

Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century

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BACKGROUND: Infertility is estimated to affect as many as 186 million people worldwide. Although male infertility contributes to more than half of all cases of global childlessness, infertility remains a woman's social burden. Unfortunately, areas of the world with the highest rates of infertility are often those with poor access to assisted reproductive techniques (ARTs). In such settings, women may be abandoned to their childless destinies. However, emerging data suggest that making ART accessible and affordable is an important gender intervention. To that end, this article presents an overview of what we know about global infertility, ART and changing gender relations, posing five key questions: (i) why is infertility an ongoing global reproductive health problem? (ii) What are the gender effects of infertility, and are they changing over time? (iii) What do we know about the globalization of ART to resource-poor settings? (iv) How are new global initiatives attempting to improve access to IVF? (v) Finally, what can be done to overcome infertility, help the infertile and enhance low-cost IVF (LCIVF) activism?

METHODS: An exhaustive literature review using MEDLINE, Google Scholar and the keyword search function provided through the Yale University Library (i.e. which scans multiple databases simultaneously) identified 103 peer-reviewed journal articles and 37 monographs, chapters and reports from the years 2000–2014 in the areas of: (i) infertility demography, (ii) ART in low-resource settings, (iii) gender and infertility in low-resource settings and (iv) the rise of LCIVF initiatives. International Federation of Fertility Societies Surveillance reports were particularly helpful in identifying important global trends in IVF clinic distribution between 2002 and 2010. Additionally, a series of articles published by scholars who are tracking global cross-border reproductive care (CBRC) trends, as well as others who are involved in the growing LCIVF movement, were invaluable.

RESULTS: Recent global demographic surveys indicate that infertility remains an ongoing reproductive problem, with six key demographic features. Despite the massive global expansion of ART services over the past decade (2005–2015), ART remains inaccessible in many parts of the world, particularly in sub-Saharan Africa, where IVF clinics are still absent in most countries. For women living in such ART-poor settings, the gender effects of infertility may be devastating. In contrast, in ART-rich regions such as the Middle East, the negative gender effects of infertility are diminishing over time, especially with state subsidization of ART. Furthermore, men are increasingly acknowledging their male infertility and seeking ICSI. Thus, access to ART

may ameliorate gender discrimination, especially in the Global South. To that end, a number of clinician-led, LCIVF initiatives are in development to provide affordable ART, particularly in Africa. Without access to LCIVF, many infertile couples must incur catastrophic expenditures to fund their IVF, or engage in CBRC to seek lower-cost IVF elsewhere.

CONCLUSIONS: Given the present realities, three future directions for research and intervention are suggested: (i) address the preventable causes of infertility, (ii) provide support and alternatives for the infertile and (iii) encourage new LCIVF initiatives to improve availability, affordability and acceptability of ART around the globe.

Key words: infertility / assisted reproductive techniques / demography / low-cost IVF / gender

Introduction

In the second decade of the new millennium, infertility remains a highly prevalent global condition. Infertility is estimated to affect between 8 and 12% of reproductive-aged couples worldwide (Ombelet *et al.*, 2008a, b), with 9% currently cited as the probable global average (Boivin *et al.*, 2007). However, in some regions of the world, the rates of infertility are much higher, reaching ~30% in some populations (Nachtigall, 2006; Ombelet *et al.*, 2008a, b). This is especially true in a number of regions of high infertility prevalence, including South Asia, sub-Saharan Africa, the Middle East and North Africa, Central and Eastern Europe and Central Asia (Mascarenhas *et al.*, 2012b).

IVF—the assisted reproductive technique (ART) initially designed to overcome blocked fallopian tubes—is now more than 35 years old (i.e. the first IVF baby was born in 1978). Yet, IVF remains absent, inaccessible or unaffordable for the majority of the world's infertile couples. The lack of IVF clinics in some countries and the high cost of IVF in many others has inspired clinician-led efforts to bring 'low-cost IVF' (LCIVF) to resource-poor settings. Without access to LCIVF, many infertile couples must incur catastrophic expenditures to fund their IVF cycles, or engage in cross-border reproductive care (CBRC) to seek lower-cost IVF services outside of their home countries.

This article explores five key questions surrounding infertility, ART, LCIVF and CBRC in the 21st century. First, why is infertility an ongoing global reproductive health problem, particularly for women in low-resource settings? Secondly, what are the gender effects of infertility, and are they changing over time? Thirdly, what do we know about the globalization of IVF services, including their mal-distribution and inaccessibility in some parts of the world? Fourthly, how are new clinician-led initiatives attempting to improve access to IVF in resource-poor settings, particularly through the provision of LCIVF? Finally, in a world where 95% of adults express their desire for children (Lampic *et al.*, 2006; Boivin *et al.*, 2007)—including in Western countries such as the USA (Newport and Wilke, 2013)—what can be done to prevent infertility from obstructing this major life goal? This article attempts to answer these five key questions, and to suggest three future directions for infertility and IVF activism.

Methods

An exhaustive literature review using MEDLINE, Google Scholar and the keyword search function provided through the Yale University Library (i.e. which scans multiple databases simultaneously) identified 103 peer-reviewed journal articles and 37 monographs, chapters and reports from the years 2000–2014 in the areas of: (i) infertility demography, (ii) ART in low-resource settings, (iii) gender and infertility in low-recourse settings and

(iv) the rise of LCIVF initiatives. The International Federation of Fertility Societies (IFFSs) Surveillance reports were particularly helpful in identifying important global trends in the ART sector between 2005 and 2010 (Jones *et al.*, 2007, 2010). Similarly, ten world reports on the availability, efficacy and safety of ART conducted between 1995 and 2004, five of them by the International Committee for Monitoring Assisted Reproductive Technology (ICMART) (de Mouzon *et al.*, 2009; Nygren *et al.*, 2011; Sullivan *et al.*, 2013), were consulted. ICMART has also worked with the World Health Organization (WHO) to publish an extensive glossary of ART terminology (Zegers-Hochschild *et al.*, 2009), and to estimate the levels of international CBRC (Nygren *et al.*, 2010). Finally, a series of articles published by Willem Ombelet and other scholars on the growing LCIVF movement were also invaluable (Ombelet *et al.*, 2008a, b; Ombelet, 2009, 2011, 2012, 2013, 2014; Ombelet and van Balen, 2009; Hammarburg and Kirkman, 2013; Van Blerkom *et al.*, 2014).

Infertility demography

Infertility, or the inability to conceive, remains a problem of global proportions. In the second decade of the new millennium, six demographic realities regarding infertility remain salient (Table I). The first demographic reality is that *millions of people around the globe suffer from infertility*. The total worldwide population of infertile people is very difficult to estimate because of: (i) heterogeneity in the criteria used to define infertility (e.g. 1 versus 2 versus 5 years of 'trying'); (ii) the critical differences between estimates of infertility based on large-scale population surveys versus epidemiological studies of infertility and (iii) whether infertility is defined as being located in 'women', 'couples', 'people' or 'individuals' (Gurunath *et al.*, 2011; Mascarenhas *et al.*, 2012a), units of analysis that are often used interchangeably or without precision.

Nonetheless, three demographic surveys published in the new millennium put the infertility figures in the many millions. The first study, which was supported by WHO, utilized data from 47 Demographic and Health Surveys (DHSs), focusing on measures of childlessness, primary and secondary infertility, self-reported infecundity and indications of secondary infecundity among ever-married women of reproductive age (15–49 years) (Rutstein and Shah, 2004). The study showed that in 2002, more than 186 million women in all of the developing countries surveyed (except China) were infertile because of primary or secondary infertility—a number representing more than one-quarter of ever-married women of reproductive age in these countries.

A second study of infertility prevalence and treatment-seeking utilized 25 population surveys from a variety of developed and developing countries dating back to 1990. All of the population surveys had attempted to estimate infertility prevalence and the proportion of couples seeking help (Boivin *et al.*, 2007). Based on a total sample of 172 413 women surveyed over time—and extrapolating from current world population

Table I Global infertility: six demographic realities.

Demographic reality	Related issues
1 Millions of people around the globe suffer from infertility	<ul style="list-style-type: none"> • Difficult to estimate precise numbers • Differing definitions of infertility • Complete absence of information on numbers of infertile men • Three global infertility prevalence surveys published in the new millennium (2004, 2007 and 2012) with differing results (48.5–186 million)
2 Women in many low-resource settings continue to suffer from high rates of secondary infertility	<ul style="list-style-type: none"> • Secondary infertility (the inability to conceive following a prior pregnancy) is the most common form of female infertility • Several regions of high prevalence (sub-Saharan Africa, South Asia, East Asia and the Pacific, Central and Eastern Europe, Central Asia) • Rates declining in sub-Saharan Africa • Rates remain high in Central and Eastern Europe and Central Asia due to unsafe abortion
3 Africa continues to suffer from inordinately high rates of infertility	<ul style="list-style-type: none"> • Ongoing ‘infertility belt’ of primary and secondary infertility across central Africa • High rates of untreated or poorly managed RTIs, including STIs • Most cases of infectious infertility are preventable, representing a regional tragedy
4 High rates of infertility coexist with high rates of fertility in Africa—a demographic paradox known as ‘barrenness amid plenty’	<ul style="list-style-type: none"> • Africa has the world’s highest total fertility rates, even in the midst of high rates of infertility and HIV infection • Adolescent fertility levels are particularly high • Contraceptive prevalence rates remain low, including among women who want to delay or stop childbearing • Desire for children remains strong • Infertility is a form of agony, especially for women, who face suffering and rejection • Infertile women are at increased risk of HIV infection • Infertility represents ‘social death’, and HIV represents physical death for many women
5 Lack of infertility prevention and treatment services is often justified as a form of population control, particularly in high-fertility settings such as sub-Saharan Africa	<ul style="list-style-type: none"> • Infertility is deemed a low-priority issue in the context of scarce health care resources • Infertility may be justified as a natural solution to achieving the ‘demographic dividend’ (accelerated economic growth from declining fertility and smaller dependent populations) • A tacit eugenic view exists that infertile people in developing countries are unworthy of treatment • Overcoming infertility contradicts Western interests in population control • With the exception of the WHO, few international organizations have prioritized or funded infertility efforts • UN’s ‘ICPD Beyond 2014’ does not include infertility care in its Programme of Action on sexual and reproductive health services
6 Those parts of the world with the highest rates of infertility are least likely to offer reliable diagnosis and treatment, including IVF services	<ul style="list-style-type: none"> • Poor access to IVF is a form of global reproductive health disparity • Parts of the world with the greatest unmet need for IVF have the least access to this technology • IVF is designed to overcome blocked fallopian tubes, the major form of female infertility in developing countries • Developing countries have a huge unmet need for IVF • Sub-Saharan Africa has been bypassed in the new millennial race to IVF

STI: sexually transmitted infection, RTI reproductive tract infection, WHO: World Health Organization, UN: United Nations, HIV: human immunodeficiency virus.

estimates—the study predicted that in the year 2007, 72.4 million women were currently infertile, with 40.5 million of them (56%) seeking medical care, at similar rates in both the developed and developing countries.

The most recent study, supported by WHO and the Bill and Melinda Gates Foundation as part of the 2010 Global Burden of Disease Study, provided a global examination of infertility trends based on analysis of 277 reproductive and health surveys available from 190 countries and territories during the period 1990–2010 (Mascarenhas *et al.*, 2012b).

Instead of using WHO’s clinical or epidemiological definitions of infertility (i.e. absence of conception after 1 or 2 years of trying, respectively), this study defined primary infertility as ‘inability to have any live birth’ and secondary infertility as ‘inability to have an additional live birth’. This study used live birth as the outcome measure over a 5-year exposure period, based on stable union status, lack of contraceptive use and desire for a child. Using this demographically based definition of infertility, the study estimated that 48.5 million couples were affected by infertility in 2010—a number that is considerably lower than in previous reports.

According to WHO, reducing the time frame from 5 to 2 years would increase the total number of infertile couples 2.5-fold (to 121 million) (World Health Organization, 2014).

Despite the differing estimates of global infertility prevalence—and the complete absence of information on the total number of infertile men, who contribute to more than half of all cases of childlessness (World Health Organization, 2014)—infertility rates themselves do not appear to have increased significantly over the past two decades (Mascarenhas et al., 2012b). This is partly because global fertility rates have dropped significantly—i.e. fewer people are trying to have children as population growth has slowed (ESHRE Task Force, 2009; Mascarenhas et al., 2012b).

The second important demographic reality is that *women in many low-resource settings continue to suffer from high rates of secondary infertility*. Secondary infertility—or the inability to conceive following a prior pregnancy—is the most common form of female infertility around the globe (Lunenfeld and van Steirteghem, 2004; Rutstein and Shah, 2004; Nachtigall, 2006). Secondary infertility is often due to reproductive tract infections (RTIs), which, if left untreated, damage a woman's fallopian tubes causing irreversible tubal blockages. Secondary infertility is most common in regions of the world with high rates of unsafe abortion and poor maternity care, leading to post-abortive and postpartum infections. In 14 of 23 sub-Saharan African countries surveyed in 2002, the percentage of women with secondary infertility was >25%; eight of these countries had rates higher than 30% (Rutstein and Shah, 2004). Indeed, in Zimbabwe alone, the percentage of women aged 25–49 years with secondary infertility was estimated at 62%, or nearly two-thirds of all reproductive-aged women (Lunenfeld and van Steirteghem, 2004; Rutstein and Shah, 2004; Nachtigall, 2006).

The good news for Africa is that rates of both primary and secondary infertility seem to be decreasing, probably due to overall reductions in unsafe abortions (Sedgh et al., 2012), as well as sexually transmitted infections (STIs), which may be decreasing in response to the human immunodeficiency virus (HIV) epidemic (Mascarenhas et al., 2012b). However, sub-Saharan Africa still remains a global 'hot spot' of secondary infertility, affecting more than 10% of reproductive-aged women overall. Other high-prevalence regions include South Asia, East Asia and the Pacific, Central and Eastern Europe and Central Asia. In the latter two post-Soviet regions, rates of secondary infertility range between 16 and 25%, or one in every 4–6 women, probably due to high rates of unsafe abortions (Mascarenhas et al., 2012b).

The third demographic reality is that despite some encouraging trends, *Africa continues to suffer from inordinately high rates of infertility*. Repeated cross-national surveys have demonstrated the existence of very high infertility prevalence rates in parts of West, Central, and Southern Africa, when compared with relatively lower rates in North and East Africa (Mascarenhas et al., 2012b). Demographers of Africa have described this as Africa's 'infertility belt' (Collet et al., 1988; Ericksen and Brunette, 1996; Larsen, 2000). Very high rates of both primary and secondary infertility are found in the central African countries of Angola, Cameroon, Central African Republic, Equatorial Guinea, Gabon, Liberia, Mozambique and Sierra Leone (Lunenfeld and van Steirteghem, 2004; Nachtigall 2006; Mascarenhas et al., 2012b). High rates of African infertility are largely due to the sequelae of poorly managed or untreated RTIs; >85% of infertile women in sub-Saharan Africa have a diagnosis of infertility attributable to an infection, compared with 33% of women worldwide (Mascarenhas et al., 2012b). It is estimated that ~70% of pelvic infections

are due to STIs, while the rest are due to pregnancy-related sepsis (i.e. postpartum, post-abortion and iatrogenic infections) (Ombelet et al., 2008a). Furthermore, STIs, primarily gonorrhea and chlamydia, can also lead to male infertility, due to obstructions along the seminal tract (i.e. the epididymis or vas deferens, which are needed for sperm transport). Almost half of men in sub-Saharan Africa have a medical history of STIs, a rate that is two to four times higher than the rest of the world (Ombelet et al., 2008a). Although rates of both primary and secondary infertility seem to have diminished in sub-Saharan Africa over the past two decades (Mascarenhas et al., 2012b), the high rates of infertility overall represent a regional tragedy—especially given that most cases are preventable with early detection and appropriate antibiotic treatment of the infections that cause them.

The fourth demographic reality is that *high rates of infertility coexist with high rates of fertility in Africa—a demographic paradox known as 'barrenness amid plenty'* (Inhorn and van Balen, 2002; Nachtigall, 2006). Overall, sub-Saharan Africa has the world's highest total fertility rates, even in the midst of high rates of infertility and life-threatening HIV infections. Because children are greatly desired in high-fertility societies, and because family planning methods are not always widely available, the rates of contraceptive prevalence use remain low in sub-Saharan Africa. For example, WHO data from 2000 to 2008 indicate that nearly one-quarter (24%) of women wanting to delay or stop childbearing were not using a family planning method (World Health Organization, 2010a). Adolescent fertility levels were particularly high in the WHO African Region, at 118 births per 1000 women aged 15–19 years, or about 2.5 times the global average. The shortage of appropriate health services, especially for adolescent African girls, is part of the reason why contraceptives are not always widely available and fertility levels are high, especially in rural areas (World Health Organization, 2010a). Furthermore, fear of side-effects and contraceptive opposition remain strong, even among African women who say they want to avoid pregnancy (Darroch et al., 2011).

However, desire for children also remains strong in most parts of sub-Saharan Africa (Cui, 2010). Numerous anthropological studies have shown the daily suffering—the 'agony of infertility' (Cui, 2010)—among women in African communities where large families are still the social norm (Boerma and Mgalla, 2002; Inhorn and van Balen, 2002; Ombelet and van Balen, 2010; Gerrits et al., 2012). As noted in one review, 'Women who are unable to bear children are rejected by their husbands and ostracized by society, often living as outcasts and perceived as inferior and useless' (Lunenfeld and van Steirteghem, 2004: 321). Furthermore, infertile women in sub-Saharan Africa are at significantly increased risk of HIV infection, because of greater marital instability and the higher likelihood of extramarital sexual partners when a couple is frustrated by the inability to have a child (Favot et al., 1997). Women who are already infected by HIV have diminished fertility in the later stages of infection (Lewis et al., 2004; Lunenfeld and van Steirteghem, 2004). Whereas HIV leads to physical death for many reproductive-aged women in sub-Saharan Africa, infertility leads to a kind of 'social death', which is why access to both kinds of ART (i.e. antiretroviral therapies and ARTs) is so vital (Bochow, 2012; Dhont et al., 2012).

Yet, the fifth demographic reality is that *lack of infertility prevention and treatment services is often justified as a form of population control, particularly in high-fertility settings such as sub-Saharan Africa*. Infertility may be invoked as a 'solution to overpopulation', or, more benevolently, as a 'low-priority issue' in the context of scarce health care resources, poor

medical infrastructure, and the heavy burden of other life-threatening problems such as HIV/AIDS (acquired immune deficiency syndrome), malaria and maternal mortality (Rutstein and Shah, 2004; Mascarenhas et al., 2012b; Allahbadia, 2013). Furthermore, in Africa, high fertility is said to be blocking the 'demographic dividend'—the accelerated economic growth that results from a decline in a country's fertility and the overall size of its dependent population (Gribble and Bremner, 2012). Because sub-Saharan Africa is expected to experience a rapid increase in the size of its 15 to 24-year-old population in the coming decade (the so-called 'youth bulge') (United Nations, 2014), maintenance of high infertility rates (i.e. lack of prevention and treatment) may be justified as a natural solution to achieving the demographic dividend. These kinds of arguments certainly reflect a tacit eugenic view that infertile people in developing countries are unworthy of treatment; thus, overcoming infertility problems, including through provision of ART, may contradict Western interests in population control.

Perhaps this is the major reason why so few international organizations have prioritized or funded infertility efforts. WHO is the exception in this regard. For many years, it has viewed infertility as a major global public health issue, has collected infertility prevalence data and has issued international standards for infertility laboratory testing and diagnosis (World Health Organization, 2010b). However, outside of the WHO, infertility is rarely acknowledged as a key reproductive health priority (Ombelet, 2011). For example, some of the most important philanthropic, non-governmental and international reproductive health organizations do not mention 'infertility care in developing countries' as an issue they support (Ombelet, 2011). This would include, for example, the William J. Clinton Foundation, Compton Foundation, Ford Foundation, Bill and Melinda Gates Foundation, William and Flora Hewlett Foundation, International Planned Parenthood Federation, John D. and Catherine T. MacArthur Foundation, David and Lucile Packard Foundation, West Wind Foundation and the United Nations Population Fund (Ombelet, 2011).

Indeed, it is noteworthy that in the UN's recent initiative, 'ICPD Beyond 2014', infertility care is not included in its Programme of Action (United Nations, 2014). The sexual and reproductive health services that are identified as 'most needed, especially by women and girls, are contraception; maternal health services throughout pregnancy, delivery and postpartum; safe abortion and treatment for the complications of unsafe abortion, including post abortion care; prevention and treatment of sexually transmitted infections and HIV and AIDS; and prevention, timely detection and treatment of cancers of the female reproductive system' (United Nations, 2014: 16). Infertility prevention may be an important side benefit of some of these reproductive health interventions. However, infertility *per se* is not cited as a specific reproductive health concern for women and girls, let alone men, who are largely missing from the ICPD document, except as potential detriments to women's health (Wentzell and Inhorn, 2014).

The sixth and final demographic reality relates to infertility services: namely, *those parts of the world with the highest rates of infertility are least likely to offer reliable diagnosis and treatment, including IVF services*. Poor access to IVF and related ART can be considered a global reproductive health disparity (Jain, 2006; Nachtigall, 2006; King and Davis, 2006). Indeed, parts of the world with the greatest unmet need for IVF are often those with the least access to this technology (Vayena et al. 2002b, 2009; ESHRE Task Force, 2009). To reiterate an important point, IVF was designed to overcome blocked fallopian tubes—the major form of female infertility in many developing countries. Yet,

these are the very nations that are least likely to be served by IVF clinics. This is especially true in sub-Saharan Africa, the vast region of the world that has a huge unmet need for IVF, but seems to have been largely bypassed in the new millennial race to IVF (Jones et al., 2010; Ory and Devroey, 2013).

Globalization of ART

Over the past decade, there has been a significant increase in the number of IVF clinics, and hence the number of ART cycles performed worldwide. The globalization of ART has occurred because of the new-millennial establishment of IVF clinics in many countries, a process that has been followed and charted by the IFFS. Since 1998, the IFFS has undertaken an international surveillance project in an attempt to assess the number of clinics (if any) in each country, the services offered, and the nature of each country's ART legal and regulatory environment (Jones et al., 2010; Ory and Devroey, 2013). The IFFS surveillance project, which has been repeated every 3 years, has provided invaluable information on the inexorable global growth of the IVF sector in some places, but not others.

By the year 2000, IVF services were only available in about *one-quarter of the world's nations*, or 45 of the 191 WHO member states (24%). These were mostly the affluent, Western nations accounting for 91% of the world's gross domestic product (Collins, 2002). By the middle of the decade (2005), that number had expanded to nearly *one-third of the world's nations* (59 of 191, or 31%) (Jones et al., 2007). But by 2010, when the IFFS survey was repeated for a fifth time, there was dramatic news to report. According to the survey team, 'There has . . . been an explosion in IVF in the developing world, with over 500 clinics in India. This globalisation of IVF has also seen a doubling in the number of countries included in the survey. Many developing world countries have only recently introduced IVF and were keen to be involved' (International Federation of Fertility Societies, 2010: 1).

By 2010, *more than half of the world's nations* had developed, or were on the cusp of developing, IVF services (105, or 55%) (Jones et al., 2010). In that year, between 4000 and 4500 IVF clinics were estimated to exist. More than one-quarter of these clinics were located in just two countries, Japan (606–618 clinics) and India (500 clinics). Other nations with large numbers of IVF clinics included the USA (450–480), Italy (360), Spain (177–203), Korea (142), Germany (120–121) and China (102–300), the latter offering the least precise estimate.

Yet, according to the IFFS report, not all of the IVF clinic development by 2010 had occurred in the West or in the 'Asian tiger' nations (Jones et al., 2010). By the mid-2000s, both the Middle East and Latin America had shown remarkable development of their IVF sectors, with widespread regional coverage and the existence of many clinics in some countries (e.g. Argentina, Brazil, Egypt and Turkey). Among the 48 countries performing the most ART cycles per million inhabitants, nine Middle Eastern countries could be counted, with Israel ranking first, ahead of all other world nations, followed by Lebanon (6th), Jordan (8th), Tunisia (25th), Bahrain (28th), Saudi Arabia (31st), Egypt (32nd), Libya (34th) and the United Arab Emirates (UAE) (35th) (Adamson, 2009). Latin American nations were all in the bottom quartile. Nonetheless, as in the Middle East, nine Latin American countries—Argentina (37th), Uruguay (38th), Brazil (40th), Chile (41st), Peru (43rd), Mexico (44th), Ecuador (45th), Dominican Republic

(47th) and Guatemala (48th)—all made the list of the top 48 nations offering the most IVF cycles per capita (Adamson, 2009).

The success of these three regions—Asia, the Middle East, and Latin America—stands in stark contrast to the relative absence of sub-Saharan African nations in the surveillance report. As given in Table II, less than one-third of sub-Saharan African nations hosted an IVF clinic as of 2010 (15 of 48 nations, or 31%) (Jones et al., 2010). Of these 15 nations, seven had just one IVF clinic. Three nations—Ghana (7 clinics), Nigeria (16–20 clinics) and South Africa (12–15 clinics)—could be considered comparative regional success stories. Nigeria led the way in Africa in 1984, and reported its first IVF birth 5 years later in 1989 (Giwa-Osagie, 2007). But the vast majority of African nations had nothing to report to the IFFS surveillance team in 2010. In fact, Congo, Swaziland and Namibia simply reported '0' on the IFFS survey, as given in Table II.

The relative absence of IVF clinics in sub-Saharan Africa in 2010—compared with the relative density of IVF clinics in parts of Asia, the Middle East and Latin America—is graphically depicted in Figs 1 and 2. Figure 1 shows the number of IVF clinics per capita in these four world regions. Figure 2 represents the number of IVF clinics per 100 000 infertile women, using estimates of both primary and secondary infertility (Mascarenhas et al., 2012b). What is especially clear from these regional maps is that sub-Saharan Africa—with its high infertility estimates—is relatively deprived of IVF clinics, especially when compared with the IVF-saturated region of the Middle East and North Africa, just to the north. These dramatic inequalities in regional IVF clinic development have been described by a European Society for Human Reproduction and Embryology (ESHRE) Task Force as 'islands of high-tech infertility treatment

in a sea of generalized poverty and medical neglect', a situation they deem 'highly inappropriate' (ESHRE Task Force, 2009: 1010). In a similar vein, James Ferguson, one of the leading anthropologists of sub-Saharan Africa, laments that 'modern social and medical services, where they exist at all, are more likely to be provided by transnational non-governmental organizations (NGOs) than by states—and this at a time that the AIDS epidemic is creating unprecedented need for such services' (Ferguson, 2006: 13).

Although this tale of African absences is unacceptable given the high unmet need, Africa is by no means the only 'global shadow' (Ferguson, 2006) on the uneven world map of IVF clinic development. Several other regions of the world were missing altogether in the 2010 IFFS surveillance report. For example, none of the large Central Asian countries of Afghanistan, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, and Uzbekistan were included in the report (although Kazakhstan was said to host one IVF clinic in 2002, and a dozen by 2013) (Collins, 2002; Ory and Devroey, 2013; Ory et al., 2014). The absence of IVF in most of Central Asia is especially troubling, given that it has the world's highest rates of secondary infertility—probably due to unsafe abortions in this mostly resource-poor, post-socialist region of the world (Mascarenhas et al., 2012b).

Even within 'successful' regions, such as the Middle East, marked disparities could be detected as a result of political isolation and violence. To take two salient examples, Iraq and Syria were both in an inchoate stage of IVF development when wars broke out in 2003 and 2011, respectively (Inhorn, 2012a). Infertile Iraqis were said to be traveling in large numbers to neighboring Iran, as only one IVF clinic existed in the city of Erbil,

Table II IVF: a regional comparison.

Sub-Saharan Africa	No. of clinics	Asia	No. of clinics	Latin America	No. of clinics	Middle East and North Africa	No. of clinics
Burkina Faso	1	Bangladesh	10	Argentina	22–25	Algeria	7
Cameroon	2	China	102–300	Brazil	150	Egypt	52–55
Congo	0	Hong Kong	7	Chile	8–9	Iran	40
Democratic Republic of Congo	1	India	500	Colombia	19–21	Israel	24–30
Ethiopia	1	Indonesia	12	Cuba	1	Jordan	19
Ghana	7	Japan	606–618	Dominican Republic	4	Kuwait	12
Ivory Coast	3	Malaysia	26	Ecuador	6–8	Lebanon	20
Kenya	4	Nepal	3	El Salvador	1–4	Libya	9–10
Mali	1	Pakistan	10	Mexico	Uncertain	Morocco	18
Namibia	0	Philippines	4	Panama	7	Saudi Arabia	24–40
Nigeria	16–20	Singapore	9	Paraguay	1–3	Tunisia	8
Senegal	2	Sri Lanka	5	Peru	5–7	Turkey	112–116
South Africa	12–15	Taiwan	72–78	Trinidad and Tobago	1–2	United Arab Emirates	10
Sudan	4	Thailand	35	Uruguay	4		
Swaziland	0	Vietnam	11–12	Venezuela	17–18		
Togo	1						
Uganda	1						
Zimbabwe	1						

Adapted from Jones et al. (2010), 'International Federation of Fertility Societies: Surveillance 2010'.

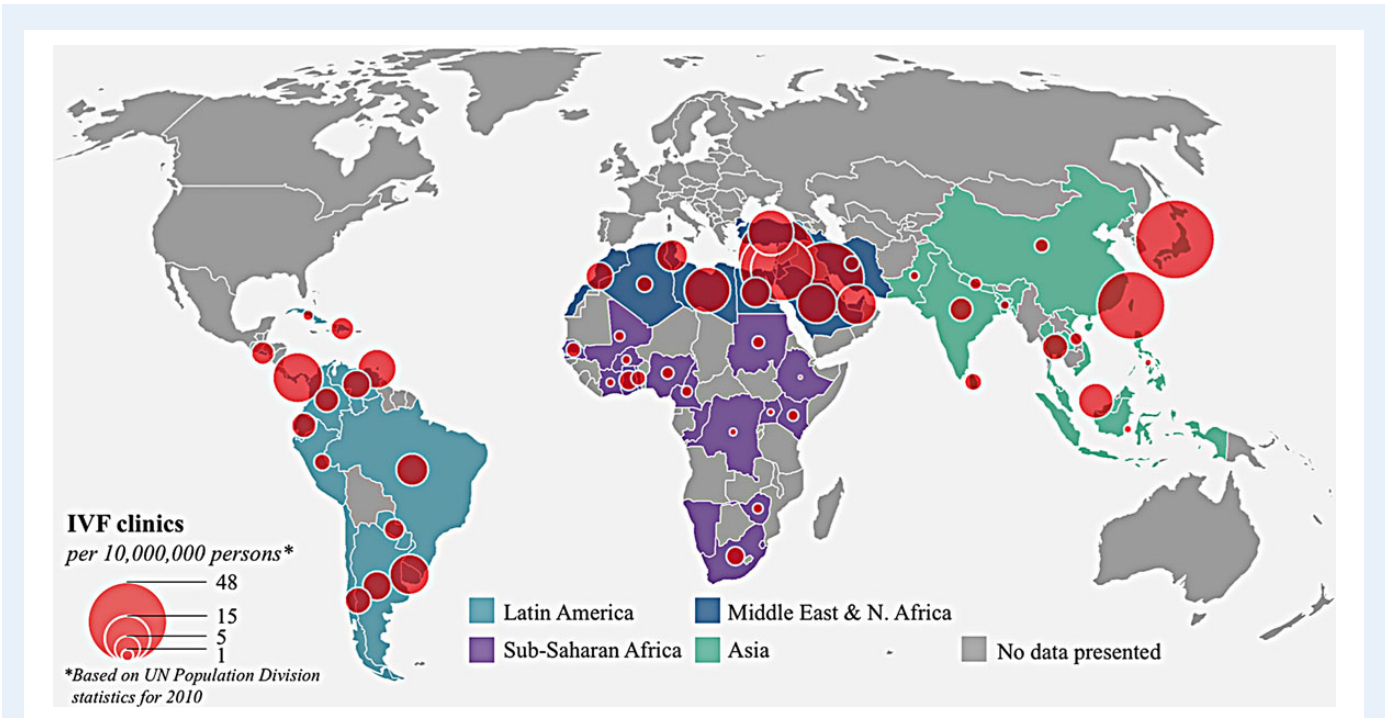


Figure 1 Comparative regional distribution of IVF clinics per capita.

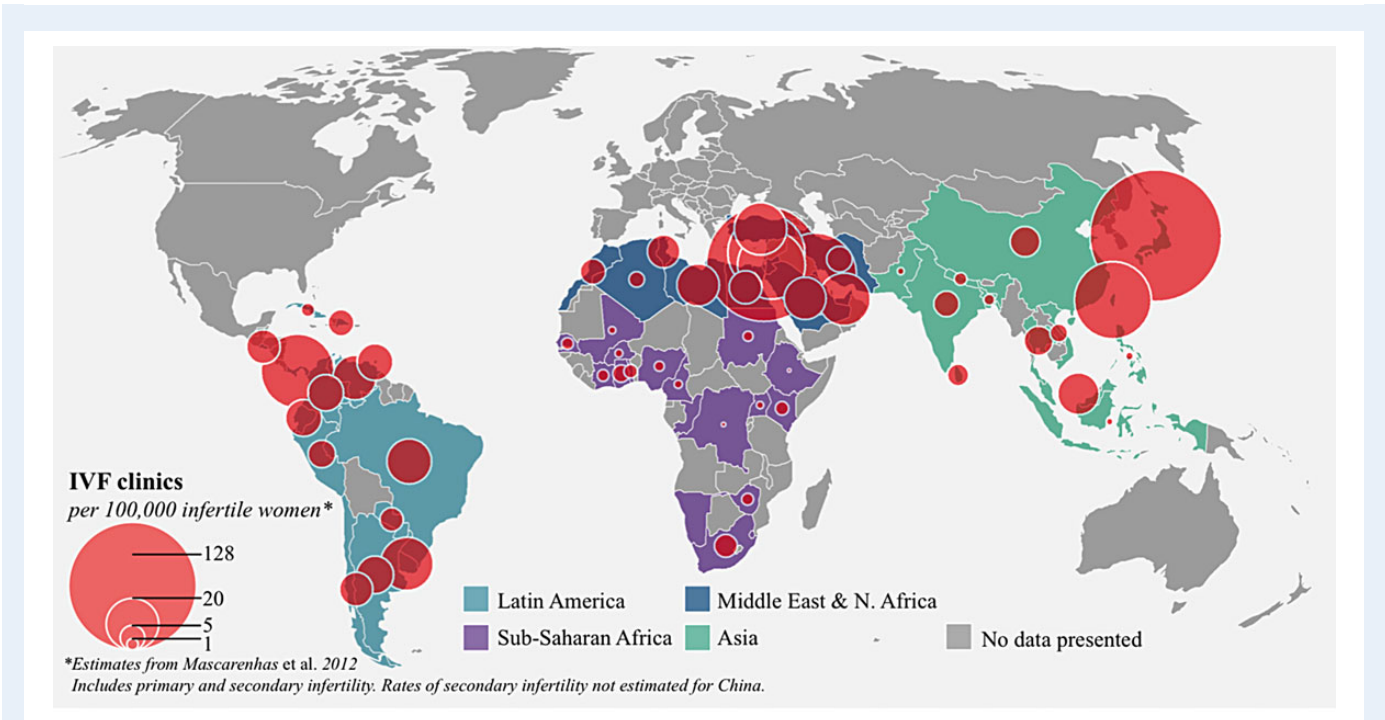


Figure 2 Comparative regional distribution of IVF clinics per estimated numbers of infertile women.

located in Iraqi Kurdistan. Similarly, infertile Syrians were crossing the borders into neighboring Lebanon or Jordan (Inhorn, 2012a). Within the Arab Gulf, IVF disparities could be detected between more central, resource-rich versus peripheral, resource-poor nations

(Inhorn, 2012b, 2015). For example, Saudi Arabia was one of the first three countries (along with Egypt and Jordan) to open an IVF clinic in 1986 (Inhorn, 2003a). Yet, Saudi Arabia's southern neighbors, Oman and Yemen, were more than two decades behind. Although both had

opened at least one IVF center by the early 2000s, neither was reported on the IFFS list of nations as of 2010 (Jones *et al.*, 2010).

South Asia—the region of the world that now outstrips sub-Saharan Africa in terms of absolute numbers of infertility cases (14.4 versus 10 million, respectively) (Mascarenhas *et al.*, 2012b)—also showed pronounced regional disparities in IVF clinic development. Whereas India had become the new millennium's emblem of IVF globalization—boasting ~500 IVF clinics and a growing industry of commercial gestational surrogacy (Pande, 2010, 2011; Rudrappa, 2010, 2012)—the neighboring South Asian states of Bangladesh and Pakistan, with populations of 161 million and 179 million, respectively, had opened only 10 clinics each by 2010 (Jones *et al.*, 2010). These two countries, therefore, were meeting < 1% of their citizens' projected needs for IVF services.

Sadly, both Bangladesh and Pakistan slipped off the list—along with 43 other nations—in the more recent 2013 IFFS surveillance report (Ory and Devroey, 2013). A new surveillance team and transition to a web-based survey method meant that many nations—including those with less information technology infrastructure—were lost to the follow-up in the IFFS surveillance project. For example, only 7 of the 18 sub-Saharan Africa countries that had reported in 2010 were included in the 2013 surveillance report. Furthermore, these seven nations (i.e. Cameroon, Democratic Republic of Congo, Ivory Coast, Senegal, South Africa, Togo and Uganda) showed zero growth in their IVF sectors between 2010 and 2013. In fact, Ivory Coast reported the loss of one IVF clinic (out of three), while Ghana and Nigeria, both IVF leaders in sub-Saharan Africa, were 'lost to follow-up' in the 2013 surveillance. Overall, only 60 nations reported in 2013, as opposed to 105 in 2010 (Ory *et al.*, 2014). Thus, the actual number of IVF clinics around the globe—and the ongoing IVF absences in many resource-poor regions of the world—is even more obscure than before.

As suggested by the cases of Bangladesh, Pakistan and sub-Saharan Africa overall, there remains a high 'unmet demand' for IVF services around the globe (Connolly *et al.*, 2010). At the beginning of the new millennium, an ESHRE workgroup estimated that 1500 couples per million population required ART treatment annually (ESHRE Capri Workshop Group, 2001). Indeed, 1500 cycles per annum was considered a conservative estimate, given that many couples may need to undergo more than one ART cycle in a given year (Collins, 2002). Furthermore, only half of couples in both the developed and developing nations are able to seek any medical assistance for their infertility problems (Boivin *et al.*, 2007). In the end, only about one-quarter of infertile couples (22%) actually obtain help (Boivin *et al.*, 2007). This is true even within more developed countries. With the exceptions of Australia, Israel and the Scandinavian countries, few developed nations have met the ESHRE benchmark of 1500 cycles per million population per annum (Collins, 2002; Connolly *et al.*, 2010). For example, only 25 and 40% of the optimal number of ART cycles were being carried out in North America and the UK, respectively, as of 2009 (Chambers *et al.*, 2009; Connolly *et al.*, 2010).

ART and changing gender relations

Clearly, there is still a huge unmet need for ART around the globe—from the least to the most developed nations. For many infertile women, the absence of IVF access may have significant social consequences,

particularly in the realm of marriage, as shown by many studies in a variety of resource-poor settings (Inhorn, 1996; Feldman-Savelsberg, 1999, 2002; Boerma and Mgalla, 2002; Cui, 2010). According to a 47-country DHS survey, women who are married but have never born a child with their husbands are much more likely to be divorced or separated—at a rate of 14% overall (Rutstein and Shah, 2004). These effects are much more pronounced in Latin America, where 21% of childless women (one-fifth) are likely to be divorced or separated. In two Latin American countries, Nicaragua and Dominican Republic, more than 40% of all childless women are divorced or separated. Overall, childless women who are divorced are 13% more likely to have married more than once than women with children. Furthermore, in societies where polygyny is allowed, men may prefer to take a second wife instead of divorcing or separating. For example, in Kenya, Jordan, Nepal and Yemen, men whose first wives are childless are 20, 19, 19 and 15% more likely to have a second wife, respectively.

In addition, childless women are more likely to be the victims of domestic violence, and may also endure various forms of verbal and emotional abuse perpetrated by their husbands and husbands' family members (Inhorn, 1996; Nachtigall, 2006; Nahar 2010, 2012; Nahar and Richters, 2011). Infertile women who are abandoned by their husbands may be forced to turn to prostitution as a form of economic survival. In this context, then, infertility may be both impoverishing and life threatening, when it places a woman at a significantly higher risk of both violence and STIs including HIV/AIDS (Lunenfeld and van Steirteghem, 2004).

Paradoxically, women are often blamed for infertility, even when it is their husbands who are the infertile partners (Inhorn, 1996, 2002, 2003a, b; Cui, 2010; Hoerbst, 2010; Wischmann and Thorn, 2013). Male infertility remains a 'hidden' reproductive health condition, even though it contributes to more than half of all cases of childlessness worldwide (Irvine, 1998). Due to the genetic aetiology of many cases, male infertility is often impossible to prevent and difficult to treat, lasting over the course of a man's lifetime, even if he attempts to have children by changing partners (Devroey *et al.*, 1998; Irvine, 1998; Kamischke and Nieschlag, 1998; Maduro and Lamb, 2002; Maduro *et al.*, 2003; Inhorn, 2012a, b, c). In the other words, male infertility is a chronic reproductive health condition for millions of men worldwide, even though it is rarely recognized as such. As a result, women with infertile husbands are often mistakenly blamed for the childlessness. Sometimes, they also 'protect' their infertile husbands by claiming the infertility problem as their own (Inhorn, 1996, 2003a, b, 2012a).

Having said this, the gender and marital effects of infertility are not necessarily straightforward, with husbands automatically blaming their wives and divorcing them in the absence of a pregnancy. Indeed, the gender relations surrounding infertility appear to have changed significantly over time, as diagnostic semen analysis techniques and ART spread around the globe (Inhorn and Birenbaum-Carmeli, 2008). In many developing countries, the introduction of ART has created new hope for infertile couples, encouraging them to remain together. Overall, access to ART appears to be changing gender relations in several positive ways through: (i) increased knowledge of both male and female infertility among the general population; (ii) normalization of both male and female infertility problems as medical conditions that can be overcome; (iii) decreased stigma, blame and social suffering for both men and women; (iv) increased marital commitment as husbands and wives seek ART services together and (v) increased male adoption

of ART, especially for male infertility problems. In the other words, the coming of ART to previously ART-poor settings can lead to major, positive impacts on marriage and on gender relations more generally (Inhorn 2004, 2012a).

As infertile couples remain together in their search for ART, demand for these services also grows, potentially fueling the regional development of the IVF sector. Nowhere is this more apparent than in the Middle East, a region that has witnessed a veritable proliferation of ART services over the past three decades (Inhorn and Tremayne, 2012). In 1980, the first authoritative *fatwa* permitting assisted reproduction was issued by the Grand Shaykh of Al Azhar, one of the world's oldest and most important Islamic universities in Cairo (Serour, 1996, 2008; Inhorn, 2003a). By 1986, IVF clinics had opened in Egypt, Jordan and Saudi Arabia. By 1996, the Middle East was in the midst of an IVF 'boom period', with multiple clinics opening in major cities from Casablanca to Cairo to Tehran (Inhorn, 2003a). Today, the Middle East boasts of one of the strongest ART industries in the world, with more than 110 IVF clinics in Turkey, more than 70 in Iran, more than 50 in Egypt and more than a dozen clinics in many smaller countries, such as Lebanon and the UAE (Inhorn, 2012a, 2015; Tremayne and Inhorn, 2012).

Considerable anthropological research emerging over the past two decades from the Middle Eastern countries of Egypt (Inhorn 1994, 1996, 2003a), Iran (Tremayne, 2006, 2009, 2012; Abbasi-Shavazi et al., 2008), Lebanon (Clarke, 2006, 2009; Inhorn 2006, 2012a), Turkey (Gürtin, 2012, 2013) and the UAE (Inhorn, 2015) suggests that the presence of ART has had a major salutary effect on infertile marriages. Because marriage is a highly valued Islamic precept, Middle Eastern Muslims are among the 'most married' people in the world, with well over 90% of adults marrying at least once in a lifetime and divorcing at rates much lower than in the West (Omran and Roudi, 1993; Parker-Pope, 2010). Marriage is also a major source of intergenerational wealth transfer in the Middle East (Singerman and Ibrahim, 2004); thus, with both economic and religious incentives to stay together, couples often work hard to maintain their marriages, even under the threat of infertility and childlessness. 'Conjugal connectivity', or the deeply felt marital commitments of many infertile couples, has been demonstrated across the region, from Egypt (Inhorn, 1996, 2003a) to Lebanon (Inhorn, 2012a) to Turkey (Gürtin, 2013). Thus, the coming of ART to the Middle Eastern region has been a major marital asset, promoting conjugal connectivity through couples' hopes of making a 'test-tube baby' together (Inhorn, 2003a; Gürtin, 2014). Perhaps most significantly, the widespread emergence of ICSI as the solution for the region's highly prevalent male infertility problems has facilitated the development of 'emergent masculinities' (Inhorn and Wentzell, 2011; Inhorn, 2012a). Namely, as ICSI becomes normalized, Arab men are beginning to openly challenge the victim-blaming of women within childless marriages. In general, the emergence of ART has been a positive force in men's more general attempts to overturn patriarchy, challenge negative male stereotypes, and nurture companionate marriages characterized by love, commitment and fortitude in the face of adversity (Inhorn, 2012a).

These positive effects on gender can be seen most clearly in the Middle Eastern nation-states that have made ART most accessible. This includes Algeria, Egypt, Iran, Turkey and the UAE, all of which offer some form of public financing, either through insurance reimbursement (Algeria and Turkey), or government-sponsored IVF clinics for the poor (Egypt, Iran and UAE) (Inhorn, 2015). However, Turkey is exceptional in its

commitment to ART state subsidization (Gürtin, 2013). In 2005, Turkey began fully funding two IVF cycles for all Turkish citizens, when the Turkish Ministry of Health began to provide IVF health insurance redeemable at both state and private clinics. Since then, the demand for IVF in Turkey has dramatically increased, causing a doubling in the number of IVF clinics in the country—from 66 in 2005 to more than 110 in 2013, the largest number in any single Middle Eastern country. As shown by medical sociologist Zeynep Gürtin (2013, 2014), the ability of Turkish couples of all social classes and backgrounds to access IVF and ICSI has had dramatic and positive effects on demand for ART services, especially among poorer segments of the Turkish population. IVF and ICSI are becoming normalized among Turks, especially Turkish men, who are remaining in their childless marriages as they seek ART solutions with their wives (Gürtin, 2014). The Turkish example provides compelling evidence that low-income infertile couples benefit tremendously when ART services are provided for free or at very low cost. In the Middle East at least, Turkey has made a national commitment to overcome its unmet need for ART, providing affordable IVF for all.

The LCIVF movement

As of 2015, however, relatively few countries have followed the Turkish lead, which is why an alternative social movement, called the LCIVF movement, is gaining momentum. LCIVF represents a new millennial activist attempt to respond to the Universal Declaration of Human Rights mandate (Article 16:1), which states that 'Men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and found a family' (United Nations, 1948). LCIVF is thus a reproductive justice movement, driven by the goal of helping the world's infertile, most of whom are located in resource-poor settings (Ombelet et al., 2008a, b; Hammarberg and Kirkman, 2013).

As given in Table III, the LCIVF movement has been more than a decade in the making, and has involved many prominent IVF practitioner-scholars (Vayena et al., 2002b, 2009; Lunenfeld and van Steirteghem, 2004; Dhont, 2011). In Europe, ESHRE has supported the LCIVF movement, which is being headed in Europe by Willem Ombelet of the Genk Institute for Fertility Technology in Belgium (Ombelet et al., 2008a, b; Ombelet, 2009, 2011, 2013, 2014; Ombelet and van Balen, 2009). As the co-ordinator of the ESHRE Special Task Force on Developing Countries and Infertility (ESHRE, 2008, 2013; Gerrits et al., 2012), Ombelet has led the ESHRE efforts to prioritize infertility as a global reproductive health problem, and to innovate solutions through LCIVF.

Ombelet's non-profit organization, 'The Walking Egg (WE)', has invented an LCIVF method that was first announced at the ESHRE annual meeting in London in July 2013. There, ESHRE issued a press release announcing, 'IVF for 200 euro per cycle: first real-life proof of principle that IVF is feasible and effective for developing countries' (ESHRE, 2013). Ombelet explained to reporters at the conference that the technique appears to be as effective as conventional IVF, and that 12 healthy LCIVF babies had already been born (Gallagher, 2013).

The new LCIVF technique essentially bypasses the need for a costly IVF laboratory, by simplifying embryo culture methods and eliminating high-end equipment. The 'WE lab IVF culture system developed by The Walking Egg is a low-cost embryo culture system, 'designed for simple assembly and to fit within a container for transport' (Ombelet, 2014, p. 271). According to Van Blerkom et al. (2014), the designer of the low-cost culture system, the 'WE lab IVF culture system is designed

to 'fit in a shirt pocket', and go anywhere, including 'off the grid'. The system uses low-cost components, does not require complex microprocessor-controlled incubators, and is a closed system that uses inexpensive, common chemicals. Following field-testing in several sites in Europe and North America, the intent is to field-test the ³WE lab IVF culture system in a variety of sub-Saharan African settings (Ombelet, 2014; Van Blerkom *et al.*, 2014).

Before the new LCIVF method can be fully implemented, it must be replicated in different laboratories and under field conditions; assessed for long-term safety issues and hidden costs and involve the training of experienced embryologists in low-resource settings, who might otherwise fail to embrace LCIVF for fear 'that some of their skills may become largely redundant' (Johnson, Cohen, and Grudzinskas, 2014, p. 266). Furthermore, LCIVF cannot mitigate the high costs of ICSI—the variant of IVF designed to overcome male infertility. As yet, ICSI laboratory techniques cannot be replicated in a low-cost format. Thus, the new LCIVF culture method must be viewed as a kind of half-measure, applicable only to cases requiring conventional IVF methods.

Given these cautions and concerns, other LCIVF strategies and initiatives are taking hold. A North American-based non-profit organization called 'Friends of Low-cost IVF' (FLCIVF) (www.friendsofivf.org) was created in 2011 by Prof. Alan Trounson, emeritus professor at Monash University in Melbourne, Australia, Karin Hammarberg and a number of North American colleagues. Since 2011, FLCIVF has conducted annual meetings and a postgraduate course (2013) through the American Society for Reproductive Medicine (ASRM). FLCIVF raises funds through private donations from individuals and charities interested in the LCIVF cause, and works with IVF clinics willing to donate their services pro bono. The two main aims of FLCIVF are: (i) to provide simplified clinical IVF services for a minimal cost to reduce the burden of childlessness; and (ii) to deliver reproductive health education to prevent infertility and avoid transmission of HIV and other STIs.

The founders of FLCIVF have devised a simplified ovarian stimulation protocol without the use of injectable gonadotrophins, intended to be implemented with simplified IVF equipment. Together with other volunteers, they train local professionals, oversee the implementation of and adherence to the simplified treatment protocols, and monitor the protocols' success in terms of live birth rates per treatment cycles. Adoption of FLCIVF programmes can serve to widen access to infertility care, and the milder stimulation protocols can reduce treatment invasiveness and complications for women. The first successful pilot initiative of social solidarity supported by FLCIVF was started in Monterrey, Mexico in 2012. It is still actively functioning by offering IVF to low-income patients without the use of injectable gonadotrophins. As of 2015, FLCIVF programmes are being implemented at 'no-cost-to-patient' clinics in Sudan and Tanzania. Sites for future programmes are being explored in South Africa, Nigeria, Tunisia, Burkina Faso, Ethiopia and Uganda. Low-resource populations in the USA and in other developed Latin American countries are also under consideration, given that the suffering of low-income infertile patients often goes unnoticed in those nations. (In fact, obvious disparities in IVF access commonly provoke reactions of disbelief and discomfort among health care providers in the Americas, as shown in several qualitative studies) (Becker *et al.*, 2006; Teramoto and Kato, 2007).

In general, the new global LCIVF movement is part of a reproductive justice mission being supported by many prominent IVF clinicians and organizations. For example, the ESHRE Task Force on Ethics and Law

has argued explicitly that 'Low-cost IVF will make treatment more accessible and thus reduce injustice. The fact that it is very unlikely to be within everyone's reach is no valid argument for not offering it at all' (ESHRE Task Force, 2009: 1009). In addition to investments in LCIVF, the ESHRE Task Force has made a number of other important recommendations for providing infertility treatment in resource-poor countries. These include: (i) increasing attention to infertility prevention, partly through national investments in reproductive health and sex education; (ii) research to improve the cost-effectiveness of infertility diagnosis and treatment, with technologies adapted to local conditions; (iii) modified ovarian stimulation protocols, using simplified and mild stimulation procedures or controlled natural cycles, to reduce the risks of ovarian hyperstimulation syndrome; (iv) single-embryo transfer to reduce multiple pregnancies; (v) efforts by international organizations to fund research and organize infertility diagnosis and treatment training courses in low-resource settings and (vi) support to governments to regulate ART practice by licensing providers, monitoring clinical activities and verifying success rates of low-cost approaches (ESHRE Task Force, 2009). In addition, major efforts to improve diagnosis and management of infertility through evidence-based methods are also underway in Europe (Ombelet *et al.*, 2008a; Devroey *et al.*, 2009). The ultimate goal is to optimize the efficacy and safety of infertility diagnosis and treatment with ART, primarily through promoting the uptake of single-embryo transfer in all IVF facilities around the globe (Devroey *et al.*, 2009).

Catastrophic expenditure and CBRC

These various LCIVF initiatives hold out great promise for the world's infertile couples. Yet, the techniques and strategies of LCIVF are still in the formative stages. In the absence of LCIVF, a huge unmet need for IVF exists in both the developed and developing countries. To reiterate an earlier point, only about half of all infertile couples in either developed (56%) or developing countries (51%) seek any form of infertility care (Boivin *et al.*, 2007), presumably because services are either limited, unavailable, or too expensive. Furthermore, because of the high cost of IVF, few governments have been able or willing to subsidize ART cycles within their national health insurance schemes, meaning that IVF exists primarily within the private medical sector (Collins, 2002; Spar, 2006; Jones *et al.*, 2010). Problems of accessibility, cost, and rationing of IVF services in some health care systems create 'an almost insurmountable obstacle to adequate reproductive health care' for many infertile couples around the world (Lunenfeld and van Steirteghem, 2004, p. 321).

The term 'financial access' has been used to describe the problem of IVF affordability (Connolly *et al.*, 2010). As noted by a prominent group of health economists, 'ability to pay for treatment... plays a critical role in overall access to fertility treatment,' and 'choice to pursue expensive treatments, such as ART, [is] highly influenced by income' (Connolly *et al.*, 2010: 607). According to John A. Collins, who has undertaken the most extensive international survey of the health economics of IVF, 'IVF and ICSI treatments are costly technologies that involve several professions and expensive laboratory facilities. The direct costs of a cycle of IVF treatment arise from the medical consultation and visits, drugs, laboratory charges (general, hormone and embryology), ultrasound procedures, IVF procedures (oocyte retrieval and embryo transfer),

Table III Low-cost IVF: a brief history.

Date	Event
1948	UN's Universal Declaration of Human Rights, Article 16:1, states: 'Men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and found a family'
1994	UN International Conference on Population and Development in Cairo calls for 'sexual and reproductive health for all by the year 2015'
2001	WHO meeting on 'Medical, Ethical and Social Aspects of Assisted Reproduction' in Geneva recommends that 'Infertility should be recognized as a Public Health issue worldwide, including in developing countries', and that 'Research is needed on innovative, low-cost ART procedures that provide safe, effective, acceptable and affordable treatment for infertility' (Ombelet et al., 2008a)
2002	WHO publishes <i>Current Practices and Controversies in Assisted Reproduction: Report of a Meeting</i> (Vayena et al., 2002a)
2002	IVF activist-scholars publish an article, 'Assisted Reproductive Technology in Developing Countries: Why Should We Care?' in the major North American IVF journal, <i>Fertility and Sterility</i> (Vayena et al., 2002b)
2002	Bertarelli Foundation holds its second global conference in Prague to discuss 'Infertility in the Third Millennium'; an overview article is published in <i>Human Reproduction Update</i> (Lunenfeld and van Steirteghem, 2004)
2004	World Health Assembly adopts the first global strategy on reproductive health entailing five core components; one of these is 'providing high-quality services for family planning, including infertility services' (Vayena et al., 2009)
2005	National Institutes of Health hold a scientific workshop on 'Health Disparities in Infertility' in Bethesda, Maryland, to encourage 'improved strategies for the prevention and treatment of infertility in different racial, ethnic, and socioeconomic status populations'; the workshop is followed by publication of a special issue of <i>Fertility and Sterility</i> (King and Davis, 2006)
2006	ESHRE establishes a Special Task Force on Infertility and Developing Countries, chaired by Willem Ombelet of the Genk Institute for Fertility Technology in Belgium
2007	Meeting of 37 experts on 'Developing Countries and Infertility' is held in Arusha, Tanzania, followed by a special issue in the major European IVF journal, <i>Human Reproduction</i> (Ombelet et al., 2008b); the 'Arusha Project' is borne 'to implement accessible infertility programmes in resource-poor countries'
2007	Nonprofit organization called the Low-cost IVF Foundation is formed by a group of international IVF practitioners, with the mandate to 'encourage the support of low-cost ART options' and the goal of demonstrating that 'material costs for a cycle of IVF can be less than 200 euros' (Vayena et al., 2009)
2007	International Society for Mild Approaches in Assisted Reproduction is established and registered as a charity in Great Britain to encourage the development and use of simpler, more cost-effective IVF protocols (Vayena et al., 2009)
2008	ESHRE holds a pre-congress course on 'Developing Countries and Infertility' during the 2008 annual ESHRE meeting in Barcelona, followed by publication of an ESHRE monograph (ESHRE, 2008)
2009	ESHRE holds an expert meeting on 'Social Aspects of Accessible Infertility Care in Developing Countries' in Genk, Belgium, organized by the ESHRE Special Task Force on Developing Countries and Infertility and the Genk Institute for Fertility Technology; this is followed by publication of a special monograph of <i>Facts, Views and Vision in ObGyn</i> (Ombelet and van Balen, 2009)
2009	IVF activist-scholars publish an article, 'Assisted Reproductive Technology in Developing Countries: Are We Caring Yet?' as a follow-up to their 2002 publication in <i>Fertility and Sterility</i> (Vayena et al., 2009)
2010	NGO called 'The Walking Egg' is founded by Willem Ombelet to realize the goals of the Arusha Project (Dhont, 2011)
2011	ESHRE Special Task Force holds a workshop on 'Biomedical Infertility Care in Poor Resource Countries: Barriers, Access and Ethics' in Genk, Belgium, in cooperation with The Walking Egg, the University of Amsterdam, and the WHO; the workshop is followed by publication of a special monograph of <i>Facts, Views and Vision in ObGyn</i> (Gerrits et al., 2012)
2011	Friends of low-cost IVF (FLCIVF), a non-profit organization, is created in North America by Alan Trounson and Karin Hammarberg to remedy infertility and empower women globally; FLCIVF raises funds and works with IVF clinics willing to donate their services pro bono, with the two main aims of: (i) providing simplified clinical IVF services for a minimal cost; and (ii) delivering reproductive health education to prevent infertility and avoid transmission of HIV and other STIs
2012	Study begins in Genk, Belgium, on a new method of LCIVF, which eliminates expensive IVF laboratory procedures; with a 30% success rate, 12 LCIVF babies are born in Belgium; the technique has yet to be field-tested in resource-poor countries
2013	Development of LCIVF, costing less than 200 euros (i.e. \$253, or LE 170), is announced at the ESHRE annual meeting in London on July 8 (ESHRE, 2013)
2014	<i>Reproductive BioMedicine Online</i> devotes an editorial, an 'important paper' by Van Blerkom et al. (2014), and a commentary to the subject of LCIVF; the editors of the journal are cautiously supportive of LCIVF, entitling their editorial, 'Accessible and affordable IVF: is Bob Edwards' dream about to become reality?' (Johnson, Cohen, and Grudzinskas, 2014)

ESHRE: European Society for Human Reproduction and Embryology, NGO: non-governmental organization.

hospital charges, nurse co-ordinator costs, administrative charges and fees for anaesthesia. Indirect costs include lost time from employment and travel costs, which are difficult to estimate' (Collins, 2002: 267).

Factoring in just the direct costs, Collins attempted to estimate the average price of an IVF cycle in 26 countries. Using data from 2002, he found that the USA was by far the most expensive country in the world in which to undertake IVF—at \$9547 for a single cycle of IVF

and \$11 818 for ICSI. Outside of the USA, the average cost of a single IVF cycle was much lower—only \$3518, or about one-third of the American cost. However, IVF prices varied quite widely around the globe, from a low of \$1272 in Iran and Pakistan to a high of \$6361 in Hong Kong (Collins, 2002: 267). In most of these countries, the cost of a single cycle was more than half of an average individual's annual income. Thus, as noted by Robert Nachtigall in his review of international

disparities in access to infertility services, 'relatively few of the world's infertile men and women can be said to have complete and equitable access to the complete range of infertility treatments at affordable levels' (Nachtigall, 2006: 871).

In order to pay for high-cost IVF treatments, many infertile couples, especially those living in resource-poor settings, engage in a form of financial sacrifice that health economists call 'catastrophic expenditure'. Catastrophic expenditure is defined as any out-of-pocket payment that threatens household survival by exceeding 40% of annual non-food expenditures (Dyer and Patel, 2012). In general, infertile couples and particularly infertile women from resource-poor countries are at high risk of catastrophic expenditure (Dyer and Patel, 2012). To take but one example, a study in South Africa by IVF physician-activist Dyer *et al.* (2013) found that 22% of infertile couples attending a public-sector IVF clinic had incurred catastrophic expenditures. In order to cope with these IVF expenses, South African couples had reduced their expenditures on basic items such as food and clothing, depleted their savings, borrowed money and taken on extra work. The poorest of the poor were the most likely to incur catastrophic expenditure, as were couples who had been infertile for longer periods of time. Extrapolating from these South African data, Dyer *et al.* (2013) argued that 'the absence of financial risk protection for ART creates similarly significant financial burdens for households in other low-resource settings'.

Catastrophic expenditure is more likely to occur among the infertile poor—many of whom can ill afford the cost of a single ART cycle, let alone the additional cycles that may be necessary to achieve an ART pregnancy and live birth. However, catastrophic expenditure may affect even middle-class professional couples, who may be hard-pressed to pay for IVF services in their home countries (Spar, 2006; Inhorn, 2015). The high cost of IVF has been deemed one of the most important factors fueling 'CBRC', or the movement of mostly middle-to-upper-class infertile couples across regional, national and international borders. Scholars who have studied CBRC point to four broad sets of factors—resource constraints, legal and religious prohibitions, quality and safety concerns and socio-cultural barriers—which are motivating the movements of infertile couples across borders (Penning, 2002, 2004, 2006, 2009, 2010; Deech, 2003; Blyth and Farrand, 2005; Pennings *et al.*, 2008, 2009; Inhorn and Patrizio, 2009; Blyth, 2010; Gürtin and Inhorn, 2011; Hudson *et al.*, 2011; Inhorn and Gürtin, 2011).

Although the cultural, religious, legal, safety and efficacy issues promoting CBRC are extremely important, on a global level, resource constraints—namely, the high costs of IVF and the total absence of IVF clinics in many countries—may be the single most important worldwide driver of CBRC (Inhorn, 2015). As shown in the previous section, many countries lack IVF clinics altogether, especially countries in sub-Saharan Africa. In other countries, specific IVF services may be unavailable due to a lack of clinical expertise or equipment. Even when IVF clinics are present, specific IVF services may be unavailable due to resource shortages. This is true not only in resource-poor countries of the Global South, but also in countries such as the UK, where publicly financed IVF services are tightly controlled and where rationing of services leads to long waiting lists (Hudson and Culley, 2011; Culley *et al.*, 2011). In settings where the costs of IVF are prohibitive, or where couples may spend years languishing on IVF waiting lists, travel to another country where IVF services are more available and affordable is a decision that many middle-class infertile couples are increasingly willing to take (Inhorn and Patrizio, 2009, 2012a, b; Inhorn, 2012b, 2015; Inhorn *et al.*, 2012).

Although the extent of such cross-border travel is difficult to assess, CBRC appears to be a growing global phenomenon (McKelvey *et al.*, 2009; Collins and Cook, 2010; Gürtin, 2010; Mainland and Wilson, 2010; Whittaker and Speier, 2010; Franklin, 2011; Hudson *et al.*, 2011; Inhorn, 2015). The largest empirical study to date—sponsored by the ESHRE Taskforce on Cross Border Reproductive Care—involved 46 IVF clinics in six 'destination' countries in Europe (Belgium, Czech Republic, Denmark, Switzerland, Slovenia and Spain) (Shenfield *et al.*, 2010). Based on the analysis of 1230 completed patient questionnaires, the study estimated a minimum of 24 000–30 000 cross-border IVF cycles in Europe each year, involving between 11 000 and 14 000 patients. Beyond Europe, only one attempt has ever been made to assess the extent of CBRC on a global level (Nygren *et al.*, 2010). As part of an international ICMART data collection effort, clinics in 11 countries were surveyed about 'outgoing' treatment cycles. Data showed that patients from these countries had undertaken ~5000 cross-border IVF cycles in more than 25 other nations. Of 15 'recipient' country clinics reporting, an estimated 7000 couples traveled from nearly 40 countries to receive IVF. However, the authors acknowledge that these data are incomplete and largely estimates (Nygren *et al.*, 2010). In general, the absence of any kind of global registry of IVF clinics and minimal international monitoring of cross-border IVF cycles are obstacles to the collection of reliable international statistics.

In the largest anthropological study of CBRC undertaken to date, Inhorn (2015) interviewed 125 infertile couples traveling from 50 countries to Dubai—the Middle East's most cosmopolitan 'global city' and the only one to develop a significant reputation as a medical tourism hub. Inhorn *et al.* (2012) found that infertile couples were traveling to Dubai from both wealthy Western countries, as well as many resource-poor nations in Africa, Asia and the Middle East where IVF services were less available. Indeed, resource constraints—including the high costs of IVF, the rationing of IVF services in some countries, and the complete absence of IVF in many others—were a key factor underlying infertile couples' decisions to travel to Dubai. Many couples lamented their situations, feeling that they had been impoverished by IVF spending, or effectively exiled from home countries by virtue of absent IVF services (Inhorn and Patrizio, 2009). Ultimately, the unmet need for affordable, accessible and acceptable IVF services 'back home' underlay couples' costly 'repro-travel' (Inhorn, 2015).

Future directions

If resource constraints and absences of IVF facilities are fueling the cross-border movements of thousands of infertile couples each year, as suggested by the aforementioned studies, then it is fair to state that the provision of safe, affordable and reliable IVF services around the globe is far from realized in the 21st century. In fact, a group of prominent IVF scholar-activists have joined forces to ask the global reproductive health community, 'Are We Caring Yet?' (Vayena *et al.*, 2009). As they have pointed out, relatively little progress has been made on a global level to ensure IVF access for the world's infertile. The vast majority of IVF cycles are delivered in the private medical sector, meaning that costs may be prohibitive for the citizens of most countries, and certainly for those living in resource-poor settings.

But what can be done to achieve reproductive justice for the world's infertile population? We conclude by suggesting three major avenues for reproductive health activism, all of which would help to prevent the need

for both costly CBRC and catastrophic expenditure among the world's infertile citizens.

The first avenue should be *infertility prevention*—namely, eclipsing the preventable forms of infertility before they can take hold in men's and women's reproductive bodies (Inhorn, 2009). Infertility prevention entails many different strategies and the work of both reproductive health specialists and public health educators. Infertility prevention involves the early detection and treatment of RTIs, including STIs such as gonorrhoea and chlamydia, which can wreak havoc on the male and female reproductive organs, as well as postpartum, post-abortion and medically iatrogenic infections, which are a major cause of secondary infertility in women (Mascarenhas *et al.*, 2012b). Furthermore, in some parts of the world, including the Arab Gulf and South Asia, a new infertility 'epidemic' is raging, and is linked to the triad of overweight/obesity, insulin resistance/diabetes and polycystic ovary syndrome (PCOS), the global solution of which remains obscure (Gambineri *et al.*, 2002; Mehta *et al.*, 2013; Inhorn, 2015). Health education about PCOS is desperately needed to explain the genetic and lifestyle factors that are linked to this increasing global cause of women's primary infertility.

The same is true for men's reproductive health (Inhorn, 2012a). Of the world's 1 billion smokers, 81% are men. Yet, very few men, including highly educated ones, seem to have any recognition that smoking is toxic for spermatogenesis (Irvine, 1998; Marinelli *et al.*, 2004; Inhorn, 2013). Anti-smoking campaigns need to address the reproductive health outcomes of tobacco consumption for men, and not just for pregnant women. Furthermore, men who work in agriculture, heavy industry and the military should be aware of the exposure to various environmental risk factors, including toxic metals and weaponry, certain pesticides and endocrine disruptors, which can deleteriously affect male fertility (Inhorn *et al.*, 2008).

However, not all infertility can be prevented. Thus, a second important pathway to pursue involves *support of the infertile*. Much more global effort must be directed at de-stigmatizing infertility, and supporting the infertile men—but especially the infertile women—who find themselves ostracized within societies where parenthood is socially mandatory (Cui, 2010). Infertility support groups need to be developed and sustained in low-resource settings, perhaps with input from NGOs dedicated to reproductive health and reproductive rights (Vayena *et al.*, 2009). Furthermore, efforts should be directed at creating new routes to social parenthood, particularly through the encouragement of adoption and fostering (Inhorn, 1996, 2003a, 2012a). Moreover, in parts of the world where marriage and parenting have provided exclusive routes to adulthood, entirely new social pathways need to be forged. These include promotion of new ways of being, including 'single by choice,' 'happy couples,' 'dual-income, no kids' and 'child-free living' (Inhorn, 2012a, 2015; Nandy, 2014). Furthermore, assurance of basic human rights for girls and women—particularly in the realm of education and career opportunities—would diminish the agony of infertility and provide alternative pathways for infertile women, especially in cases where they find themselves alone and in need of economic support.

Finally, *LCIVF initiatives* that have emerged over the past 5 years need to be supported and embraced by others in the IVF and reproductive health community. The mission of LCIVF is to make safe, affordable, effective IVF accessible to all of those who need it, but primarily those infertile couples living in resource-poor settings. Making LCIVF a global reality remains a formidable challenge. But recent efforts and technological innovations to encourage cost-effective, evidence-based diagnosis and

treatment, including modified ovarian stimulation protocols and single-embryo transfer, as well as efforts to make a simple, transportable IVF laboratory system, are certainly a step in the right direction. So are efforts to provide IVF training courses in low-resource settings and to verify success rates of these various low-cost approaches. So far, LCIVF has gained major support from WHO and ESHRE, with increasing interest from ASRM. Other global health agencies and philanthropic organizations need to take up this charge, thereby making infertility and provision of affordable IVF integral parts of the global reproductive rights and reproductive justice agendas.

Conclusion

As shown in this review, infertility remains an ongoing global challenge, particularly for women living in low-resource settings. Despite the massive global expansion of ART over the past decade (2005–2014), ART services remain inaccessible in many parts of the world, particularly in sub-Saharan Africa, where IVF clinics are absent in most countries. To rectify this situation, an LCIVF movement is emerging in both Europe and North America, and is aimed at bringing LCIVF to the Global South. Without access to affordable IVF, many infertile couples must incur catastrophic expenditures to fund their IVF cycles, or engage in CBRC to seek lower-cost IVF services outside their home countries. Given these present realities, it is important for the global reproductive health community to engage in three forms of 21st-century activism: (i) address the preventable causes of infertility; (ii) provide supports and alternatives for the infertile, especially in resource-poor settings where parenthood is socially mandatory and (iii) make common cause with the growing LCIVF movement, which seeks reproductive justice for those living with infertility around the globe.

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