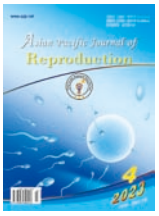

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The barriers of joining *in vitro* fertilization programs among infertile couples in developing countries: A scoping review

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ABSTRACT

Objective: To determine the barriers of joining *in–vitro* fertilization (IVF) programs among infertile couples in developing countries.

Methods: This study assessed infertile couples and the barriers or associated factors resulting in delayed decision-making of joining IVF program by searching databases PubMed, ScienceDirect, EBSCO, ClinicalKey, and Cochrane Library from inception until December 31, 2021. Additional search strategies were snowballing literature search and citation tracking.

Results: Eleven articles were included in the scoping review. The cost was the greatest barrier of joining IVF program. Limited access and lack of assisted reproductive technology centers, few qualified infertility trained staff, insufficient government support, low priority in government policy, along with sociocultural factors, such as religion and false beliefs or myths were also majorly considered to be associated obstacles.

Conclusions: The main barrier associated with IVF program among infertile couples in developing countries is the high cost of the IVF services.

KEYWORDS: *In vitro* fertilization; Assisted reproductive technology; Barrier; Developing countries

I. Introduction

The World Health Organization classifies infertility as a disease of the reproductive system which is defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse[1]. Up to 10% of the world's population has primary infertility, and secondary infertility reaches up to 35%. In fact, most of these couples live in developing countries[2,3]. Infertility in developing countries raises distinct and complex problems, which are significantly more than in developed countries. It has been argued that infertility is relatively less important in low-resource countries where fatal and contagious diseases remain rampant. The opposite arguments include more priorities in family planning, prevention of reproductive infection, and education. Otherwise, the pro arguments stated that infertility is a disease that requires medical treatment and negative consequences of childlessness are much more prominent in developing countries[4]. These developing countries are heterogeneous, diverse in cultural and moral values, religions, and their rate of development. Many cultures in developing countries hold a common belief that womanhood is defined through motherhood; thus, infertile women are usually labelled as the culprit for the couple's inability to conceive. Moreover, in the absence of social security systems especially in countries with low resources, older people are financially dependent on their children. As a result, the women without any child are mostly stigmatized, neglected, isolated, and often face domestic violence, human trafficking subjected to polygamy[3,5,6].

Generally, the cases of couple infertility are usually due to either female factors, male factors, or a combination of female and male factors, which can equally contribute to the incidence of infertility in approximate thirds[7–9]. In poor resource areas and developing countries, the demand for infertility treatment is enormous, but the proportion of couples seeking medical care is still low compared with developed countries and the proportion of infertile couples receiving care is substantially less in developing countries[10,11]. These disparities are real dilemmas since there is a significant gap in

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access to infertility care between areas with poor and rich resources or developing countries and developed countries[9,12].

Therefore, this scoping review was conducted in order to systematically map the available evidence regarding factors associated with barriers of joining *in–vitro* fertilization (IVF) program among infertile couples in developing countries.

2. Materials and methods

2.1. Protocol

Scoping review methods serve to map evidence on a topic and identify main concepts, theories, sources, and knowledge gaps following a systematic approach[13]. Our protocol was developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)[14].

2.2. Eligibility criteria

Inclusion and exclusion criteria were determined and guided by the previous conceptual framework developed for this study. Peer-reviewed papers were included if the papers were published between the periods of 2011–2021, written in English, only involved human participants, and discussed the barriers or associated factors which may influence the decision-making for enrolling in an IVF program by infertile couples, and were conducted in developing countries. Papers or review articles which did not provide information about the barriers or associated factors were excluded.

2.3. Sources and search strategies

In identifying relevant studies, the Population-Concept-Context framework developed by the Joanna Briggs Institute was used[15]. This review only included the studies that focused on the infertile couples (population) and the barriers or associated factors resulting in delayed decision-making of joining IVF program (concept) in developing countries setting (context). Comprehensive literature searches were conducted by two authors. Initially, we searched the following five electronic databases from inception until December 31, 2021: PubMed, ScienceDirect, EBSCO, ClinicalKey, and The Cochrane Library. The search strategies were restricted by language (English only) and year (published in the last 10 years). Additional search strategies were snowballing literature search and citation tracking. Some of the keywords were adopted from Medical Subheading (MeSH) and Boolean was utilized to improve sensitivity. The following search terms were: ("fertilization *in vitro*"[MeSH Terms] OR "reproductive techniques, assisted"[MeSH Terms] OR "reproductive technologies, assisted"[MeSH Terms]) AND (barriers OR obstacles OR difficulties) AND ((developing OR low-income OR low resources OR poor OR less developed) AND countries*).

2.4. Study selection process

All reviewers worked on the selection of sources or evidence included in this scoping review. Two reviewers working in pairs sequentially evaluated the titles, abstracts, and then full-text articles/reviews. Articles meeting the inclusion criteria were further studied. We resolved peer disagreements by discussion with a third reviewer to reach consensus.

2.5. Data synthesis and charting process

For the included articles, we extracted data concerning study characteristics, objectives, terminology used, methodological steps, engagement characteristics, and contextual factors in the conduct of the scoping review. A data-charting form was developed by two reviewers to verify which variables to extract. Then, the other two reviewers independently charted the data, discussed the results and continuously updated the data-charting form in an iterative process.

All the included articles were categorized by year of publication, country of origin, type of publications, study design, methods, setting, and sample size. Subsequently, the included studies were extracted and we summarized the barriers or associated factors contributing to delayed decision-making in infertile couples to enroll the IVF program. We also grouped the barriers based on the majority mentioned and presented from most to the least mentioned in the studies. At the end, three categories of barriers in taking IVF program were established: the barriers from the patients' perspective, healthcare providers' perspective, and the stakeholders' perspective.

3. Results

3.1. Selection of sources of evidence

The literature search resulted in 309 citations, including snowballing and/or citation tracking. After deduplication and relevance screening, 45 articles met the criteria based on the titles and abstracts. Thirty-two articles were excluded after investigated for eligibility, because the majority of these articles predominantly discussed or presented data from developed countries rather than developing countries. Subsequently, a total of 11 articles were included in this review. The flowchart of the articles' selection process from identification to final inclusion is represented in Figure 1.

3.2. Study characteristics

There were 11 articles included in this scoping review, with 81.8% published between 2010-2015 (Supplementary Table 1). Each article represented different developing countries worldwide. The most common study design used was qualitative study (81.8%), with the majority method using deep interview (45.5%). Most articles used

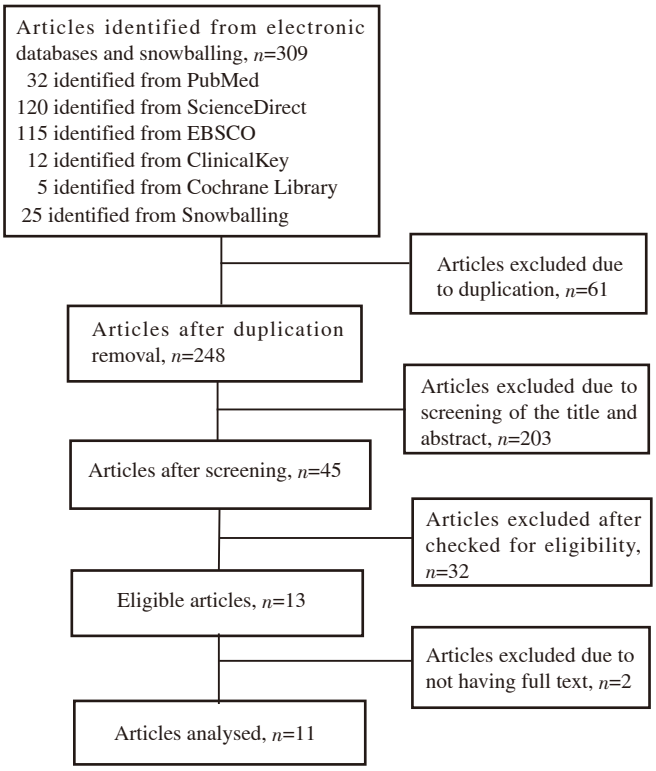

Figure 1. Flowchart of study screening process.

infertility clinics or assisted reproductive technology (ART) centers as the setting of the studies (63.6%) and the majority sample of the included studies were patients (45.5%).

3.3. Data extraction of the included studies

Information and specific details regarding the data extraction of the included studies are available in Table 1. Of the 11 articles, the most common research purpose was to explore the barriers of infertility couples in developing countries to enroll in an IVF program.

3.4. Synthesis of results

We synthesized our findings and described all the barriers that prevented infertile couples from joining an IVF program in developing countries based on the 11 articles in our scoping review. The cost was the most commonly mentioned barrier in our included studies. It was mentioned by 8 of the included articles in this study. Lack of ART services and limited accessibility to ART services were stated each by 5 articles. These were followed by sociocultural factors, no government subsidy, lack of infertility trained staff, religion, financial concerns, myths and beliefs, government policy and priority, the fears of procedures and side effects, ethical issues, low confidence in treatment, lack of spousal support, lack of well-defined referral system, stigma, men's denial of infertility, and use of traditional medicine, all of which were only mentioned by 2-4 articles. The least stated barriers which were only mentioned by 1 article were legal matters, alternate adoption, poor knowledge, surgery treatment before ART, lower relationship satisfaction, depression, and medical problems (Supplementary Figure 1).

In Figure 2, we divided the identified barriers into 3 main points of view: patient's perspective, health provider's perspective, and stakeholder's perspective. As a result, we were able to identify the obstacles from various different perspectives that prevented couples from participating in an IVF program in developing countries. Accordingly, it may be more feasible to find solutions that can be implemented to improve the problems from each group of patients, health providers and stakeholders.

Table 1. Summary data extraction of included studies.

No.	Authors	Year	Country origin	Findings
a	Akande *et al*[16]	2019	Nigeria	Interviews and semi-structured questionnaire of 202 patients found that the cost is the major barrier to ART program, followed by patient's belief, myth and religion which were in contradiction with ART. Other barriers were fear if abnormalities happen to the baby, fear of the procedures and side effects, concerns over the risks and hospital visit may be too stressful or painful. Poor knowledge of ART, limited access to ART clinic and absence of qualified medical personnel, lack of spousal agreement or willingness to opt ART, bad stigma of child who born from ART program were other reasons to seek infertility treatment.
b	Hiadzi and Woodward[17]	2019	Ghana	Depth interviews with 45 patients who were seeking treatment revealed the contestations which arise between infertility couples and affect infertility treatment decision-making: lack of male partner empathy or pathetic apathy, blaming female partner for failure to conceive, internal depression and anxiety between couple, lower relationship satisfaction and financial concerns.
c	Khalifa and Ahmed[18]	2012	Sudan	Obstetrics & gynecology physicians specializing in infertility care were interviewed to state obstacles among their services. Lack of ART center, no partner satellite fertility centers, no referral mechanisms or partnerships with public fertility care have been established. There was no government subsidy or support, thus making the high cost of ART services. Other barriers were lack of qualified local trained staff, embryologists and fertility nurses. Arising ethical issues, communities feared that IVF/ICSI would be forbidden in Islam. They also feared mixing of ova, sperm or embryos in laboratories. The last issue was sociocultural in Sudan, since traditional healers are a first point for consultation. It causes considerable delay in seeking proper biomedical care.
d	Murage *et al*[19]	2011	Kenya	Cross-sectional online survey to 188 obstetricians and gynecologists registered with the Kenya Obstetrics and Gynecology Society showed the high cost of treatment, patients' limited finances, and limited local services were almost universally cited as the main barriers to ART services in Kenya.

Table 1. Summary data extraction of included studies (continued).

No.	Authors	Year	Country origin	Findings
e	Makuch and Bahamondes[20]	2012	Brazil	Health authorities reported the lack availability of infertility services within the public healthcare network, including the services that provide ART procedures followed by lack of resources and lack of trained professionals. No ART services were available within the Sistema Único de Saúde-unified health system in their administrative region. The healthcare professionals and the patients interviewed in this study reported that access to infertility services performing ART procedures was limited. Patients considered costs to be "very high" and one of the greatest impediments to accessing ART procedures.
f	Makuch *et al*[21]	2011	Brazil	There were 19 healthcare professionals and 48 patients from 5 centers interviewed. Patients complained that the cost were very high. Some procedures, including ultrasound monitoring or laboratory tests are part of the list of approved procedures performed under coverage of Sistema Único de Saúde-unified health system for infertility and other gynecological conditions. But, others such as the drugs used for stimulation of follicles, anesthesia, disposables and a fee for the general operative costs, were charged directly to the patients. Couples who needed surgery or treatment prior to initiating ART procedures had an additional delay, mainly related to where the procedure would be done: in a public service, in a health maintenance organization or in a private clinic. According to the patients, the bureaucracy for scheduling, the delay in making an appointment for screening or for the initial consultation at the ART center and the entire procedure of obtaining ART was difficult and constituted a substantial hurdle. According to the health professionals, the services were unable to attend to the existing demand for ART procedures. They were unable to assess the size of the unmet demand since they only had contact with patients who had been able to obtain access to the service.
g	Bennett *et al*[22]	2012	Indonesia	Three Indonesian infertility clinics in major cities were used to enroll 212 female infertility patients for an interviewer-administered survey. Patients identified a number of barriers to access biomedical infertility care, including: low confidence in infertility treatment and high rates of switching between providers (physicians), the lack of number and location of clinics, the lack of a well-established referral system, the high cost of treatment, and patients also experienced of embarrassment, fear of the procedure examination and fear of receiving a diagnosis of sterility.
h	Pashigian[23]	2012	Vietnam	The sociocultural pressures like blaming women as the cause of infertility or women must bear baby boy to propitiate the ancestors can lead to divorce, polygamy, or physical violence. Wives pursue treatment without the knowledge of their husbands for fear of marital instability, so the complete examination of infertility among couples will not accomplished. Another issue involved legal matters, since Vietnam has a ban on surrogacy, limited services for single women, restricted the use of donor ova to married couples, restricted the use of Vietnamese donor gametes to ethnic Vietnamese only and sperm banks were largely restricted to the state sector. The cost of IVF is expensive compared to the average household income. This study also found some women pursue traditional medicine first and delay biomedical evaluation and treatment.
i	Kulkarni *et al*[24]	2014	India	This retrospective study was conducted among couples in the age group of 20-40 years who opted for IVF at tertiary care hospital and a private infertility center in India. Medical records for 3 years (2009-2012) were included in the study for analysis. Eighty-eight cases of IVF were conducted in this study. Financial burden, adoption of alternate methods such as adoption, reduced ovarian reserves and Crohn's disease were the major reasons for couples to drop out from an ongoing IVF cycle.
j	Nahar[25]	2012	Bangladesh	Through the analysis of stakeholders' interviews on infertility policies and services *via* a vertical process found that infertility was not a priority issue for the Bangladesh government's health agenda, and nor were donors interested in it. So, it influences the government policy makers. The representatives strongly believed that there were many other priority issues within reproductive health that needed to be focused on, for example fertility control and maternal health prioritized maternal mortality reduction. The non-government organization representatives added that infertility services require specialist training for the doctors, pathology lab workers and the organizations did not have these human resources.
k	Tremayne[26]	2012	Iran	Iran as a Muslim country, seems to be ahead of most countries in the world in its coverage and legalization of ARTs, offering considerable services and facilities, both public and private. The cost of ART remains a major constraint to infertile couples seeking treatment, even though this is low in comparison to many other countries, which attracts infertile couples from other Muslim countries. Cultural norms and practices can also act, not only as barriers to the use of ART, but also lead to problems afterwards. Infertility remains a major stigma, where male infertility in particular is more problematic and studies show that infertile men go to great lengths to deny or hide their infertility.

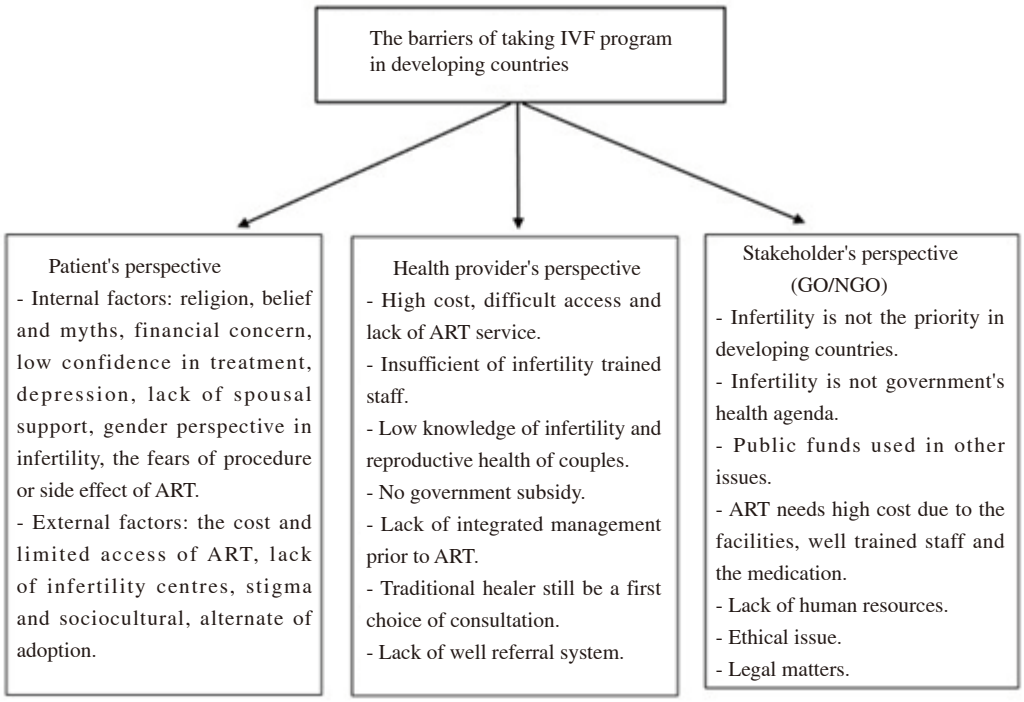

Figure 2. The barriers of taking IVF program in developing countries from different perpective. IVF: *in–vitro* fertilization; ART: assisted reproductive technology; GOs: governments; NGOs: non-government organizations.

4. Discussion

Tubal damage is the most common reasons for infertility in the developing countries as a result of sexually transmitted diseases, septic miscarriages, and puerperal sepsis[3]. The irony of this condition is that women with bilateral tubal occlusions can only be managed by IVF. Unfortunately, the reproductive technology warranted as the most effective intervention to treat bilateral tubal occlusion is either unavailable or very high-priced in developing countries[2]. In developing countries there are always arguments pro and contra about infertility among couples. The problem of overpopulation in resource-poor countries cause infertility not to be a priority issue. These countries put family planning or contraception, prevention of infections, vaccinations, malaria and human immunodeficiency virus (HIV) as the most important issues to be handled with more diligence. Although the negative consequences of childlessness are much more severe in developing countries, the limited budgets of these governments (GOs) and the related non-government organizations (NGOs) give rise to a 'domino-effect' or dilemma with several severe consequences. It is unsurprising that governments choose to invest in infertility prevention rather than costly technologies that are unlikely to be cost-effective. The domino-effect occurs as one factor leads to another, creating a cycle of neglect and underinvestment in infertility issues in developing countries[9]. Limited budgets lead to prioritization of other pressing health concerns, which in turn influences resource allocation decisions and leads to a lack of emphasis on infertility. This cycle perpetuates the under recognition and underfunding of infertility as a public health concern in developing countries. It is important to note that the consequences of this domino-effect can be severe for individuals and couples facing infertility, as they may experience social, psychological, and economic challenges without adequate support and access to appropriate care.

Infertility is a complex and multi-faceted medico-socio-cultural problem associated with gender-based suffering. It may lead to suffering on many levels in society, including the psychological, social, or even economic aspects of the couples. Additionally, childlessness in developing countries may create other significant social issues such as stigmatization, isolation, even domestic violence, especially for women. Generally, the woman will be the first blamed for not getting pregnant. Due to the gender imbalance in the field of fertility care, women are more likely to receive treatment and undergo intrusive investigations than their male counterparts. This is despite the fact that female factors are not the sole cause of a couple's problems. Since men are not always included in the process of biomedical fertility care, they are actually more likely to suffer from various issues related to their reproductive health[16,17,26]. In developing countries, the future child is the heir of a family and this is deeply rooted in socio-cultural norms. Without children, women will suffer and become the 'talk of the society'. In some cases, the absence of a child triggers conflict in a family[27].

Religion and culture were some of the factors that prevented people from fully utilizing ART. This was mainly due to the concerns about the ethical status of the embryo. Religious laws tend to be

predictable, yet they can also be remarkably adaptive. Third-party reproductive assistance is never used in the Sunni Muslim world, which includes most Arab countries and Turkey, and is prohibited by religious edicts, bioethical and professional norms of medical behavior, and legal formulations[28]. Indonesia which is home to the world's biggest Muslim population, while its laws and social norms related to ART closely resemble those of the country's Islamic beliefs, this country prohibits against gamete donation and surrogacy, while only married heterosexual couples are allowed to engage in the use of ART[29]. Assisted reproduction is accepted in nearly all its forms by followers of Hinduism, Buddhism and Judaism, but Orthodox Jews refuse third party involvement. Conversely, fundamentalists in Roman Catholicism designate any treatment of assisted reproduction as unacceptable practices while paradoxically forbidding all forms of contraception. Meanwhile, Protestants, Anglicans, Coptic Christians, Orthodox Christians and Sunni Muslims accept most of its forms, but debate or refuse third party involvement[30].

Simplifying the ART program should not reduce or compromise the service quality, and careful attention should be emphasized to reduce complications such as multiple pregnancy. The initiatives for simplifying diagnostic and clinical procedures in establishing the case of infertility must be achieved. Then, the ovarian stimulation protocols have to be modified to milder forms to reduce the fee for the medication needed and the risk of complications. The laboratory set-up and procedures also need to be simplified, since laboratory equipment and tools are expensive[4]. Another challenge is the fact that most developing countries have a lack of well-trained professional gynecologists, embryologists and nurses who work in the infertility field. Knowledge, skills and experience must be required for assisted reproductive interventions[31].

Knowledge levels about infertility were poor among couples who live in developing countries, especially in rural areas. Attitudes towards infertility in these people incorrectly identified that infertility is not a disease. In many developing countries, traditional practitioners are the first point of contact for women seeking medical attention. They still believe in supernatural power to cure a woman's fertility issues. However, this traditional healer can also cause delays in seeking proper medical care[18,32].

This study also highlighted the ethical and cultural issues surrounding the funding of ART when couples are trying to establish their relationship. If the partner is not able to become pregnant due to male infertility, the couple has better chances of sustaining the funding. On the other hand, if the partner has been diagnosed with female-factor infertility, the likelihood of the man seeking a second marriage will rise more than the initiative to treat his wife with IVF[18].

Infertile couples in developing countries often have to struggle in finding an IVF center which is conveniently located near them. Most of time these centers are only available in large cities. The lack of accessibility to IVF centers is one of the most common barriers for couples to join an IVF program. Indonesia as a developing country is one example of this condition. The fertility centers are profoundly clustered in big cities on only the island of Java. Certainly, Indonesia's rate of IVF uptake is also remarkably low relative to the size of its population. Undeniably, restricted access to infertility care in Indonesia causes the services of IVF to be not readily available to everyone, particularly those residing in rural areas[22]. Wide disparities exist in the availability and quality of infertility services in developed and developing nations[10]. Furthermore, as seen in all studied countries, infertility services are available only in the capital city or big cities, causing the total expenses for accommodations and travel to increase the cost of treatment. Thus, as with many areas of health care, geographical distance to clinics is an additional barrier to fertility treatment, increasing access inequity[18,19].

The unaffordable IVF can lead to social inequality, since only those who have the financial means to pay for IVF will be able to access it, while others who cannot afford it will not have the same opportunity to conceive a child through this method[33]. This inequality can have wider societal implications, because it can exacerbate existing disparities between socioeconomic groups. For example, if only the rich can access IVF, this may perpetuate existing disparities in health outcomes and access to healthcare between different income brackets. It is essential to address this issue by improving access to IVF for those who need it, regardless of their financial situation, such as through government funding and insurance coverage or advocating for policy changes, in order to promote greater social equality and improve overall reproductive health outcomes.

Factors related to the stakeholder's (GO/NGO) perspective are the fact that infertility is not a high priority in many developing countries, infertility is not the government's health agenda, and public funds are being used for other issues. The issue of infertility in developing countries is often neglected, not only by local governments, but also by the non-profit organizations. Currently, the implementation of infertility treatment is not a primary objective for most of the international non-profit organizations. Infertility programs in developing countries may only be implemented if they are supported by local policy makers, yet the fact is that establishing fertility centers in developing countries is not considered a priority. The strategy is to convince the medical/chemical industry of the value of infertility treatment in developing countries and to gain their support from GOs/NGOs in this area[2,9]. A policy should be based on an extensive cost/benefit analysis with an evaluation of the functioning health care structure regarding infertility. Those parts to be taken by the primary, secondary, and tertiary levels of health services should be carefully described, in order to gain a cost-effective referral system[3].

It is important to understand that governments have limited resources and must prioritize the allocation of those resources based on a variety of factors, including the prevalence and severity of different health issues[25]. Maternal mortality and infectious diseases are certainly important health concerns that require diligent

attention and sustainable allocation of the available resources, but it is also important to advocate for greater government support for infertility treatment and to raise awareness about the importance of addressing infertility as an important public health issue, considering the potentially significant impact of infertility on the society, and community as well as on the individual levels of the couple and their future family life. Increasing awareness about infertility as a public health issue requires a multi-faceted approach involving education and information dissemination, media engagement, support groups and counseling collaboration with healthcare providers, advocacy and policy change, partnership with NGOs and community engagement. By implementing these strategies, it is possible to create a greater understanding of infertility and its implications, reduce stigmas, and promote access to appropriate care and support for individuals and couples facing infertility challenges.

5. Limitations

This study has lack of limited depth of analysis. Scoping reviews primarily aim to map and summarize existing literature, including a wide range of study designs and methodologies. Despite these limitations, it remains valuable for providing an overview of existing studies, identifying research gaps, and informing the development of future research.

6. Conclusions

The high cost of IVF services is the main barrier in seeking infertility treatment that causes delays in joining in IVF programs in developing countries. Infertility is and will continue to be a serious concern in countries with low resources in the near future. Thus, the affordable, acceptable and effective IVF program is needed for infertility treatment.

Conflict of interest statement

There are no conflicts of interest to be declared.

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Authors' contributions

Andriana K Dewi and Anggi L Wicaksana designed study and guided methodology. Andriana K Dewi and Muhammad Lutfi were responsible for searching, selection, data extraction and wrote the first draft. Andriana K Dewi, Anggi L Wicaksana and Agung Dewanto reviewed and discussed the manuscript. All authors approve and are responsible for publication.

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