, 1977*; *Asha Bai et al., 1981*; *Edo et al., 1985*). The outcomes examined were time to first birth, never having been pregnant, childlessness, mean number of pregnancies and live births, number of miscarriages, stillbirths and neonatal deaths (Supplementary Table 13). Study quality was average for 20 studies and high for five studies (Supplementary Table 14).

Eight meta-analyses compared CSG couples with those who were unrelated (**TABLE 1**). No difference was found in average time to first birth (mean difference = +0.24, 95% CI −0.39 to 0.87) (Supplementary Figure 17) and miscarriage (OR 1.10, 95% CI 0.93 to 1.30) (Supplementary Figure 18). The CSG couples were less likely to have never been pregnant (OR 0.66, 95% CI 0.45 to 0.98). For sensitivity analysis see Supplementary Figure 19 and Figure S20; however, no association was found with childlessness (OR 0.83, 95% CI 0.67 to 1.03) (Supplementary Figure 21) confirmed in subgroup analysis according to marital duration (Supplementary Figure 22). The CSG couples had significantly more pregnancies (mean difference = +0.40, 95% CI 0.16 to 0.63) (Supplementary Figure 23) and live births (mean difference = +0.25, 95% CI 0.08 to 0.41) (Supplementary Figure 24 and Supplementary Figure 25 with sensitivity analysis) than unrelated couples. More still births (OR 1.28, 95% CI 1.04 to 1.57) (Supplementary Figure 26) and neonatal deaths (OR 1.57, 95% CI 1.22 to 2.02) (Supplementary Figure 27) were found in the CSG couples. Egger's test was carried out for seven out of the eight analyses, but this was not possible for the 'time to first birth' analysis because it comprised only two studies. None of the Egger's tests were significant (all $P > 0.05$), indicating a lack of publication bias (funnel plots not shown).

Female genital mutilation and cutting

Seven studies were included in the meta-analysis (see PRISMA flowchart) (Supplementary Figure 28), sample size across studies ($n = 24{,}457$) (Supplementary Table 15). Five were cross-sectional (*Larsen and Yan, 2000*; *Morison et al., 2001*; *Larsen, 2002*; *Klouman et al., 2005*; *Yount and Carrera, 2006*) and two case-control studies (*Inhorn and Buss, 1993*; *Almroth et al., 2005*). The outcomes reported were infertility, childlessness and a comparison of cases with tubal infertility and pregnant controls (Supplementary Table 16). Quality assessment showed that six out of seven studies were high quality, one average quality (Supplementary Table 17). Three meta-analyses were conducted (**TABLE 1**). The first analysis shows two studies, indicating that females with FGM/C were not more likely to be infertile (>12 months) compared with females without FGM/C (OR 1.17, 95% CI 0.84 to 1.63) (Supplementary Figure 29). Three studies were included in the second analysis and the odds of being childless were marginally higher in females with FGM/C than females without FGM/C (OR 1.22, 95% CI 0.99 to 1.52) (Supplementary Figure 30). The third analysis included two studies showing females with FGM/C Type II and III (severe types) were more likely to be diagnosed with TFI than females who had undergone Type I (OR 2.06, 95% CI 1.03 to 4.15) (Supplementary Figure 31). Egger's tests conducted for the meta-analysis were not significant at $P > 0.05$, indicating the lack of publication bias (funnel plots not shown).

Dilatation and curettage

Four studies met inclusion criteria, three cohort (*Sotnikova, 1986*; *Ben-Baruch et al., 1991*; *Ben-Ami et al., 2014*) and one cross-sectional study (*Taylor and Graham, 1982*) (see PRISMA flowchart and Supplementary Figure 32, with sample size across studies ($n = 1109$) (Supplementary Table 18). Pooled estimates could not be calculated because the studies all used different outcomes (see Supplementary Table 19 for design characteristics). Quality assessment showed that two studies were high quality, one average and one low quality (see Supplementary Table 20 for quality ratings). Results were summarized narratively in relation to specific study details (Supplementary Table 21) for additional considerations of four studies reviewed for D&C). In a cohort study (*Ben-Ami et al., 2014*), females who had undergone D&C to remove retained products of conception experienced longer time to pregnancy and more 'new infertility' diagnoses compared with females who had undergone hysteroscopy. In a cross-sectional study (*Taylor and Graham, 1982*), females who had a history of D&C as part of infertility investigation had significantly more pelvic inflammatory disease than females who had no such history. In a cohort study (*Sotnikova, 1986*), females who had undergone D&C developed more gynaecological disease, e.g. inflammation of the fallopian tubes, endometriosis, irregular uterine bleeding, and menstrual irregularity than females who had vacuum aspiration, received prostaglandins, or both. In a cohort study (*Ben-Baruch et al., 1991*), no differences were found in the number of future pregnancies, normal deliveries, miscarriages and infertility in females who had undergone D&C after miscarriage

compared with females who had experienced expectant management.

Vitamin D deficiency

A recent high-quality systematic review (*Muscogiuri et al., 2017*) summarized research on the association between vitamin D deficiency and fertility, making an update unnecessary. This review found molecular and epidemiological evidence suggesting vitamin D involvement in physiologic processes of markers for ovarian reserve, e.g. anti-Mullerian hormone). Evidence from molecular, epidemiological and meta-analyses for a relationship between vitamin D deficiency and polycystic ovary syndrome was not consistent. Molecular evidence suggests that vitamin D could modulate inflammation and proliferation in endometriosis, but epidemiological evidence was inconsistent. The investigators identified methodological shortcomings, e.g. small samples, in the primary studies affecting interpretation of results. We additionally suggest that the inconsistency could be due to the phenotypical expression of such a relationship (physiologic processes), may be more complex and therefore difficult to measure, and confounding effects, e.g. better nutrition and health overall, not consistently measured or reported.

Water-pipe smoking

A systematic search for water-pipe smoking was not necessary as water-pipe is only a different method of consuming tobacco and the WHO reported that use of water-pipe smoking is as hazardous to human health as cigarette smoking (*World Health Organization, 2015a*). Specifically, a 1-h water-pipe session is thought to be equivalent to inhaling 100–200 times the volume of smoke in a single cigarette (*WHO, 2015a*) and the effect of smoking cigarettes on fertility is well established (*Dechanet et al., 2011*).

Multifactorial risk model

To summarize, TABLE 1 and individual SRF presentations suggest FGM/C, HIV, GTB and bacterial vaginosis should be considered risk factors for reduced fertility. Also, CSG should be considered if definition of fertility problems extends beyond ability to achieve pregnancy, e.g. neonatal death. The potential effect of the SRF was significant, with the largest effect size being a nine-fold increased risk of reduced fertility, i.e. GTB. Results of all meta-analyses were aggregated with extant evidence and used to construct a model that depicts how reviewed SRF could be associated with fertility problems using outcomes reported in the primary studies. FIGURE 3 shows that SRF could have multiple ways of affecting fertility. The solid black lines are supported directly by meta-analysis from the current studies, whereas the dashed black line is supported by meta-analytic evidence from extant studies, with the grey lines indicating support from primary studies (not yet subject to meta-analysis). The primary studies reviewed, however, do not systematically investigate all outcomes (or paths); therefore, an incomplete picture is garnered from the literature. None of the results were obtained from randomized controlled trials; therefore, the Bradford–Hill criteria were applied to each risk factor to ascertain probability of each SRF being a causal risk factor (Supplementary Table 22). Application of these criteria confirmed that a causal relationship is likely in the case of bacterial vaginosis, GTB, FGM/C, CSG and D&C in that order (more criteria met) (Supplementary Table 22). Generic pathways for effects were suggested in FIGURE 1, with FIGURE 3 specifying paths with the SRF examined in meta-analysis (bacterial vaginosis, GTB, FGM/C and CSG) and one narrative review (D&C). No evidence, however, was found for a causal relationship for HIV and fertility outcomes, according to evidence and Bradford Hill criteria. A previously published systematic review on Vitamin D also did not support an association of this deficiency with fertility outcomes.

DISCUSSION

Principal findings

The SRF investigated were associated with fertility through multiple biological, behavioural and clinical care pathways. Meta-analytic results were mainly consistent with past narrative reviews but additionally provide estimates of association through meta-analysis for most risks. Genital tuberculosis showed a nine-fold higher risk of inability to become pregnant, and HIV and bacterial vaginosis an almost threefold higher risk of inability to become pregnant within 12 months, versus comparator group. Female genital

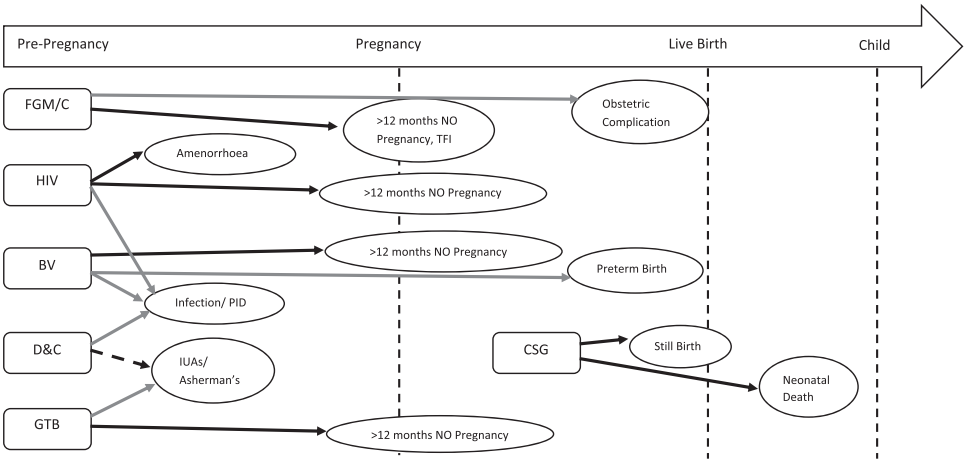

FIGURE 3 Association between risk factor and fertility problems according to type of evidence and proposed timing of effect in reproductive process. Type of evidence: evidence from current meta-analysis (solid black arrow), evidence from previous meta-analysis (dashed arrow), evidence from primary studies or narrative reviews (grey arrow); BV, bacterial vaginosis; CSG, consanguinity; D&C, dilatation and curettage; FGM/C, female genital mutilation/cutting; GTB, genital tuberculosis; HIV, human immunodeficiency virus; IUAs intrauterine adhesions; PID, pelvic inflammatory disease; TFI, tubal factor infertility.

mutilation/cutting, Type II and III (~90% occurrence in some African nations (*Yoder and Khan, 2004*; *Fite et al., 2020*) showed a twofold higher risk of TFI, whereas CSG (50% of marriages in some nations) (*Romeo and Bittles, 2014*), was associated with postnatal mortality. The results presented indicate that the set of risks for reduced fertility considered in typical awareness tools such as the FertiSTAT (*Bunting and Boivin, 2010*), such as lifestyle risks, e.g. smoking and overweight, or reproductive risks, e.g. irregular periods, is too narrow and needs to expand to include those identified as significant in the present work if such tools are to be relevant for a broader community of users. Such tools should be updated to include bacterial vaginosis, GTB, FGM/C, CSG and D&C. More mechanistic fertility research is needed to understand how and when risks affect fertility, which can only be achieved if fertility indicators are more consistently included in health research.

Multiple global risks

A focus on prevalent risks in higher income countries or single risks could obscure the multifactorial risks to which people in the Global South could be exposed (FIGURE 4). What can and should be done about fertility-related risk exposure needs to be determined within countries and regions using a global health framework. Multifactorial risk findings reinforce the need to put fertility as an agenda in global health initiatives.

Area of the reproductive tract and reproductive stage affected by selected risk factors

Some SRF, such as bacterial vaginosis and FGM/C, seem to have an association with effect at several stages in the reproductive process. In the case of bacterial vaginosis, this could be because pre-pregnancy untreated infection that reaches the tubes will compromise ability to achieve pregnancy, whereas infection that occurs during pregnancy could damage the amniotic sac and lead to preterm birth. In the case of FGM/C, it is likely that the TFI occurs secondary to infection arising from the more severe types of cutting where the anatomy is altered drastically. It should be noted that even if the cutting did not lead to infection, a female could still be at risk of obstetric complications if the altered anatomy made delivery difficult (*Makhlouf Obermeyer, 2005*; *Berg and Underland, 2013*; *Reisel and Creighton, 2015*; *Royal College of Obstetricians and Gynaecologists, 2016*; *World Health Organization, 2017*). Therefore, it can be inferred that timing and extent of exposure to SRF could affect fertility in different ways. Prevention and management should be informed by these mechanisms. Research should target multiple outcomes and end points to capture these effects.

Common pathways (infection)

Selective risk factors could have common pathways. For example, HIV, bacterial vaginosis and D&C were all related to infection and pelvic inflammatory disease (PID). Although, with FGM/C, no data suggested a direct link with infections and PID, it can be assumed given the demonstrated association with TFI (FIGURE 3). These risk factors could result in inability to achieve pregnancy owing to the progression of infection to the reproductive tract or ascension to tubes, causing PID or tubal damage (*Cates et al., 1985*; *WHO, 2007*; *Brunham et al., 2015*; *Ruggeri et al., 2016*). No consistent findings were available to suggest that infections *per se* always led to inability to achieve pregnancy. This is probably because the effect would only appear if the infection remained untreated, as is often the case in the Global South. Infections treated before they lead to PID would have no effect on the female reproductive tract and hence future ability to achieve pregnancy (*Ross et al., 2018*; *Ross and McCarthy, 2011*). Furthermore, not all infections lead to PID and not all cases of PID lead to tubal damage (*WHO, 2007*; *Workowski, 2015*; *Das et al., 2016*). Future research should ensure that data about timing and treatment of infection are collected. Other shared pathways could exist.

What can be clearly gleaned from FIGURE 3 is that the SRF that included infection, PID or TFI in their pathways, e.g. bacterial vaginosis HIV and FGM/C, were found to be associated with an inability to achieve pregnancy, affirming historic published studies on the association between infection and infertility in Africa and other low- and middle-income countries (*Cates et al., 1985*; *Leke et al., 1993*; *Ericksen and Brunette, 1996*; *Odukogbe and Ola, 2005*; *Abebe et al., 2020*). The available evidence would suggest that infection is a shared pathway, but its potential causes are multiple. Clinicians need to be mindful of all risks for infection and not just STI and unsafe procedures (abortion, delivery), as has typically been the case (*WHO, 1987*; *Ericksen and Brunette, 1996*; *Sharma et al., 2009*).

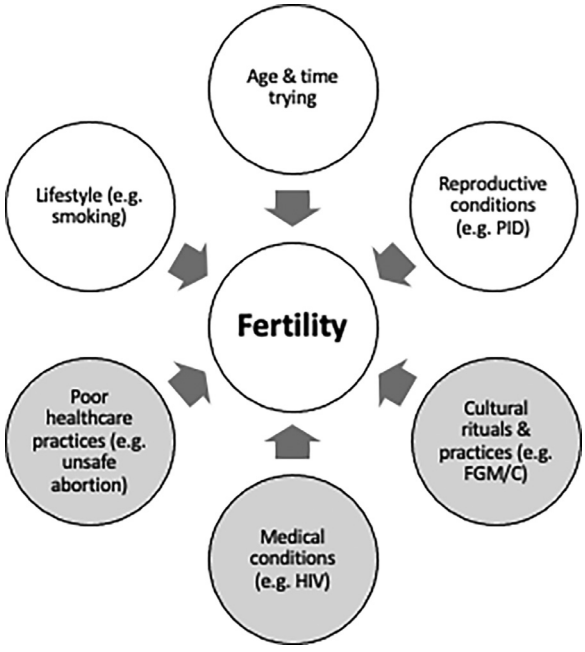

FIGURE 4 Factors impacting fertility. Some of these factors are included in fertility awareness programmes and others should be included because of the current reviews. Time trying refers to the time trying to achieve pregnancy. Reproductive refers to conditions or procedures affecting the reproductive tract. Medical conditions refer to both communicable and non-communicable diseases. White circles indicate risks that are relevant globally and grey circles indicate risks that may not be (or may be less) relevant globally. FGM/C, female genital mutilation/cutting; HIV, human immunodeficiency virus; PID, pelvic inflammatory disease.

Strengths and limitations

The review process used rigorous systematic review methodology that is replicable. The small number of studies in each meta-analysis limited the generalizability of results and potentially increased publication bias. Assessment of publication bias for all meta-analyses, however, did not alter the results.

Regardless of how rigorous the review process was, results could only be as strong as the primary studies included. Three limitations of the primary studies were similar across SRF. First, in most studies, recruitment occurred at fertility clinics, possibly limiting selection to females at higher risk of infertility (applicable to GTB, FGM/C and bacterial vaginosis). Second, the definition of outcomes, period of exposure or type of infertility were often not reported (applicable to CSG, bacterial vaginosis and HIV). Third, was the lack of inclusion of confounders potentially moderating the effect of the risk. For example, the type of circumciser in FGM/C could be linked to an increase in the likelihood of infection and comorbid sexually transmitted infections (applicable to HIV and bacterial vaginosis). Only 10 out of the 58 primary studies reported adjusted odds ratios. The use of adjusted odds ratios, however, did not alter the results of the reviews except in one instance, in which females with FGM/C reported more childlessness than females without FGM/C. Given that significance changed in only one out of eight meta-analyses, we can be reassured that the results might not have been greatly affected by the lack of reporting of adjusted odds ratios. It is important to note that, in six of the eight adjusted odds ratio meta-analyses, the magnitude of the effect size increased, or the confidence interval narrowed, indicating that the association with fertility problems was related to the SRF and not the confounders. Additionally, heterogeneity was high for most meta-analyses, suggesting heterogeneity in study design and methods, outcome measures and sample size was affecting effect size estimation.

CONCLUSION

Implications of findings

Targeting communicable and non-communicable diseases is a priority to reduce the effects of these conditions on health in general, and their effect on childbearing and parenthood goals. The findings strongly support the movement towards a more global understanding of risk for disease, and, by extension, that different settings can determine for themselves which risk factors are key for their health providers and populations. This approach would allow health promotion to encompass culturally relevant health education and promotion. This understanding could ultimately translate into more effective early detection of fertility problems in the Global South.

Clinical implications of these findings include education to the public about the effect of SRF on fertility, disseminated widely and in the most culturally appropriate manner. Results disseminated to clinicians can support discussions with individuals about these SRF, enabling more informed choices to protect reproductive capacity. The findings have wider implications for the integration of fertility within the global reproductive health agenda. Awareness of the risks should be communicated especially where the threat of the SRF is increased, e.g. high prevalence such as FGM/C in some countries, family member with tuberculosis. Appropriate education, awareness, support and training initiatives are urgently needed to empower people to maintain or improve their fertility. Research suggests that informing about risks could improve timely medical help-seeking (*Maeda et al., 2018*); however, such campaigns need to be delivered alongside campaigns that destigmatize infertility to ensure that people with risks or with infertility are not marginalized in a way that affects their quality of life and productivity (*Gerrits et al., 2023*).

Unanswered questions and future research

Future research needs to determine what is the best method for selecting risk factors, methods to systematically evaluate pathways leading to fertility problems, particularly more rigorous prospective designs or randomized controlled trials aimed at modifying risks (where possible).

Specific research directions for each SRF were informed from the gaps in primary studies and include the following: using more rigorous methodology, such as randomized controlled trials where that is ethical and possible, or longitudinal cohort studies; inclusion of well-defined and consistent outcomes; and inclusion of confounders. Future research should also target an understanding of the causal pathways; for example, more molecular level investigations. Uncovering more exact causal pathways would enable specificity in clinical recommendations and best practice guidelines. Furthermore, research endeavours can be enhanced with the adoption of a more systematic approach to studying fertility globally. Regular review of risk factors is also relevant as new risks are identified, or as the number of studies available for systematic review increases.

Most importantly, the results highlighted the necessity of multinational cooperation between research teams to fill the gaps identified. To understand and address these gaps in the Global South requires a multidisciplinary approach involving public health, reproductive medicine, the emerging field of global health psychology and other relevant fields.

DATA AVAILABILITY

Data will be made available on request.

STUDY REGISTRATION

The study was registered with the PROSPERO registry, PROSPERO registration number CRD42016048497; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=48497

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2023.04.008.

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