Running title: Systematic review infertility risk factors

Title: A Critical Systematic Review and Meta-Analyses of Risk Factors for Fertility Problems in a Globalized World

Authors: Rasha R. Bayoumi PhD[a*], Human M. Fatemi MD PhD[b], Lisa Hurt PhD[c], Gamal I. Serour MD PhD[d], Sheryl van der Poel MD PhD[e], Christos Venetis MD PhD[f], Ning Zhang MD[g], Yin Jun Law MD[h] and Jacky Boivin PhD[i]

[a] Assistant Professor, University of Birmingham, Dubai Academic City, Dubai, UAE; School of Psychology, Cardiff University, Cardiff, Wales, UK; Takemi Fellow, Takemi Program in International Health, Harvard T.H. Chan School of Public Health, Boston, USA, r.bayoumi@bham.ac.uk
[b] Professor of Obstetrics and Gynecology, Group Medical Director, ART Fertility Clinics, Abu Dhabi, UAE
[c] Senior Lecturer, Division of Population Medicine, Cardiff University School of Medicine, Cardiff, Wales, UK
[d] Professor of Obstetrics and Gynecology, Al Azhar University, Cairo, Egypt
[e] Independent Consultant, La Capite, Geneva, Switzerland
[f] Associate Professor, Centre for Big Data Research in Health, University of New South Wales, Sydney, Australia
[g] Department of Obstetrics and Gynaecology, Royal North Shore Hospital, Sydney, Australia
[h] Department of Obstetrics and Gynaecology, The Canberra Hospital, Australian Capital Territory, Australia
[i] Professor of Psychology, School of Psychology, Cardiff University, Cardiff, Wales, UK

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Corresponding Author:
Rasha R. Bayoumi
Assistant Professor of Psychology
Head of Research, Dubai
University of Birmingham Dubai
Dubai International Academic City,
Tel: +971505869079
Email: r.bayoumi@bham.ac.uk

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Abstract

Globally fertility awareness efforts include well-established risk factors (RFs) for fertility-problems. However, risks disproportionately affecting females in the Global South are neglected. To address this gap, we conducted systematic reviews and meta-analysis of relevant RFs, to examine association between RFs and fertility-problems. We searched Medline, Embase, Cochrane library, regional databases and key organizational websites. Three authors screened and extracted data independently. We included studies assessing exposure to risk (clinical, community-based samples) and excluded studies without control groups. Outcome of interest was fertility-problems (inability to achieve pregnancy, live-birth, neonatal death). Newcastle-Ottawa Scale used to assess study quality. We identified 3843 studies, and included 62 (58 in meta-analyses, 115,810 patients). Results revealed nine-fold risk of inability to become pregnant in genital-tuberculosis (OR=8.91, CI=1.89-42.12), almost threefold in HIV (OR=2.93, CI=1.95-4.42) and bacterial-vaginosis (OR=2.81, CI=1.85-4.27). Twofold risk of tubal-factor infertility in Female Genital Mutilation/Cutting–Type II/III (OR=2.06, CI=1.03-4.15) and post-natal mortality in consanguinity (stillbirth, OR=1.28, CI=1.04-1.57; neonatal death, OR=1.57, CI=1.22-2.02). It appears RFs impacted 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.

Key Message: Access to quality reproductive healthcare remains inequitable, and fertility-problems are associated with intimate partner violence. Systematic reviews on risk factors for fertility-problems disproportionately affecting the Global South, uncovered several preventable risk factors. The results can inform future research, practice, advocacy and policy change, improving overall health and safety of women.

Introduction

General introduction

"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.(Assembly, 2015) A World Health Organization (WHO) policy paper identified fertility care as a critical reproductive health service (World Health Organization (WHO), 2017) and a recent WHO fact sheet on infertility emphases the importance of prevention of infertility as key component of fertility care.(World Health Organization (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.(Harper et al., 2017; Van Der Poel, 2012) Awareness is becoming an integral aspect of preventative healthcare.(Hammarberg et al., 2017; Macaluso et al., 2010) 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.

The impact of reducing burden of disease by targeting distal and proximal risk factors (RFs) through tailored prevention programs and recommendations applied to communicable and non-communicable disease could potentially be applied to fertility problems.(Angell, Danel, & DeCock, 2012) These recommendations include the continued development of tools for effective community based education and referral,(World Health Organization (WHO), Canada, & Canada, 2005) contextualization(Miranda, Kinra, Casas, Davey Smith, & Ebrahim, 2008) with integration and adaptation that is responsive to the variation in socio-cultural, environmental, institutional, and economic determinants of health(Huynen, Martens, & Hilderink, 2005) with special focus on integration of female health.(World Health Organization (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.(World Health Organization (WHO), 2002) Targeting risk in fertility problems could reduce its burden.

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 socio-economic and cultural factors affect the risk profile for female fertility problems.(Bosdou, Kolibianakis, Tarlatzis, & Fatemi, 2016; Leke, Oduma, Bassol-Mayagoitia, Bacha, & Grigor, 1993; Serour & Serour, 2021) Reproductive health experts suggest that owing to geographic variation in prevalence and quality of reproductive health services, females in certain socioeconomic or cultural religious settings could be differently exposed to risks. Complex multifactorial risk profile for fertility problems in the Global South, in addition to global risks (e.g., smoking) includes exposure to communicable disorders (e.g., tuberculosis, HIV), poorly managed infections (e.g., bacterial vaginosis [BV]) or reproductive events (e.g., birth), consequences of cultural practices (e.g., consanguineous marriages, Female Genital Mutilation/Cutting [FGM/C]) or dubious use of procedures (e.g., Dilatation and curettage [D & C]).(Bayoumi, Van der Poel, El Samani, & Boivin, 2018) One or many of these risks could affect fertility with higher co-occurrence in the Global South. Risk factors (RFs) could influence female fertility directly by compromising integrity or function of reproductive organs (e.g., genital tuberculosis [GTB], BV) or indirectly through variations in patterns of help-seeking or healthcare provision (e.g., screening programs availability for GTB, HIV detection)(World Health Organization (WHO), 2015, 2016) and any social stigmatisation associated with seeking treatment for STIs.(Bayoumi et al., 2018)

For this review, RFs were limited to those affecting female fertility and were selected based on literature searches, expert consultations (Bayoumi et al., 2018) and commonly used considerations for selection of RFs(Ezzati et al., 2002; World Health Organization (WHO), 2002) (Supplemental Figure S1).

A multifactorial risk profile (Supplemental Figure S2) associated with fertility includes global (e.g. age, smoking) and non-global RFs that are bounded by geography, healthcare resources or culture (e.g. HIV, FGM/C). Systematic review evidence exists for effects of a number of global RFs on female fertility (Supplemental Table S1). However, a systematic review of Selected RFs (SRFs) long suspected as critical (especially in the Global South) is now possible due to the

emergence of evidence from primary research studies. A systematic review of these SRFs would allow an in-depth understanding and translation of the risk profile of communities into fertility education and awareness tools, a necessary step to reduce the burden of fertility problems globally.

The current review

The aim of this review was to systematically identify and critically appraise the evidence on the association of SRFs with female fertility. For each SRF we systematically reviewed the literature and any suggested plausible causal mechanisms for effects on fertility based on reported reproductive outcomes. The eight SRFs identified were: genital tuberculosis (GTB), HIV, bacterial vaginosis (BV), consanguinity (CSG), female genital mutilation/cutting (FGM/C), poor health including unsafe abortion, post-partum infection and iatrogenic causes, vitamin D deficiency and water-pipe smoking.

Selected risk factors reviewed

GTB represents 15-20% of extrapulmonary TB and affects about 12% of females who have pulmonary TB.(Muneer, Macrae, Krishnamoorthy, & Zumla, 2019) GTB has been shown to cause lesions in the female reproductive tract and complications as a result of these are implicated in fertility problems.(Ahmadi, Zafarani, & Shahrzad, 2014; Chavhan et al., 2004; Gatongi et al., 2005; Ghosh & Chowdhury, 2011; Shaheen, Subhan, & Tahir, 2006; J. B. Sharma, Sharma, Sharma, & Dharmendra, 2018; Tripathy & Tripathy, 1998; Varma, 2008)

According to the UNAIDS 2021 reference report, there were "37.7 million [30.2 million–45.1 million] people living with HIV in 2020, including 10.2 million [9.8 million–10.2 million] who were not on HIV treatment.".(UNAIDS, 2021) HIV has been associated with reproductive problems, with consistent published evidence for menstrual irregularities, comorbid sexually transmitted infections (STI), tubal blockage, reduced pregnancy and birth rates, increased miscarriage(Kushnir & Lewis, 2011; Lo & Schambelan, 2001; Van Leeuwen et al., 2007; Waters, Gilling-Smith, & Boag, 2007) but less consistent evidence for reduced ovarian

functioning and amenorrhea.(King, Albert, & Murray, 2019; Kushnir & Lewis, 2011; Lo & Schambelan, 2001; Van Leeuwen et al., 2007; Waters et al., 2007)

BV is an infection characterized by an overgrowth of anaerobic bacteria causing an imbalance in naturally occurring vaginal flora.(Mastromarino et al., 2014; Money, 2005; Patel & Daniels) A recent systematic review and meta-analysis has found that "population prevalence of BV is high globally, ranging from 23% to 29% across regions. (Europe and Central Asia, 23%; East Asia and Pacific, 24%; Latin America and Caribbean, 24%; Middle East and North Africa, 25%; sub-Saharan Africa, 25%; North America, 27%; South Asia, 29%)".(Peebles, Velloza, Balkus, McClelland, & Barnabas, 2019) Although BV is not restricted to the Global South, the management of BV might be suboptimal and thus impact of untreated infection might be more common. BV has been reported to be associated with miscarriage, Pelvic Inflammatory Disease (PID), increased susceptibility to viral and other pathogenic bacterial infection, infertility, and preterm labour.(Hay, 2004; Mastromarino et al., 2014; Morris, 2001; Patel & Daniels; Ravel, Moreno, & Simón, 2021; Van Oostrum, De Sutter, Meys, & Verstraelen, 2013)

A consanguineous marriage is one between close biological relatives.(A. H. Bittles, 2001) Prevalence is highest in North Africa, West, Central and South Asia (20-50%).(A. H. Bittles, 2001; A. H. Bittles, 2014) CSG has been suspected to increase pooling of recessive genes that could potentially reduce fertility(Bhasin, 2012; A. H. Bittles, & Black, M. L., 2010) or increase gamete compatibility and maternal reproductive span that can enhance fertility.(A. H. Bittles, Grant, J. C., Sullivan, S. G., & Hussain, R., 2002; Hussain, 2004)

FGM/C is defined as "all procedures that involve partial or total removal of the external female genitalia or other injury to the female genital organs for non-medical reasons".(World Health Organization (WHO), 2022) Prevalence is highest in North East Africa (Somalia 98%, Egypt 87%, Sudan 88%) and Northern West Africa (Guinea 97%, Mali 89%).(Fite, Hanfore, Lake, & Obsa, 2020; Ministry of Health and Population (Egypt); UNFPA-UNICEF, 2014; Yoder & Khan, 2004) FGM/C has been suspected of being associated with infections, tubal damage and obstetric complications.(Obstetricians & Gynaecologists, 2016; Perron et al., 2013; World Health Organization (WHO), 2022)

D&C is a gynaecological procedure performed to remove tissue from the uterus after birth, miscarriage or abortion, to treat abnormal uterine bleeding or for diagnosis and treatment of disease.(Team, 2013) Negative reproductive outcomes such as intrauterine adhesions (IUAs), secondary infertility and recurrent miscarriages have been reported as complications of D&C performed after spontaneous miscarriage.(Schenker, 1996; Wallach, Schenker, & Margalioth, 1982) Repeated D&C has been found to be associated with IUAs in meta-analysis,(Hooker et al., 2014) and a single D&C as compared to hysteroscopy was associated with more IUAs.(Ben-Ami et al., 2014; Hooker, Aydin, Brölmann, & Huirne, 2016) Cervical Cauterization is a gynaecological procedure that uses electricity to destroy tissue in the cervix.(Guidelines, 2017, May 14) It is used to treat inflammations, cysts and cancerous or precancerous tissue with anecdotal reports suggesting a cause for infertility in the Global South(Inhorn & Buss, 1993).

Evidence for the association of vitamin D deficiency on fertility in non-human animal and human studies suggest a role of vitamin D in supporting various reproductive processes.(Anagnostis, Karras, & Goulis, 2013; Chu et al., 2021; Karimi, Arab, Rafiee, & Amani, 2021; Lerchbaum & Obermayer-Pietsch, 2012) Vitamin D deficiency is more prevalent in countries where a restrictive dress code is enforced due to social or religious customs (e.g., in the Middle East).(Bosdou et al., 2016)

The methods for using tobacco differ worldwide (e.g., cigarettes, chewing tobacco, and water-pipe use), however the impact on the human body is similar across methods.(World Health Organization (WHO), 2006) The WHO advises that water-pipe smoking is as hazardous to human health as cigarette smoking.(World Health Organization (WHO) & Regulation, 2015)

Figure 1 depicts a generic template of how SRFs could potentially be associated with fertility outcomes. In this figure, the 'exposure' column represents different SRFs; the 'mechanism' column, the potential pathways via which exposure is potentially associated with fertility outcomes; and, the 'outcome' column represents consequences from exposure (Supplemental Figures S4, S9, S16, S22, S43, S51, and S53 show proposed SRF pathways).

Insert Figure 1. Proposed pathways describing potential association between selected risk factors and fertility.

Materials and Methods

The review was registered with PROSPERO (registration number CRD42016048497), and is reported in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist.(Stroup et al., 2000)

Selection of RFs

RFs were selected based on a preliminary literature search, an online survey of international infertility experts, and face-to-face consultations with a regional panel of infertility experts in the Middle East.(Angell et al., 2012) To identify the most relevant RFs,(World Health Organization (WHO), 2015, 2017) we considered whether: 1) the RF was likely to be among the primary causes of infertility globally and regionally; 2) the RF was prevalent or hazardous or highly prevalent amongst specific sub-populations; 3) there was a likely causal association based on interdisciplinary scientific knowledge; 4) data on risk levels and exposure was available or could be extrapolated; and 5) the risk was potentially modifiable. At the end of this process, eight SRFs were identified for inclusion in the review.

Eligibility criteria: Topic of interest

We developed Population, Exposure/Risk Factor, Comparison, Outcome (PECO) questions 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. We included studies where outcomes in females with an SRF were compared with outcomes in females without the SRF. To reflect the wide range of outcomes in fertility research, we used a broad definition of "fertility problems": an inability to achieve a pregnancy, a live birth, or living children. This means that we included studies that examined primary or secondary infertility, specific causes of infertility (e.g., tubal infertility, amenorrhoea), childlessness (including due to neonatal death), and cumulative number of pregnancies.

Exclusion criteria were studies: 1) using animal data only, 2) using male data only, 3) not reporting a fertility-related outcome, 4) not reporting the association between the SRF and fertility outcome, 5) where time to birth/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 6) using secondary or qualitative data or a duplicate record of an included study.

Eligibility criteria: Types of studies

All quantitative study designs were included. We included published studies, and excluded those that had only been published as conference abstracts and unpublished PhD or Master's theses. No limits on language or date were used.

Search Strategy

Ovid Medline was searched from 1946 to July 2016, with updates conducted in January 2018, January 2022 and December 2022 (see Supplemental Figures S23, S29-S31, Supplemental Tables S23-S26).

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' (see Supplemental Materials, Appendices A-F). To ensure that the search terms were comprehensive, we conducted supplementary searches for all SRFs using MeSH terms for specific indicators of fertility problems (e.g., tubal occlusion, amenorrhea). 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. We searched key organizational websites including the WHO, United Nations Population Fund,(UNFPA-UNICEF) as well as regional sites of these organizations such as the Eastern Mediterranean Regional Office (EMRO) and African Regional Office (AFRO) of the WHO. The reference lists of included articles were

searched, and authors were contacted for missing information. Supplemental Figure S3 shows flowchart of steps taken in the review process.

Searches from each database were imported into excel, after duplicates were removed, studies were selected based on eligibility criteria. Screening was conducted independently by RRB, N.Z and Y.J.L. both at titles and abstracts and full-text. Disagreements at all stages were resolved by discussion amongst the reviewers.

Data Extraction and Quality Assessment

Information was extracted, using a standard form, 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 NOS assessment independently for each included paper. A third reviewer evaluated all discrepancies, and these were resolved in consultation with others in the review group.

Data Synthesis and Analysis

We used RevMan Version 5.3. to calculate effect sizes, conduct meta-analyses, and generate forest plots. The primary outcome measure of association was the odds ratio (OR), either as presented in the papers or calculated from raw data.

When means and standard deviations were presented in the primary studies, the primary outcome measure was the mean difference (Guidelines) between exposed and non-exposed groups and original units of measurement were used.

We used random effects meta-analyses 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, subgroup/sensitivity analysis were conducted. The subgroup analyses were based on differences in methodological characteristics of the study e.g., type of control group, subcategories of infertility (tubal factor vs ovulatory). When

there were insufficient primary studies to calculate pooled estimates, a narrative synthesis was conducted.

Assessment of Bias

We assessed study quality using the modified version of the Newcastle-Ottawa Scale [NOS].(Wells et al., 2000) Studies were classified as high, medium or low quality.

Publication Bias

Funnel plots (where there were 10 or more studies), Egger's test and trim and fill (to impute the number of "missing" studies in the meta-analysis, and to calculate the adjusted pooled effect estimate with the "missing" studies) procedures were used to evaluate publication bias using Comprehensive Meta-Analysis Version 3.(Borenstein, 2013)

Results

Search outcome and identified studies

We screened 3354 articles, and 190 full-text articles were assessed for eligibility. Sixty-two primary studies were included in the review, 58 were included in meta-analyses and four reviewed narratively, see Figure 2. The 58 studies included in meta-analyses encompassed a total patient sample of 115, 810 (GTB=1210; HIV=13,290; BV=6.020; CSG=69,725; FGM/C=24,457; D&C=1108). Data were available for meta-analysis for five of the eight new SRFs. Results for each factor are presented below and are summarized in Table I (see Supplemental Materials for the forest plots, where applicable).

Insert Table I. Results of meta-analysis for the five selected risk factors for which it was possible to calculate pooled estimates

Insert Figure 2. Summary PRISMA Flow Diagram showing the exclusion of articles at the different stages.

Genital tuberculosis (GTB)

Five cross-sectional studies met inclusion criteria for this SRF. The outcomes reported were infertility, amenorrhea and primary vs. secondary infertility. Three meta-analyses, each including two studies, were performed (Table I). In the first, females with GTB were more likely to be infertile (>12 months) than females without GTB. In the second, females with GTB were equally likely to report amenorrhea as females without GTB. In the third, females with GTB were more likely to have primary infertility than secondary infertility compared to females without GTB.

HIV

Nine studies met inclusion criteria for this SRF: two case-control, one cohort study and three cross-sectional data embedded within cohort studies. The outcomes reported were cumulative pregnancy rate, amenorrhea, 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. Five meta-analyses were performed (Table I). In the first, two studies were included; HIV+ females had fewer pregnancies than HIV- females. In the second, two studies were included; HIV+ group were equally likely to report miscarriages as HIV- group. Three studies were included in the third analysis; HIV+ group were more likely to have amenorrhea than HIV- group. Two studies were included in the fourth analysis; HIV+ group were equally likely to have FSH >25 IU/l as HIV- group. Two studies were included in the fifth analysis; HIV+ group were more likely to be infertile than HIV- group.

Bacterial vaginosis (BV)

Eleven studies were included in this meta-analysis, 10 case-control and one cross-sectional study (Table I). The outcomes reported were cases of BV in infertile and fertile females. Females with BV were more likely to be infertile than females without BV. For this SRF, there were enough studies to also conduct pre-specified subgroup analysis, to determine association with a specific type of infertility, Tubal Factor Infertility (TFI). Subgroup analysis comprising females with TFI only and subgroup comprising females with multiple types of infertility were both significant and the difference between subgroups was significant with TFI more likely to be infertile than multiple types of infertility (Supplemental Figure S20).

Consanguinity (CSG)

Twenty-five studies, 21 cross-sectional and four cohort studies were included in eight meta-analyses (Table I). 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. Eight meta-analyses were performed comparing CSG couples and those who were unrelated (Table I). There was no difference in average time to first birth and miscarriage. CSG couples were less likely to have never been pregnant but there was no association with childlessness. CSG couples had significantly more pregnancies and live births than unrelated couples. More still births and neonatal deaths were found in the CSG couples. Two meta-analyses were updated to include the study retrieved in the latest search, but meta-analyses results were unaffected.

Female genital mutilation/cutting (FGM/C)

Seven studies were included in the meta-analysis, five cross-sectional and two case-control studies. The outcomes reported were infertility, childlessness and a comparison of cases with tubal infertility and pregnant controls. Three meta-analyses were performed (Table I). The first included two studies showing that females with FGM/C were not more likely to be infertile (>12 months) than females without FGM/C. 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 (and significantly higher using adjusted ORs). 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.

Dilatation and curettage (D&C)

Four studies met inclusion criteria, three cohort and one cross-sectional study. Pooled estimates could not be calculated because the studies all used different outcomes; therefore, results are summarized narratively. In a cohort study, females who had undergone D&C to remove retained products of conception (RPOC) experienced longer time to pregnancy and more 'new infertility' diagnoses compared to females who had undergone hysteroscopy.(Ben-Ami et al., 2014) In a cross-sectional study, females who had a history of D&C as part of infertility investigation had significantly more PID than females who had no such history.(Taylor & Graham, 1982) In a

cohort study, females who had undergone D&C developed more gynaecological disease (e.g., endometriosis, irregular uterine bleeding) and menstrual irregularity than females who had vacuum aspiration and/or received prostaglandins.(Sotnikova, 1986) In a cohort study, there were no differences in the number of future pregnancies, normal deliveries, miscarriages, and infertility in females who had undergone D&C after miscarriage compared to females who had experienced expectant management.(Ben-Baruch et al., 1991)

Vitamin D deficiency and water-pipe smoking

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

A systematic search for water-pipe smoking was not necessary since water-pipe is only a different method of consuming tobacco and the WHO recently reported that use of water-pipe smoking is as hazardous to human health as cigarette smoking.[72] Specifically, a one hour water-pipe session is thought to be equivalent to inhaling 100-200 times the volume of smoke in a single cigarette(World Health Organization (WHO) & Regulation, 2015) and the impact of smoking cigarettes on fertility is well established.(Dechanet et al., 2011)

Multifactorial Risk Model

Results of all meta-analyses were aggregated with extant evidence and used to construct a model that depicts how reviewed SRFs could be associated with fertility problems using outcomes reported in the primary studies, see Figure 3.

Insert Figure 3. Association between risk factor and fertility problems according to type of evidence and proposed timing of effect in reproductive process.

Discussion

Principal findings

The SRFs 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 estimate of association through meta-analysis for most risks. GTB showed a nine-fold higher risk of inability to become pregnant, and HIV and BV an almost threefold higher risk of inability to become pregnant within 12 months, versus comparator group. FGM/C, Type II and III (~90% occurrence in some African nations)(Fite et al., 2020; Yoder & Khan, 2004) showed a twofold higher risk of TFI, whereas CSG (50% of marriages in some nations)(A. H. Bittles, 2014) was associated with post-natal mortality. Results indicate a too narrow focus on risks for reduced fertility in many countries and need for more mechanistic fertility research and implementation of fertility indicators more consistently 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, see Figure 4. What can and should be done about fertility-related risk exposure needs to be determined within countries and regions utilizing a global health framework. Multifactorial risk findings reinforce the need to put fertility as an agenda in global health initiatives.

Where in the reproductive tract the impact appears to be

Some SRFs such as BV and FGM/C seem to have an association with impact at several stages in the reproductive process. In the case of BV this could be because pre-pregnancy untreated infection that reaches the tubes will compromise ability to achieve pregnancy, while 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 as noted in the literature.(Berg & Underland, 2013; Makhlouf Obermeyer, 2005; Obstetricians & Gynaecologists, 2016; Reisel & Creighton, 2015; World Health Organization (WHO), 2017) Therefore, it can be inferred that timing and extent of exposure to SRFs could affect fertility in different ways. Prevention and management should be informed by these mechanisms. Research should target multiple outcomes and endpoints to capture these effects.

==Insert== Figure 4. Factors impacting fertility

Common pathways (infection)

SRFs could have common pathways. For example, HIV, BV and D&C were all related to infection and PID. Although with FGM/C there were no data suggesting 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 due to the progression of infection to the reproductive tract or ascension to tubes, causing PID or tubal damage.(Brunham, Gottlieb, & Paavonen, 2015; Cates, Farley, & Rowe, 1985; Ruggeri et al., 2016; World Health Organization (WHO), 2007) However, there were no consistent findings to suggest that infections per se always led to inability to achieve pregnancy. This is probably because the impact 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 impact on the female reproductive tract and hence future ability to achieve pregnancy.(Jonathan Ross, Guaschino, Cusini, & Jensen, 2018; J Ross & Mc Carthy) Furthermore, not all infections lead to PID and not all cases of PID lead to tubal damage.(Das, Ronda, & Trent, 2016; Workowski, 2015; World Health Organization (WHO), 2007) Future research should ensure that data about timing and treatment of infection is collected. Other shared pathways could exist.

What can be clearly gleaned from Figure 3 is that the SRFs that included infection, PID or TFI in their pathways (e.g. BV, HIV and FGM/C) were found to be associated with an inability to achieve pregnancy, affirming historic reports in the literature about the association between infection and infertility in Africa and other Low and Middle Income Countries (LMIC)(Abebe, Afework, & Abaynew, 2020; Cates et al., 1985; Ericksen & Brunette, 1996; Leke et al., 1993; Odukogbe & Ola, 2005). 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 STIs and unsafe procedures (abortion, delivery) as has typically been the case.(Ericksen & Brunette, 1996; S. Sharma, Mittal, & Aggarwal, 2009; World Health Organization (WHO), 1987)

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. However, assessment of publication bias for all meta-analyses did not alter the results (Supplemental Figures S21, S35, and S48).

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 SRFs. First, in most studies, recruitment occurred at fertility clinics, possibly limiting selection to females at higher risk of infertility (applicable to GTB, FGM/C, BV). Second, the definition of outcomes, period of exposure or type of infertility were often not reported (applicable to CSG, BV, 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 STIs (applicable to HIV and BV). Only 10 of the 57 primary studies reported adjusted ORs. However, the use of adjusted ORs did not alter the results of the reviews except in one instance, where females with FGM/C reported more childlessness than females without FGM/C. Given that significance changed in only one of eight meta-analyses we can be reassured that the results might not have been impacted greatly by the lack of

reporting of adjusted ORs. It is important to note that in six of the eight adjusted OR meta-analyses the magnitude of the effect size increased indicating that the association with fertility problems was related to the SRFs and not the confounders. Additionally, heterogeneity remained the same or decreased in seven of the eight adjusted meta-analyses, indicating that the confounders were indeed increasing the heterogeneity.

Conclusion

Implications of Findings

Targeting communicable and non-communicable diseases is not only a priority to reduce the effects of these conditions on health in general but also their impact on childbearing and parenthood goals. The findings strongly support the movement toward having a more global understanding of risk for disease, and by extension different settings can determine 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 fertility impact of these SRFs, disseminated widely and in the most culturally appropriate manner. Results disseminated to clinicians can support discussions with individuals about these SRFs 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 TB). Appropriate education, awareness, support, and training initiatives are urgently needed to empower people to maintain or improve their fertility, quality of life, and productivity.

Unanswered Questions and Future Research

Future research needs to determine what is the best method of selecting RFs, methods to systematically evaluate pathways leading to fertility problems, particularly more rigorous prospective designs or RCTs aimed at modifying risks (where possible). The methodological

rigor enhanced reliability, however, the small number of primary studies and inconsistencies in outcome measures were limitations.

Specific research directions for each SRF were informed from the gaps in primary studies and include: using more rigorous methodology like RCTs 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.

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.

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

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

The study was submitted as preprint:
Bayoumi, R. R., Boivin, J., Fatemi, H.M., Hurt, L., Serour, G.I. and van der Poel, S., (2021), Looking beyond the obvious: a critical systematic review on risk factors for fertility problems in a globalized world, Medrxiv Preprint. Available from:
https://www.medrxiv.org/content/10.1101/2021.05.06.21256676v1

Detailed results available in the Supplemental Materials and additional data are available upon request from the corresponding author. Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available. This will include (but not be limited to): study protocol, statistical analysis plan and data from included primary studies. These data will be available online with publication.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Conflict of interest
The authors declare no conflicts of interest.

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Table I.
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 meta-analysis	Number of events/total Exposed group	Number of events/total Non-exposed group	Heterogeneity I² %, 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, 5 included in meta-analysis (all LMIC)	Infertile (>12 months no pregnancy)	2	102/124	127/308	72, p=0.06	8.91 (1.89-42.12)		
		Amenorrhea	2	24/301	12/389	75, p=0.05	4.24 (0.23-78.14)		
		Primary infertility	2	133/171	149/305	0, p=0.71	2.94 (1.89-4.37)		
HIV	1134 full-text articles screened, 9 included in meta-analysis (7 LMIC)	Cumulative pregnancy rate	2	532/1894	1120/4015	97, p<0.00001	0.36 (0.15-0.89)	0.32 (0.17-0.62)	
		Miscarriage	2	26/155	99/949	0, p=0.55	1.35 (0.77-2.35)		
		Amenorrhea	3	173/3942	22/1292	0, p=0.46	2.44 (1.56-3.81)	2.44 (1.81-3.98)	
		FSH >25 IU/l	2	60/1194	10/317	0, p=0.39	1.51 (0.77-2.94)	2.67 (0.8-8.9)	
		Infertile (> 12 months no pregnancy)*	2	107/146	432/780	0, p=0.43	2.93 (1.95-4.42)	3.55 (1.85-6.79)	
BV	267 full-text articles screened, 11 included in meta-analysis (8 LMIC)	Infertile (> 12 months no pregnancy)*	11	846/1421	1443/4597	83, p<0.00001	2.81 (1.85-4.27)	2.97 (2.03-4.35)	
CSG	585 full-text articles screened, 25 studies included in meta-analysis (12 LMIC)	Time to first birth	2			0, p=0.96			+0.24 (-0.39-0.87)
		Miscarriage	6	1069/3372	1030/3485	50, p=0.09	1.1 (0.93-1.30)		
		Never-pregnant	3	92/3241	186/4120	49, p=0.14	0.66 (0.45-0.98)		

Selected Risk Factor	Evidence reviewed	Outcome reported	Number of studies in meta-analysis	Number of events/total Exposed group	Number of events/total Non-exposed group	Heterogeneity I² %, P value	Pooled effect estimates (random effects)		
							Crude OR (95% CI)	Adjusted OR (95% CI)	Mean Difference (95% CI)
		Childlessness	5	380/6651	717/10240	60, p=0.04	0.83 (0.67-1.03)		
		Mean number of pregnancies	6			66, p=0.02			+0.40 (0.10-0.71)
		Mean number of live-births	7			79, p<0.0001			+0.24 (0.05-0.43)
		Stillbirth	6	243/3372	211/3485	7, p=0.36	1.28 (1.04-1.57)		
		Neonatal Death	4	151/2072	144/2232	0, p=0.46	1.57 (1.22-2.02)		
FGM/C	274 full-text articles screened, 7 studies included in meta-analysis (all LMIC)	Infertile (> 12 months no pregnancy)	2	117/1090	61/655	0, p=0.52	1.17 (0.84-1.63)	1.26 (0.89-1.78)	
		Childlessness	3	352/9903	251/7760	3, p=0.36	1.22 (0.99-1.52)	1.20 (1.0-1.46)	
		Infertile 2 years (TFI)*	2	72/276	15/76	0, p=0.68	2.06 (1.03-4.15)	2.75** (1.15-6.57)	

Note: See Supplemental Materials for the forest Plots and funnel plots; SRF = selected risk factor; OR = odds ratio; CSG = consanguinity; FGM/C = female genital mutilation/cutting; GTB = genital tuberculosis; BV = bacterial vaginosis; D&C = dilatation and curettage; FSH = follicle-stimulating hormone; LMIC = low and middle income countries; TFI = tubal factor infertility; * = original study case-control design, OR calculated to reflect infertile in exposed vs. non-exposed, ** = one study TFI only, one study all infertile.