Clinical, epidemiological and socio-cultural aspects of infertility in resource-poor settings.

Evidence from Rwanda.

Doctoral Thesis submitted to the Faculty of Medicine and Health Sciences

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Preface

When I came in January 2005 to Rwanda, the most densely populated country of Africa, I had no idea that two years later I would be researching infertility. The HIV/AIDS epidemic, the high fertility rate and the high maternal and infant mortality rate were the needs everybody was concentrating on. But, during my first years of working in a rural district hospital in Rwanda I noticed that infertility was a surprisingly common complaint among women in the outpatient clinics. Later, when planning this reproductive health research project, my African colleagues argued, to my surprise, that infertility was a serious and common problem but entirely neglected and that there was an urgent need to invest more in infertility. When eventually writing this project proposal and still not entirely convinced about giving priority to infertility above over-fertility, Patricia Claeyys, who was scientific director of ICRH at the time, pointed out to me that family planning and infertility care belong together. This was the start of a change in my way of thinking which has shaped this research and which has resulted in some of the conclusions described at the end of this thesis.

Since virtually nothing has been written on this subject in the Rwandese context we decided to take an explorative approach including clinical and epidemiological aspects. More specifically we wanted to explore the link with HIV infections and other STIs and its wider implications. The most fascinating aspect of infertility is its socio-cultural dimension which was only to a certain extend explored in this work. To understand the social consequences of infertility in Africa and in most other resource poor countries it is important to realise that one’s place in these societies is defined by the web of relations which are formed with the nuclear and extended family including the dead and the unborn, the village and the nation. Without children this web is cut short. As an individual you have almost no meaning. This is the principle of what is called in Bantu language ‘Ubuntu’ and means ‘I am what I am because of what we are’. This contrasts with classical western thinking where individual freedom and happiness are central values. The suffering caused by infertility in resource-poor countries has arguably more and larger dimensions than in resource-rich countries.

While working on this project, I have met many humanitarian aid workers who were indignant over the possibility of using aid money for the problem of infertility in a country with a combination of poverty and overpopulation. I have come to think of this attitude as un-humanitarian. If we are not giving infertility the importance it deserves, we apparently do not think our fellow-men in developing nations worthy of our own ideals of individual freedom and happiness.
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INTRODUCTION
DEFINITIONS

Infertility is the inability to conceive after 1-2 years of unprotected intercourse according to medical guidelines and textbooks [1,2]. In common language ‘infertile’ means ‘impossible to conceive’ or ‘unable to have a child’ in the sense of being sterile. Therefore the term subfertility has been adopted by some authors to avoid the definition issues associated with infertility. Some have even recommended to avoid using all of these terms and replace them by descriptive, diagnostic and prognostic statements [3]. Currently both terms continue to be used [4]. The literature reviewed for this thesis includes clinical, epidemiological and demographic reports in which the term infertility is more often used than subfertility but its meaning varies according to the discipline. The differences relate to:

1. The endpoint measured: conception, live births or living children
2. Length of time to endpoint used: 1 to 7 years
3. Period covered by survey: current status or lifetime

There is on the one hand the definition used by clinicians, who are mainly interested in knowing when to initiate investigation and treatment of the infertile couple. The classical clinical definition is the absence of conception after 12 months of regular, unprotected intercourse and is based on the self reports of patients about waiting time to conception and relates to the current status of the couple [5,6]. Inability to conceive within two years of exposure was the epidemiological definition recommended by the WHO in the past [7]. Recently a consensus was published by the WHO on ART terminology defining infertility as follows: a disease of the reproductive system defined by a failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse—it was added that this was the clinical definition[8,9]. Finally, demographers shifted the endpoint from conceptions to live births and define infertility as the inability of non-contracepting, sexually active woman to have a live birth during a certain period of time. Demographic analyses of infertility are often based on secondary data such as the Demographic Health Surveys (DHS) which contain complete birth histories but often incomplete reporting about induced and spontaneous abortions, miscarriages and stillbirths and no data on whether the couple (woman) wishes to have childbirth. Because it is difficult to assess exposure from secondary data relatively long periods of exposure are used (5 to 7 years)[10].

An important distinction need to be made between primary and secondary infertility. Primary infertility is defined as no conception in someone who never had any conceptions. Secondary infertility is defined as the inability to conceive after at least one pregnancy (not necessarily a live birth). If the woman has breastfed a previous infant then exposure to pregnancy is calculated from the end of the period of lactational amenorrhoea [7].

Another related keyword is fecundity which is defined as the capacity of a woman (couple) to produce a live birth and infecundity as the complete lack of that capacity [1,6]. Childlessness is easily understood as the condition of being without offspring and can be the result of infertility, infecundity and/or infant mortality. In demographic studies childlessness among women at the end of their reproductive years is...
sometimes used as an approximate lifetime measurement of primary infertility. It is important to acknowledge that in developing countries secondary infertile women are often childless because of the high incidence of abortions (spontaneous or induced) and stillbirths, and because of high infant mortality rates [11].

Ulla Larsen found that the infertility definition used makes a difference for the estimation of infertility prevalence in a cross sectional study in Tanzania using 6 definitions of infertility. They recommend epidemiological and demographic studies of infertility to use primary data based on the question “How long have you tried to get pregnant?”[5]. Interestingly it was found that definitions not including whether the woman tried to conceive result in exaggerated estimates of secondary (not primary) infertility because they include non-contracepting women who do not want to conceive also referred to as women with unmet need for family planning.

Because infertility is often a consequence of reproductive tract infections (RTIs) or sexually transmitted infections (STIs) and these terms will appear frequently in this thesis, it is important to define these terms. STIs are infections transmitted through sexual intercourse and include bacteria, viruses, protozoa, ectoparasites and fungi. In the leading volume on sexually transmitted diseases by K Holmes et al a distinction is made between sexually transmitted and sexually transmissible pathogens, the former are transmitted predominantly by sexual intercourse, the latter can be sexually transmitted but not as predominant mode [12]. RTIs are infections of the genital tract. One category of RTIs (such as syphilis and gonorrhoea) are sexually transmitted, a second category consists of endogenous infections, a third one of iatrogenic infections. In women, overgrowth of endogenous microorganisms normally found in the vagina may cause RTI (yeast infections, bacterial vaginosis). These infections are usually not defined as STIs. Medical interventions may provoke iatrogenic infections in several ways – endogenous organisms from the vagina or sexually transmitted organisms in the cervix may be pushed into the upper genital tract during a transcervical procedure or delivery and cause serious infection of the uterus, the fallopian tubes and other pelvic organs. Organisms from outside the body can also be introduced into the upper genital tract if infection control is poor [13].

Finally the term pelvic inflammatory disease (PID) also needs to be defined. In Holmes’ reference work PID is defined as a spectrum of upper genital tract inflammatory disorders among women including any combination of endometritis, salpingitis and tuboovarian abscess and pelvic peritonitis [14]. They restrict the term pelvic inflammatory disease to infections of the upper genital tract caused by microorganisms that ascend from the cervix or vagina; the term excludes blood-borne infections such as tuberculosis. Infections following delivery or induced abortion are also categorized separately as puerperal or postabortion infection. This definition is not endorsed by all authors, some of which do include the latter when they refer to PID [15]. In this thesis we have used the ‘restrictive’ definition of PID excluding postpartum and post abortion infections and pelvic infections caused by tuberculosis.
MAGNITUDE OF THE PROBLEM

The reported international prevalence of infertility is estimated at approximately 8-10% of married and cohabiting couples with a total of 50-80 million couples suffering from infertility [16-18]. In a recent review of existing population surveys on the prevalence of infertility the authors concluded that infertility prevalences are similar between more and less developed nations. Since the largest proportion of the world population lives in developing countries we can conclude that the majority of infertile couples are living in developing countries. The use of different definitions and methodology makes comparison of data difficult. There are only a few population based studies that assess the prevalence of infertility in sub-Saharan Africa (SSA). In a population based survey in rural Malawi 19.6% of women and men reported to have ever had difficulties in getting pregnant and in rural Ghana this was 13.8% [19,20]. In a household survey in Gambia 9.2% of women reported to have currently some kind of fertility problem [21]. There are two reports gauging national levels of infertility analysing the birth histories found in Demographic and Health Surveys (DHS) of 28 African countries[10,15]. They concluded that primary infertility is relatively low, exceeding 3% in less than a third of countries and in most countries well below the expected biological minimum of 4%. In contrast elevated levels of secondary infertility prevail in most countries. Secondary infertility for women age 20-44 ranges from 5% in Togo to 23% in Central African Republic. As contraception is very rarely used at start of sexual live in African couples, the age of first pregnancy is usually not very different from the age at first intercourse [10]. Many initially fertile women acquire infertility during their sexual active years. The high incidence of STIs, inadequate health services and poor socio-economic status make these women vulnerable for PID, puerperal infections and/or post abortion infections and subsequent tubal damage [16]. Rwanda with a total infertility level of 9.3-12% according to Ericksen and Brunette or 7% according to Larsen, emerges as one of the African countries with the lowest levels of infertility [10,15]. In addition to these population surveys and secondary analyses there are hospital and medical practice reports from SSA which indicate that infertility is common as underlying reason for consultation with a gynaecologist [22,23].

The prevalence in resource rich countries ranges from 3.5% to 16.7% according to estimates based on a review of population based surveys [17]. The last 30 years demand for infertility care has been booming due to two major developments. First, the introduction of in vitro fertilisation (IVF) and intracytoplasmatic sperm injection (ICSI) has improved the prognosis for infertile couples considerably and has contributed to increasing numbers of infertile couples seeking care [1]. Second, women are focusing first on education and careers and the expanding contraceptive options have allowed them to start childbearing at an older age when they are biologically less fertile, increasing the prevalence of age-related infertility. Due to this social trend and also better reproductive health care, primary infertility is much more common than secondary infertility in industrialised countries.
ETIOLOGY

The major causes of infertility include ovulatory dysfunction, tubal and peritoneal pathology, uterine pathology and male factor. When no cause can be identified the infertility is categorised as unexplained [1]. Another major cause of infertility, especially in developed countries is the age-related decrease in female fertility caused by increasing prevalence of aneuploidy in aging oocytes. Therefore unexplained infertility is more common in older couples.

In developed countries the causes of infertility on couple level are attributed to tubal and peritoneal pathology in 14-35%, male factor in 25-35%, ovulation dysfunction in 15-20%, unusual problems in 5% and unexplained infertility in 10-28% of cases [1,24].

Available data indicate that the situation in SSA is very different from more developed countries. Between 1979 and 1984, WHO conducted a multicentre, collaborative investigation of 8 500 infertile couples, in 33 medical centres in 25 countries throughout the developed and developing world. African couples were more likely to have secondary infertility, a history of STIs or pregnancy complications and infertility diagnoses (such as bilateral tubal occlusion or pelvic adhesions) suggestive of previous genital infections. The prevalence of tubal factor infertility was threefold higher in Africa compared to Western countries. These data suggest that infertility in African couples is mainly infection-induced. It was estimated from this study that about 70% of these infections were attributable to STIs and the remainder of infections associated with abortion and unsafe delivery practices [15].

Reports from smaller clinical studies performed in SSA confirm the high prevalence of fallopian tube occlusion ranging between 23 and 84% [25-28]. The results vary considerably between different studies. This might be due to regional difference or differences in quality of diagnostic work-up. Primary infertile women seem to suffer less from fallopian tube occlusion than secondary infertile [29].

Other causes of infertility identified in these studies are male factors, ovulation disorders and uterine pathology. The prevalence of male factor ranges between 22% and 68% of infertile couples, which is comparable with the prevalence in developed countries [27,30-32]. Data on the contribution of the male factor in SSA are scarce. On the one hand many men refuse to have a semen analysis, on the other hand health providers may not insist on their participation [30]. A review of the files of patients attending for infertility in Kigali University Teaching Hospital (KUTH), the main public tertiary referral hospital in Kigali, revealed that in only 30% of couples a sperm analysis was performed (unpublished data).

MICROBIAL ETIOLOGY OF TUBAL DAMAGE AND MALE INFERTILITY

At present it remains unclear which organisms contribute most to the pathogenesis of tubal infertility. In the Western world, where tubal factor infertility is less prevalent, *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoea* (NG) have long been considered as the main pathogens in PID [14]. However this
picture is changing with the exposure of new bacteriological findings. The prevalence of CT and NG in PID is still high but in up to 70% of cases other pathogens are involved. The role of other bacteria ascending from the vagina is becoming clearer. The responsibility of bacterial vaginosis related organisms such as *Gardnerella vaginalis*, gram-negative rods, and mycoplasmas have since long been established but new species continue to be identified [33]. *Trichomonas vaginalis (TV)* has also been implicated in facilitating upper genital tract infections [34-36].

There are only few data on microbiology of tubal damage in SSA. Studies involving the isolation of pathogens from the upper genital tract of women with PID are currently lacking. In Kenya NG and CT were more often isolated from endometrial and cervical specimens in women with clinical endometritis than in women without endometritis [37]. In Ivory Coast NG was detected in 50 (29.4%) and CT in 16 (9.4%) of 170 patients with acute PID, but there was no control population [38]. In another study NG was isolated twice as often from the cervix of women with pelvic inflammatory disease than of asymptomatic, postpartum women (19% versus 9% respectively) In the same study the bacteria isolated most frequently from the uterus, blood, urine, and pus from women hospitalized for puerperal sepsis were Enterobacteriaceae (36%), gonococci (28%), streptococci (25%), and anaerobes (4%). The low frequency of isolation of anaerobes was thought to be due to laboratory limitations [39]. To date, mainly serological studies have linked NG and CT with tubal infertility or PID in Africa. Data from Congo-Brazzaville, Nigeria, Gambia, Gabon and Ghana have demonstrated a higher prevalence of chlamydial antibodies among infertile women [40-44]. Four studies have examined the association between gonococcal serology and tubal infertility in SSA and all of them found a positive association [41,45-48]. The association between bacterial vaginosis (BV) and tubal factor infertility has not been examined in SSA so far.

The role of viral STIs in tubal pathogenesis remains even more obscure. In Western countries, *herpes simplex virus* -2 (HSV-2) has been detected in the endometrium and fallopian tubes of women with acute PID [49-51]. Furthermore, HSV-2 was found to be associated with infertility, with ectopic pregnancy and with PID. In none of these studies the association was adjusted for other RTIs or high risk sexual behaviour. In SSA the association between HSV-2 infection and infertility has not been examined to date.

There is also some limited evidence that certain parasitic diseases could cause tubal damage including two common parasitic diseases: schistosomiasis and trichomomas vaginalis infection [52-56].

Special attention deserves the role of HIV infection in infertility. This is the subject of a separate chapter (see chapter 7). In summary, HIV infection lowers the fertility of infected couples considerably through several mechanisms, some of which are not well defined. In turn the high risk sexual behaviour of infertile couples can increase the risk for HIV acquisition. There are some limited data showing an increased HIV prevalence in African infertile couples.
Infection and inflammation of the male reproductive tract are accepted as important etiological factors of infertility but there is little consensus on the nature of the causative pathogens [57-59]. In men, the wide margin between subfertility and normal fertility makes it difficult to demarcate the precise role of infection on post-infection fecundity, but it seems less important than in women [60]. For some pathogens such as CT, HSV-2 and HIV some evidence exist that they can contribute to male infertility [61-63]. As STIs are more widespread in SSA it is generally accepted that infections might play an important role in male infertility [59,64]. To date reports on the association between infections and semen characteristics in SSA are scanty. In Nigeria 10% of infertile men had bacteria such as Proteus species, Staphylococcus aureus and Escherichia coli in their semen [65].

RISK FACTORS

Risk factors can directly affect risk of transmission or progression (direct risk factors) or can exercise their effect through another variable (indirect risk factors). In addition, risk factors may be viewed on a continuum from modifiable to non-modifiable with behavioural risk factors belonging to the former and demographic risk factors belonging to the latter [33]. In order to prevent infertility the most prevalent modifiable risk factors need to be known. As most of female infertility and at least some of male infertility in SSA is probably caused by STIs we expect to find an association between high risk sexual behaviour and infertility. Secondary analyses of DHS and World Fertility Surveys, have indicated that a history of high risk sexual behaviour, such as multiple marriages and unions and early age at first sexual intercourse, put women at substantial risk for infertility [15,66]. Two studies in SSA compared the past reproductive and sexual characteristics of infertile patients with currently fertile (pregnant) women [22,67]. In Kenya, it was found that the age at first intercourse was much lower and the number of sexual partners was significantly larger in women with tubal factor infertility than in fertile women. It was argued that the reproductive and sexual events that occur during the teenage years determine the future prospects of fertility. A hospital-based study in Tanzania looked at past sexual behaviour in 154 infertile women and 259 fertile (pregnant) women. Variables included past syphilis, past genital ulcer, martial instability, lifetime sexual partners, polygamous union and age at first sex <15y. All variables were significantly more frequent among infertile women.

Very few studies have examined risk factors for secondary infertility. It is generally accepted that the high prevalence of secondary infertility in SSA is due to PID or due to puerperal and post abortion infections. These infections are either caused by STIs or by endogenous (mostly vaginal) organisms. The relative contribution of each factor (iatrogenic, endogenous, and sexually transmitted infections) is not known. In a case-control study in Nigeria an association was found between elements in the obstetric history such as induced abortion, postpartum infection, manual removal of placenta and prolonged unsupervised labour with secondary infertility [68]. In an analysis of DHS from different Central-African countries multiple unions, transactional sex and early age at first intercourse were associated with secondary infertility [66].
Data on risk factors for male infertility are even scarcer. Only one case-control study in Nigeria examined risk factors for male infertility and found that infertility in men is associated with various proxies of STIs and poor healthcare-seeking behaviour for STIs [69].

Other elements of sexual experiences in women, such as sexual violence and lifestyle factors in men and women such as smoking, alcohol and obesity, which have been associated with decreased fertility in other parts of the world, have not been examined as risk factors for infertility in SSA so far [70-73].

PERCEPTION OF CAUSES OF INFERTILITY AND TREATMENT SEEKING BEHAVIOUR

Although it is unlikely that modern assisted reproductive technologies at current cost will become available in the public services of resource-poor countries, at least in the medium-term, a call has been made by several authors to improve information, education and counselling on causes and treatments of infertility and to develop guidelines for the management of infertility on all levels of healthcare [74-78]. In order to do this, information about prevailing perceptions and treatment-seeking behaviour is needed.

From studies focusing on the knowledge of infertile couples about causes of infertility we learn that most men and women have no knowledge about the basic principles of human reproduction and a poor understanding of possible causes of infertility [78-80]. A consistent finding in these studies is that mostly the woman is blamed for the problem by women and men alike, with the exception of one study in South-Africa where male infertility awareness was high [81-83]. This explains partly why men absent themselves from seeking treatment for infertility. Many patients have concepts deviating from the classical biomedical concepts which are often understood in a different way by patients. Witchcraft, poisoning or previously used contraception are often blamed for the infertility. Few couples link promiscuous behaviour and STIs with infertility [78,80,83,84].

Previous research in Mozambique, Gambia and Nigeria has shown that many infertile couples engage in prolonged and relentless care seeking often without the desired result [21,84,85]. The formal medical sector has little to offer to these couples in most developing countries and often unnecessary treatments without prior systematic investigations are tried out. This and the fact that patients search for explanations in witchcraft, poisoning or religious factors is the reason that infertile patients often turn to traditional healers [86]. Many patients consult both the formal medical and traditional health care sector draining their already scarce resources. It is often the woman who initiates and engages most frequently in health-care seeking. Men can try to hide their problem of infertility by demanding their wife to have sex with a relative or friend. Or they simply divorce and remarry or engage in polygamous marriage [76,87].

Data from the East- African region and quantitative data on treatment-seeking behaviour for infertility and prevailing perceptions on its causes are lacking. The role of men in the health seeking process is also less well described [88]. Furthermore, we know little about factors associated with seeking care in the formal medical sector for both men and women and we have very few reports on what kind of
investigations and treatments are usually prescribed for infertility by the formal medical sector. Detailed knowledge of these factors could be helpful in designing the appropriate strategy for helping infertile couples in some African countries.

THE LINK BETWEEN HIV AND FERTILITY

There are many different aspects in the association between HIV/AIDS and fertility. HIV/AIDS can affect fertility desires or outcomes and fertility/infertility can affect the risk of HIV/AIDS. The two also share common determinants: sexual exposure, contraceptive practices and RTIs [89].

The effect of HIV on fertility desires and contraceptive needs is not clear with some studies indicating a higher desire others indicating a lower desire among HIV infected couples [90-93]. On the one hand many HIV positive women have unintended pregnancies indicating an unmet need for family planning. Mathematical modelling indicates that reducing unmet need for contraception is more cost-effective for preventing HIV-positive births than a traditional prevention of mother to child transmission (PMTCT) strategy of prophylaxis with antiretroviral drugs [94,95]. HIV is often diagnosed during pregnancy but the opportunity to initiate contraception postpartum is usually missed. However, there is increasing awareness about the need to link provision of effective family planning (FP) to HIV services [91].

On the other hand, many couples especially those with none or few children continue to want children after learning their positive status [91]. Furthermore, with the advent of antiretroviral therapy (ARV) couples are expecting to live longer and healthier which has a positive effect on reproductive desires [96].

It is now widely accepted that HIV reduces fertility in infected men and women [89,97-107]. HIV-positive women (also those with asymptomatic infection) have lower conception rates and higher rates of both early and late pregnancy loss. The lower conception rate is thought to be due to coinfection with STIs with resultant tubal factor infertility, weight loss related anovulation and amenorrhea, male hypogonadism, and impaired spermatogenesis [35,100,108-116]. But many of these mechanisms remain to be elucidated.

In one prospective study examining the association between HIV infection and infertility, it was found that in half of the patients the infertility had existed before HIV infection, suggesting that infertility is a risk factor for HIV acquisition [117]. This hypothesis is endorsed by evidence from social science research in sub-Saharan Africa showing that couples with fertility problems are more likely to face extramarital relationships, polygamous unions and divorce, all of which are known risk factors for HIV infection [67,81,84,118].

Few studies have examined the HIV prevalence in infertile patients, particularly among couples. In Tanzania, HIV infection was threefold higher among infertile women compared to fertile controls [67]. Similarly, in Nigeria, HIV infection among women undergoing laparoscopy evaluation for infertility was five-fold higher compared to HIV prevalence among pregnant women and threefold higher in women with tubal factor infertility compared to the general population [108,118]. On the other hand, prevalences of infertility among HIV infected couples in resource-poor countries have not been reported so far.
CONSEQUENCES OF INFERTILITY

To understand the social consequences of infertility in Africa and in most other resource poor countries it is important to realise that one’s place in these societies is defined by the web of relations which are formed with the nuclear and extended family including the dead and the unborn, the village and the nation. Without children this web is cut short. As an individual you have almost no meaning. This is the principle of what is called in Bantu language ‘Ubuntu’ and means ‘I am what I am because of what we are’ [119]. This contrasts with classical western thinking where individual freedom and happiness are central values. Therefore consequences of infertility for couples in developing countries, where children are highly valued for economic and socio-cultural as well as personal reasons can be far more severe than for couples in Western countries. Reports from several African countries, mostly West and South Africa, have documented the overwhelming importance of childbearing and the suffering caused by infertility in these societies [79-81,84,86,87,120-129]. According to these studies, infertility causes a wide range of psycho-social consequences: loss of marital stability, loss of social status and isolation, loss of social security, problems with gender identity, loss of continuity of family lines and general emotional distress [124].

Because motherhood is one of the most important ways for African women to enhance their status within the family and the community, childless women often carry the largest burden of the suffering. They may suffer from domestic violence, get abandoned by their partner and may end up as second wife in a polygamous marriage [84,120,122,130,131]. Initiatives to make infertility care accessible in resource-poor settings are gaining momentum [16,75,132-137]. Mapping the socio-cultural consequences of infertility in these settings is necessary to achieve this goal. Furthermore, little is known about the impact of a gender specific diagnosis on the couple’s relationship.

DEMOGRAPHIC PARADOX AND INFERTILITY-FERTILITY DIALECTIC

In the 1994 United Nations International Conference for Population and Development (ICPD), Cairo, a plea was made for the reproductive rights of couples worldwide [138]. It was stated that “Reproductive health implies that people have the capability to reproduce and the freedom to decide if, when and how often to do so...and have the information and the means to do so...” Both infertility and excessive fertility are consequences of the failure to exercise these rights. SSA has the highest fertility rates in the world and at the same time infertility rates in some regions are also among the highest in the world. This is called the demographic paradox [16]. This paradox can be easily understood if one considers that the underlying determinants of both phenomena are the same. These determinants include the socio-cultural importance of childbearing and the specific socio-economic determinants of poverty, limited access to good education, gender power inequalities, migrant labour, poorly performing health care systems and in some cases war and conflicts [139]. Children are highly valued in African communities and have many important roles in the lives of their parents and their communities, leading to fertility orientated sexual behaviour. This fertility orientated sexual behaviour and the broader socio-economic
context lead to poor use of barrier and other family planning methods, high incidence of sexual coercion and violence and frequent use of transactional sex making women vulnerable to unplanned pregnancies, STIs and HIV infection which can all lead directly or indirectly to infertility.

Data from social research on family planning in Africa suggest that an important barrier to contraception use is fear for consequent infertility [80,140]. Since infertility is a condition most feared by African women, they are reluctant to take contraceptives, they engage in unprotected intercourse from an early age on and some of them become infertile due to reproductive tract infections. This paradoxical situation was characterized as the “fertility-infertility dialectic” by Inhorn [132]. It is argued that studying this intimate connection is an important step in convincing family planning programs in developing countries to adopt a more balanced approach, one that recognises the importance of infertility [80].
OBJECTIVES AND METHODOLOGY
OVERALL OBJECTIVES

To study clinical, epidemiological and socio cultural aspects of infertility in Rwanda.

SPECIFIC OBJECTIVES

Primary objectives
To evaluate risk factors and/or determinants of infertility in Rwanda, including HIV and other reproductive tract infections.

Secondary objectives
1. To describe outcome of infertility investigations in infertile couples
2. To describe socio-cultural consequences of infertility
3. To describe treatment-seeking behaviour in infertile couples and perceptions of causes of infertility

STUDY DESIGN

Quantitative data

Unmatched case control study
The cases were sampled from a cross-section of a population with infertility (the disease outcome) and the controls were sampled from a population without infertility (fertile population). We opted for non-pregnant controls who had delivered between 6 and 18 months ago for several reasons. First, part of the services offered to all the study women was cervical cancer screening and treatment which is not usually done in pregnant women. Second, during the period of pregnancy and the immediate postpartum period women and their partners might alter their sexual behaviour drastically, making them an unsuitable control group.
In the original protocol we included the possibility of matching for age if the mean ages would appear very different in an interim analysis. However the recruitment site of the control group was changed during the course of the study. Initially the fertile control groups consisted of a hospital based group of postpartum women coming for vaccination in the health centre. An interim analysis of the first 60 enrolled fertile women revealed a HIV prevalence of around 50%. This surprisingly high prevalence was probably due to the fact that postpartum vaccination services are linked to HIV related services such as nutritional support for mother and child. We therefore switched to recruiting the fertile controls from the community using community mobilizers. This required more elaborate and unforeseen logistics and
as not to complicate matters unnecessarily we decided not to match for age but to control for it in the analysis. An interim analysis of age had shown that the difference of age was not large enough to make comparison between the two groups impossible and that it could be easily controlled for in a multivariate model. Another reason for not doing matching is that it requires specialized multivariate techniques to control for additional non-matched confounders.

**Cross sectional elements**
The cases (infertile women and men) of the case-control study were surveyed about treatment seeking behaviour and treatments received for infertility in the past.

**Prospective study**
Infertile couples were offered infertility investigations the results of which were described. When appropriate and/or available, treatment was prescribed and couples were followed up for 18 months after inclusion.

**Qualitative data**

**Focus group discussions (FGD)**
For each FGD, 7-10 participants were selected from different diagnostic groups: one FGD with women and a second FGD with men from infertile couples diagnosed with female factor only; a third FGD with women and a fourth FGD with men from infertile couples diagnosed with male factor only. This specific group assignment served two purposes: to encourage participant to speak more freely and to explore the effect of gender-specific infertility diagnosis on the experience of infertile couples. A fifth FGD included a mixture of men and women in infertile relationships irrespective of the cause of the infertility. We included a group with mixed gender, hoping that this would result in interesting discussions about the gender based differences in attitudes towards infertility.

**STUDY SETTING: RWANDA**

Rwanda is a small land locked country, situated in central Africa, and part of the East-African community. It is the most densely populated country in Africa with over 9 million inhabitants living on a surface of 28,338 sq km. The country is rebuilding itself after the 1994 genocide in which at least 800,000 people were killed and most of its infrastructure destroyed [141].

With 77% of its population living under the poverty threshold of 1.25 USD a day, Rwanda is one of the 20 poorest countries in the world [142]. Illiteracy rate among men and women is 22% and 29% respectively [143].

The country’s high population growth contributes to continuing pressure on natural resources, particularly land, which is thought to be one of the underlying causes of the ethnic tensions that contributed to the 1994 genocide. Population issues have been on the government’s agenda since 1981 when the National Office of Population (ONAPO) was created. ONAPO focused on improving access to
family planning services with a rise of contraceptive use from 11% of the population in 1983 to 21% in 1992. After the genocide the population policy shifted toward reuniting dislocated families and no activities related to slowing population growth were undertaken [144]. Recently increasing family planning uptake has become a top priority of the Ministry of Health (MOH) in Rwanda. This has resulted in spectacular increase of modern contraceptives from 10% in 2005 to 27% in 2007-2008 [143,145]. Total fertility rate is declining since 2005 but remains high at 5.5. The population is expected to reach 12 million by the year 2012.

Rwanda’s health infrastructure was severely damaged during the war. Although significant progress has been made over the recent years, the health system still faces the challenges of inadequate infrastructure and equipment, inadequate human resource capacity and a lack of financial resources. The health work force is small with only one physician per 18,000 inhabitants and 1 nurse per 1690 inhabitants. In 2010 the government allocated 12 percent of its budget to healthcare. Donor inputs account for well over 70% of health sector funding [141]. Twenty four percent of the health budget goes to the fight against HIV. Since a couple of years a community based health system is in place. In 2008 the rate of enrolment was 85%. Most of mutual health insurances in Rwanda use a policy of family subscription with the premium per household of 2-7 members varying from 5$ to 20$ (Kigali City). The patient’s contribution towards the cost of medical treatment varies between 5% and 25% of co-payment of the real cost of the care. Health care and services covered by mutual health insurance comprise all services and drugs provided at the health centre [146].

Currently the less than five mortality rate is 103 per 1000 live births and the maternal mortality rate is 750/100,000. Overall HIV prevalence was estimated at 3% in 2005 [147].

**STUDY PARTICIPANTS**

**Sample size calculations**

This study intended to recruit 300 infertile women and their partner and 300 postpartum women and their partner. As it was difficult to predict how many of the male partners would accept to participate, sample size calculations were performed for the women only.

HIV prevalence for pregnant women according to WHO data lies between 4 and 11%, hence calculations were based on a prevalence of 5% and 10% [148]. For STIs the figure of 27% was used; this figure results from a cohort study of 381 HIV negative pregnant women in Rwanda between 1992 and 1994, where 27% of the women had at least one STI [149]. The expected proportion of participants with high risk sexual behaviour in the fertile group is based on the prevalence of high risk sexual behaviour in fertile women in a case-control study in Tanzania [67]. The data on home delivery were based on the DHS 2000 [150].
Table 1: sample size calculations based on several exposure prevalences and OR.

<table>
<thead>
<tr>
<th></th>
<th>$P_0$</th>
<th>$P_1$</th>
<th>OR</th>
<th>N (power 90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>0.05</td>
<td>0.095</td>
<td>2</td>
<td>740</td>
</tr>
<tr>
<td></td>
<td>0.14</td>
<td>3</td>
<td></td>
<td>243</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.18</td>
<td>2</td>
<td>418</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>3</td>
<td></td>
<td>146</td>
</tr>
<tr>
<td>High risk sexual</td>
<td>0.1</td>
<td>0.18</td>
<td>2</td>
<td>418</td>
</tr>
<tr>
<td>behaviour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>3</td>
<td></td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.33</td>
<td>2</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td>0.43</td>
<td>3</td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>STI</td>
<td>0.2</td>
<td>0.33</td>
<td>2</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.43</td>
<td>3</td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>Delivery at home</td>
<td>0.5</td>
<td>0.66</td>
<td>2</td>
<td>211</td>
</tr>
</tbody>
</table>

$^1P_0$ is estimated prevalence in controls  
$^2P_1$ is estimated prevalence in cases  
$^3$OR=Odds Ratio  
$^4$N=total number of participants needed  
Alpha value 0.05 (two-sided)  
Beta level 0.10, representing a power of 90%

As can be deducted from table 1 a study with a sample size of 300 generated adequate statistical power to detect most of the expected differences. We hypothesized that HIV/STI infection and high risk sexual behaviour (past and present) are significantly increased in infertile couples. We expect the odds ratios to be similar to those obtained in the case-control study in Tanzania, mainly ranging between 2 and 3 [67].

Eligibility criteria

**Cases**

1. Women presenting with one of the following complaint:
   - Primary infertility (at least one year of regular unprotected intercourse with at least one partner without conception)
   - Secondary infertility (at least one year of regular unprotected intercourse with at least one partner without conception after previous pregnancy and after cessation of exclusive breastfeeding)
2. Age 21-45
3. Living in Kigali
4. Sexually active defined as having had sex at least once in the last 2 weeks
5. Willing to undergo HIV testing
6. Willing and able to give written informed consent. Illiterate women were enabled to give informed consent by thumbprint in the presence of an independent witness.
**Controls**

1. Postpartum women who delivered between 6 and 18 months ago.
2. Age 21-45
3. Living in Kigali
4. Willing to undergo HIV testing
5. Sexually active defined as having had sex at least once in the last 2 weeks.
6. Willing and able to give written informed consent. Illiterate women were enabled to give informed consent by thumbprint in the presence of an independent witness

**Recruitment procedures**

**Infertile couples:**
An infertility research clinic was opened at KUTH in Rwanda which set out to offer a basic package of infertility investigations, free of charge, to 300 couples. Initially, study participants were recruited among women attending the gynaecological consultations at KUTH and the district hospital of Muhima, the largest secondary referral hospital for gynaecological problems in Kigali. Women enrolled in the study spread the word of the research clinic which resulted in two-thirds of the enrolled participants being recruited through word of mouth. Women were asked to invite their partner to the study clinic on a separate day; a written invitation for this was handed to the woman. It was emphasised that infertility is a problem of the couple and that no treatment can be started before male partner is investigated. The investigations in the woman could proceed without the presence of the male partner however not in case when a woman needed laparoscopy.

**Fertile couples:**
Controls were recruited at the level of the community, as no appropriate control group could be selected at the hospital. A list of all residential neighbourhoods (known as umudugudu) from where the infertile couples originated was compiled (120 umudugudu in total). Fourteen neighbourhoods were randomly selected from this list by blindly hand-picking numbers from a bowl. Community mobilizers in these neighbourhoods have visited all families to identify potential eligible candidates and explained that they would receive free cervical cancer screening and treatment if indicated. After their study visit, women were asked to invite their partner to the study clinic on a separate day; a written invitation for this was handed to the woman.

**PROCEDURES**

**Case-control study**
The purpose of the study was explained to the study participants in the local language (Kinyarwanda) and eligibility criteria were checked. All participants provided written informed consent before study initiation. A female nurse interviewer addressed the women and a male medical officer the male partners. Socio-demographic characteristics and information on past sexual behaviour and lifestyle
factors were asked in face to face interviews using a structured questionnaire. Most questions had been field-tested by studies previously conducted in Rwanda; a few questions were study specific and were field tested prior to commencing the study. Almost all questions had fixed-choice response alternatives. All female participants received a clinical gynaecological examination by the same trained nurse, and supervised by a gynaecologist (the author). During the speculum examination vaginal swabs were collected for the preparation of a wet mount, potassium hydroxide testing and vaginal pH testing. Saline wet mounts were examined in the study clinic for the presence of clue cells. A patient was considered to have BV according to Amsel criteria when 3 of the 4 following signs were found: positive whiff test, presence of clue cells, vaginal pH more than 4.5 and a thin, homogenous vaginal discharge. A Gram stain slide was also prepared and read later for the presence of BV according to the morphological criteria of Nugent. A second vaginal swab was placed in 3 ml UTM-RT transport medium (Copan) and immediately frozen at –80°C. This swab was shipped, frozen on dry ice, to Ghent University Hospital for multiplex PCR for CT and NG (Abbott Laboratories, IL, USA). Thereafter, the study nurse collected blood samples for serial rapid HIV testing on site as per national algorithm: Determine Rapid HIV-1/2 Test (Abbott Laboratories, Abbott Park, IL) Uni-Gold Rapid Test (Trinity Biotech Plc, Ireland) and the Capillus HIV-1/HIV-2 Rapid Test (Trinity Biotech Plc, Ireland). Participants were advised to return for test results and, if required, received treatment according to local guidelines. The serum sample was immediately processed in 4 aliquots and stored at -80°C until analysis. One aliquot was analysed for HSV-2 antibodies (Herpeselect 2 ELISA IgG, Focus Diagnostics) in the national reference lab of Kigali. Another aliquot was shipped, frozen on dry ice to the laboratory of the Ghent University Hospital for CT-specific IgG antibodies by a synthetic-peptide based EIA test (labsystems, Helsinki, Finland).

All participants were offered HIV counselling and same-day testing; those testing positive were enrolled in an HIV care and treatment clinic at the study site. In the pretest counselling we talked about modes of HIV infection and enquired about the patient’s willingness to know the results. In the post-test counselling we talked about differences between HIV and AIDS, the window period, how not to infect others and the importance of CD4 count testing and ARV treatment.

Infertility investigations and follow-up of infertile couples

During the initial study visit all infertile women received a transvaginal ultrasound (TVUS) examination by the same gynaecologist (the author). Special attention was paid to presence of polycystic ovaries and myomas. After the initial study visit infertile women were scheduled for hysterosalpingography (HSG) to test tubal patency and to assess the uterine cavity. All HSGs were performed by the same gynaecologist (the author) in the radiology department of KUTH using a soluble contrast medium between 7th and 10th day of menstrual cycle. All women were given ibuprofen 400 mg half an hour before the procedure and prophylactic doxycycline was prescribed. They were asked to come back in case of pain, fever and abdominal pain after the HSG. Some women had been investigated with several HSGs in the past, showing evidence of tubal abnormality. In those women the HSG was omitted and they were referred directly for laparoscopy. Women with amenorrhoea were further investigated with measurement of prolactine levels and a progesterone withdrawal test.
Their male partners were referred for a semen analysis. Appropriate equipment for the proper assessment of morphology was not available and was therefore not done. If the semen analysis was abnormal a repeat semen analysis was requested.

After the completion of all investigations, the couples were invited for a follow-up appointment in which the findings were discussed in detail. Lifestyle related advice such as weight loss, discontinuation of smoking or alcohol were given where appropriate. Women with anovulation or infrequent ovulations, but otherwise normal investigations, were prescribed Clomiphene citrate 50-150 mg and followed up with transvaginal ultrasound in the research clinic. A maximum of 6 cycles were prescribed. Anovulation was defined as amenorrhoea with a positive progesterone withdrawal test and normal prolactine levels.

Women with tubal pathology were referred for laparoscopy and fertility enhancing surgery if possible in KUTH. As laparoscopy is covered by the community health insurance system but puts a huge burden on this system we agreed after discussion with the local health authorities to use strict referral criteria, including absence of significant male factor, no living children with current partner, no more than 3 living children with a previous partner, age under 43, and hydrosalpinx less than 5 cm on TVUS. Patients not qualifying could still be referred for laparoscopy but had to do it at own expense.

Men with abnormal semen analysis were prescribed a second test. In case of oligo- and/or asthenozoospermia Clomiphene citrate 25mg was prescribed during one month. In case of improvement of semen analysis after one month anti-oestrogens therapy was continued. In case of oligozoospermia split-ejaculation was also advised.

HIV positive serodiscordant couples were counseled about risk of infection and if the couples still wanted to continue childbearing they were advised to use condoms outside the fertile period. Infertility treatment such as laparoscopy was only offered if both partners were tested and aware of each other’s HIV status and if both of them were followed in a HIV care and treatment program. We also discussed at length about balancing the risk of HIV transmission on the one hand and the chance or need of conceiving.

Between 12 and 18 months after enrolment all infertile women were contacted by phone to find out about the occurrence of pregnancy. An attempt was made to record reasons for missed visits and non-participation of male partners throughout the study.

Cervical cancer screening

Although not part of the actual study procedures, for completeness, I will briefly explain the context in which the cervical cancer screening took place in this study. No further reference will be made to this in the results or the discussion. At present there is no national screening policy for cervical cancer in Rwanda and only a few women get tested occasionally with pap smears. Capacity to read pap smears and treatment modalities (cold knife conisation or hysterectomy) are very limited. As part of the European and Developing Countries Clinical Trials Partnership (EDCTP) project which co-funded this study, it was planned to build capacity for cervical cancer screening and treatment in KUTH. For this purpose colposcope and cryotherapy equipment were bought and installed in KUTH. The study women, being the first ones to benefit from this equipment provided the opportunity to train the health staff of KUTH in cervical cancer screening and treatment. In each woman a visual inspection of the cervix with acetic acid (VIA) and with Lugol’s iodine (VILI) was done. Abnormal lesions were treated with
cryotherapy. Non-eligible lesions were referred for colposcopy and biopsy. According to the colposcopy/biopsy findings the lesion was treated with either cryotherapy or cold knife conisation or more invasive surgery (in case of suspicion of cervical cancer). At present this cervical cancer screening unit is still operational in KUTH.

Table 2: overview of all study procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Infertile women</th>
<th>Fertile women</th>
<th>Infertile men</th>
<th>Fertile men</th>
</tr>
</thead>
<tbody>
<tr>
<td>interview</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV serology</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HSV-2 serology(^1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wet mount</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gram stain</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>NG/CT PCR(^2)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chlamydia serology</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HPV(^3)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Pap smear</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>TVUS(^4)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>HSG(^5)/laparoscopy</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Semen analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Herpes Simplex Virus  
\(^2\) Neisseria gonorrhoea/Chlamydia trachomatis Polymerase Chain Reaction  
\(^3\) Human Papillomavirus  
\(^4\) Transvaginal Ultrasound  
\(^5\) Hysterosalpingography

Laboratory procedures

The microbiological and serological laboratory methods are described in detail in the different chapters. Direct microscopy and rapid tests were performed on site. Microscopy for TV has a low sensitivity ranging from 40 to 80% and the results for this test were expected to include a large amount of false negatives [151]. A rapid treponemal test was used for syphilis diagnosis (SD Bioline, Syphilis 3.0, Standard Diagnostics, Inc. Korea) in parallel with a non-treponemal test (RPR, Spinreact, Spain). A double positive result was considered active syphilis. All discrepant results were tested with a classical treponemal test (TPHA, Spinreact, Spain). A positive (classical) TPHA result was then considered old treated syphilis and a negative TPHA result negative for syphilis. The Nugent Gram stain testing was done at the University lab in Butare with quality control supervised by Ghent University. HerpeSelect-2
ELISA (Focus Technologies, USA) was used for HSV-2 antibody testing and was performed at the National Reference Laboratory (LNR), Kigali, Rwanda. An index value of ≥3.5 was considered positive for HSV-2 antibodies, an index value ≤1.1 negative and values in between equivocal. The sensitivity and specificity of this test is between 96% and 100% according to the insert. The LNR has a system of internal and external quality control. Chlamydial antibodies were tested with 2 EIA assays (Anilabsystems, Finland and Vircell, USA). These two assays showed concurrent results in 86% of cases. In final reporting only the results of Anilabsystems were taken into account as this is the best performing test compared to MIF assays which are the golden standard and most used in the literature [152]. The PCR test (Abbott Laboratories, USA) for NG and CT was performed in Ghent University and according to the insert has a sensitivity and specificity for CT of 95% and 99.2% respectively and for NG of 98% and 99.7% respectively.

**Focus group discussions**

The five FGDs included a total of 21 female and 20 male participants, not necessarily belonging to the same couple, and were held in the local language, Kinyarwanda. FGD participants provided separate informed consent for FGD participation. A discussion guide was developed based on current knowledge of consequences of infertility, which included questions about relationships with partner and in-laws, experiences in the community, economic aspects, issues related to continuing the family line and relationships with ancestors, and emotional status. In addition, in each group, the effect of the gender-specific infertility diagnosis, received during the course of the study, on their relationship was explored. The role of religion did not figure in the interview guide but emerged as a very important cross-cutting theme. Qualitative FGD data on marital relationships and economic aspects were complemented with data from the quantitative survey. FGD data were also complemented with medical chart notes that were recorded by study staff during follow-up visits with the infertile couples after the infertility investigations and treatments.

All discussions were tape-recorded, transcribed verbatim in Kinyarwanda, and translated from Kinyarwanda into English. The transcripts and the medical chart notes were then coded and analysed using Nvivo 8 (QSR International, Melbourne, Australia).

**STATISTICAL ANALYSIS**

**Variables for case control study**

**Outcomes:**

As this is a case-control study the outcome is being a case, being a woman or a man in an infertile relationship. Although infertility is a problem on the couple level, in most analyses the unit of analysis was not the couple. This was mainly because of practical reasons: there were many missing male partners which would have made the sample small. Several subgroups among the cases can be identified: women with and without tubal factor infertility, men with and without male factor infertility, women with primary and secondary infertility, and men in primary or secondary infertile relationships.
Exposures:
The exposure variables can be ordered along the following categories

- **sexual behaviour:**
  - men and women age at first intercourse, lifetime number of partners, number of partners last year, number of partners last 3 months, number of current partners, ever separated or divorced, partners fidelity, condom use
  - women only: polygamous marriage, sexual violence, domestic violence, transactional sex

- **reported RTI/STIs:** (men and women): ever had STI symptoms, ever been treated for STIs, has partner ever had STIs

- **measured RTI/STIs:**
  - men and women: serology for HSV-2, syphilis and HIV
  - women only: Chlamydia serology, Trichomoniasis (wet mount), NG/CT(PCR), BV according to Amsel and Nugent criteria.

- **occupational and lifestyle factors:**
  - men and women: smoking, alcohol, weight
  - men only: toxic factor

- **obstetric events** (women with secondary infertility only): antenatal care, birth attendant, place of delivery, complications at birth, caesarean sections, unwanted pregnancies, induced abortions, curettages

- **testicular pathology** (men only): orchitis, undescended testes, testicular or inguinal surgery

Potential confounders
Education, age, occupation, income and marital status were considered a priori confounders. The aim of this study was not to study socio-economic risk factors for infertility. Since there was no matching done for age or other socio-economic factors we controlled for them in the analysis.

Diagnostic criteria
- **Primary infertility:** is defined as no conception after one year of unprotected intercourse in someone who never had any conceptions
- **Secondary infertility:** is defined as the inability to conceive after one year in someone who had at least one pregnancy (not necessarily a live birth). If the woman had breastfed a previous infant then exposure to pregnancy is calculated from the end of the period of lactational amenorrhoea.
- **Tubal factor infertility:** Women were considered to have tubo-peritoneal infertility if HSG and/or laparoscopy had shown tubal obstruction and/or peritoneal adhesions
- **Male factor infertility**: Men were considered to have a male factor if their sperm motility (total motility less than 40%) and concentration (less than 15 million per ml) was abnormal according to the new WHO reference values [153].

**Outcomes for cross-sectional study of treatment-seeking behaviour**

- Perceptions of infertility causes among infertile men and women
- Treatment-seeking behaviour among infertile men and women
- Factors associated with seeking medical care among infertile men and women
- The response of health providers towards infertile couples seeking care

**Outcomes for prospective study**

- Result of infertility investigations
- Predictors for tubal infertility
- Pregnancy rates after 18 months follow-up
- Predictors for pregnancy

**Outcomes of qualitative study**

- Consequences of female and/or male factor infertility for women and men

**Statistical methods**

*Missing data*

For each data point, participants could have: an outcome/response; a missing value; or “NA/not applicable.” Questions or data points that are skipped purposefully (i.e., because the question/response was “not applicable”) were coded as such.

There are 3 main reasons for missing data:

- Study staff left an item on the CRF blank in error. Study monitors and data managers tried to minimize the extent of this problem by flagging such missing items during monitoring. In general proportion of these missing data is very small, maximum 2 observations per variable.

- The participant either refused to answer the question or refused to undergo a clinical procedure or laboratory test or in the case of HSG the participant became pregnant before the exam was carried out. In total 39 women did not have HSG and 28 men did not have a semen analysis otherwise patients did not refuse questions or procedures.

- Change in study procedure: Due to logistic problems the first 60 enrolled participants did not have blood taken on their first visit and a number of these were impossible to trace afterwards; hence serology results for HIV (13 missing), HSV-2 (20 missing) and CT (7 missing) are missing in these. Furthermore the questionnaire was changed (a few questions were added) after 60 participants
and in some of those who never came back the answer to these added questions were missing. This concerns the question about income for which 16 observations are missing.

Where a participant had missing data for a specific item, she/he was removed from the question sample for calculation of percentages or other summary measures. If a participant was missing a response for one question, she/he was still included in samples for any other questions for which she provided data.

For randomly missing data (study staff left an item blank in error) the cases were omitted in the analysis (univariate and multivariate).

Information on missing data was presented as a footnote with the appropriate tables when presenting data in each paper.

Could the missing data have introduced bias? For the first and third type of missing data probably not since they were randomly missing data and a small proportion. For the second type, it is possible that the men or women refusing infertility investigations were more likely to be the ones with a problem. On the other hand among the men refusing semen analysis were many men claiming children in another relationship and among the women without HSG many became pregnant indicating a high probability of healthy tubes among them. In conclusion it is hard to say anything about the direction of the bias the missing infertility investigations could have introduced.

**General methodology**

Data collected during interviews and laboratory investigations were single entered, verified and cleaned using MS Access 2000 (Microsoft, Seattle, USA). Intercooled Stata 9.2 (Stata Corporation, College Station, Texas, USA) was used for statistical analysis.

Categorical variables were expressed as percentages. Continuous data were presented as means with the standard deviation or medians with the inter-quartile range depending on the symmetry of the observed distribution. Most variables were transformed in binary variables.

Socio-demographic characteristics were compared using Chi-squared tests or Mann-Whitney U-tests.

Univariate analysis: 2X2 tables to look for crude association between each exposure and the outcome, OR was used to measure association.

Logistic regression was used to adjust association for a priori confounders.

If independent associations were looked for, all predictors with association (cut-off p-value 0.2) were included in a logistic regression model. For some analyses a forward logistic regression model was used and variables were retained in multivariable models when they affected the association (odds ratio (OR)) with 10% or more.

In some analyses composite variables were constructed to reduce the number of variables in the logistic regression model.

Population Attributable Fractions (PAF%) were calculated using the following formula: \( \frac{pe(AOR-1)}{AOR} \) with pe the proportion of cases that is exposed to risk factor.

**Specific analyses**

These are described in the methods section of the different papers.
ETHICS

Ethics committee
Prior to enrolment of first participant the protocol was approved by the CNLS research committee and two ethics committees the National Ethics Committee of Rwanda, and the University of Ghent Ethics Committee in Ghent, Belgium.

Informed consent
Written informed consent was obtained from all study participants. Consent was always obtained before any study procedures took place. If an eligible individual was unable to sign his/her name, they provided a thumbprint in the presence of an independent witness.

Confidentiality
Every attempt was made to maintain the confidentiality of study participants. In this study all participants were assigned a unique personal identification number for use on all study forms containing interview, clinical, and laboratory data. This identification number was linked to women’s personal information in a central registry. Documents containing the names and/or signatures of participants (such as consent forms and locator information) were kept separately from all other study documents containing participants’ identification numbers only. Study results were presented as aggregated data, with no personal information.

Burdens and benefits to participants
Benefits for all participants included free HIV counselling and testing and free infertility investigations. Participants benefitted from free diagnosis and treatment of several common STIs/RTIs and cervical dysplastic lesions. Participants received treatment, partner notification services, and referrals as appropriate for their medical and psychosocial needs.

Participants could withdraw from study participation at any time, for any reason, without loss of benefits or services to which they may be entitled as part of normal health care.

Compensation
Participants were compensated for their travel costs and time spent in the clinic in the amount of 4000 FRW for the first visit. The infertile couples also received monetary compensations for the second visit (4000 FRW).

Treatment and referrals
Unfortunately for most causes of infertility no appropriate treatment was available in Rwanda. For ovulation disorders treatment was prescribed and patients were followed up in the unit if they chose to, otherwise referral to doctor of choice was made. For surgical procedures (e.g. curettage or tubal
surgery) the patient were referred to the department of gynaecology in KUTH or any other hospital of choice. Women who were pregnant were referred to an antenatal clinic. The study did not bear the costs for the latter or other illnesses that required treatment (apart from the previously mentioned), however study staff always tried to refer participants to the appropriate health care provider when necessary. HIV positive patients were referred to the national HIV program.

**DISSEMINATION OF RESULTS**

In Rwanda dissemination of results was done through presentations on the KUTH research meetings, on symposiums organised by Projet Ubuzima, on governing council meetings of Projet Ubuzima, in the yearly conference of the Centre National de Lutte contre le SIDA (CNLS) on HIV/AIDS in 2009 in Kigali and in the yearly European and Developing countries Clinical Trials Partnership (EDCTP) workshops in 2008, 2009 and 2010 held in Mombasa, Kenya and Kigali, Rwanda. With these meetings a great number of local policymakers, government officials, nongovernmental organisations (NGO) workers and medical staff were reached.

Results were also made available through international conferences:

- Sexual and Reproductive Health Research: making a difference, International Symposium, Monasterium Poortakker, Ghent Belgium, 19/10/2007 (oral presentation)
- Expert meeting: Infertility and developing countries: hidden and forbidden desires, Arusha, Tanzania, 15-17/12/2007 (oral presentation)
- Doelen congres 2009, Doelen, Rotterdam, The Netherlands, 4-6 March 2009 (oral presentation)
- EDCTP annual meeting, Arusha, Tanzania, 12-14/10/2009 (poster presentation)
- Royal College of Obstetricians and Gynaecologists (RCOG) annual scientific meeting, Abu Dhabi, 7-9/12/2009 (oral presentation)
- International Aids (IAS) conference Vienna, 2010 (poster presentation)
- Doelen congres 2011, Doelen Rotterdam, The Netherlands, April 2011 (oral presentation)

The following papers have been published or are submitted for publication:

**Published**


5. N Dhont, J van de Wijgert, G Coene, A Gasarabwe and M Temmerman. ‘Mama and papa nothing’: living with infertility among an urban population in Kigali, Rwanda. Accepted for publication in Human Reproduction

6. N. Dhont, J. Vyankandondera, J. van de Wijgert, A. Gasarabwe, M. Temmerman Results of infertility investigations and follow-up among 312 infertile women and their partners in Kigali, Rwanda. Accepted for publication in Tropical Doctor

**In Review or Revision**

7. N Dhont, J van de Wijgert, S Luchters, L De Naeyer, J Vyankandondera, M Temmerman. Risk factor profile of women with secondary infertility. Revision submitted to BMC Women’s Health
RESULTS
SEXUAL VIOLENCE, HSV-2 AND HIV ARE IMPORTANT PREDICTORS FOR INFERTILITY IN RWANDA
Sexual violence, HSV-2 and HIV are important predictors for infertility in Rwanda

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BACKGROUND: In order to formulate cost-effective health interventions aimed at preventing infertility it is necessary to identify modifiable risk factors for infertility in sub-Saharan Africa. This case–control study examined potential predictors and their population attributable fraction (PAF%) for various infertility types including lifestyle factors, sexual behaviour and reproductive tract infections (RTIs).

METHODS: Sexually active women aged 21–45 year presenting with infertility problems at the infertility clinic of the Kigali University Teaching Hospital (n = 312), and fertile controls who recently delivered (n = 283) were surveyed together with their male partners. Participants were interviewed about socio-demographic characteristics, sexual behaviours and lifestyle factors, and were tested for HIV and RTIs.

RESULTS: Variables significantly associated with tubal infertility were history of sexual violence [adjusted odds ratio (AOR) 2.41; 95% CI 1.36–4.25]; positive HIV (AOR 2.41; 95% CI 1.36–4.25), herpes simplex virus type 2 (HSV-2; AOR 1.67; 95% CI 1.03–2.71) and Chlamydia trachomatis serology (AOR 1.78; 95% CI 0.99–3.21), and current bacterial vaginosis by Amsel criteria (AOR 1.97; 95% CI 1.12–3.47). Among men, male factor infertility was associated with positive HIV (AOR 2.43; 95% CI 1.31–5.23) and HSV-2 serology (AOR 1.71; 95% CI 1.02–2.87) and current urologic abnormalities (AOR 2.38; 95% CI 1.01–5.31). Positive HSV-2 serostatus carried the greatest PAF% (26%) for tubal infertility, followed by positive HIV serostatus (20%) and history of sexual violence (17%).

CONCLUSIONS: Although temporal relationships are difficult to ascertain, history of sexual violence, HSV-2 infection and HIV infection are important predictors of infertility in Rwanda.

Key words: infertility / tubal factor / male factor / Africa / predictors

Introduction

Infertility is affecting a large number of couples in sub-Saharan Africa (SSA), with a prevalence of up to 29% in certain regions (Larsen, 2000; Boxin et al., 2007). The consequences of infertility for the couples involved are often more severe in traditional societies, where motherhood is more important for the woman’s status, than in Western societies (Geertes, 1997; Sundby, 1997). Since modern infertility treatment is expensive, prevention of infertility should be the main focus of action in countries with limited resources.

A WHO multicentre investigation of 8500 infertile couples throughout the developed and developing world found that most cases of infertility in African couples are infection-induced and therefore possibly preventable (Cates et al., 1985). Pelvic inflammatory disease (PID) can lead to damaged fallopian tubes in women and sexually transmitted infections (STIs) can lead to vas deferens blockage and decreased sperm quality in men (Pellati et al., 2008). Investigations of risk factors for infertility have mostly been limited to secondary analyses of Demographic Health Surveys and World Fertility Surveys, which have indicated that a history of high-risk sexual behaviour, such as multiple marriages and unions and early age at first sexual intercourse, put women at substantial risk for infertility (Ericksen and Brunette, 1996; Larsen, 2003). Studies of risk factors for male infertility in SSA have been very limited. One case–control study in Nigeria found that infertility in men is associated with various proxies of STIs and poor healthcare-seeking behaviour for STIs.
Fallopian tube occlusion. Neisseria gonorrhoeae and Chlamydia trachomatis are thought to be the major cause of PID and tubal infertility in SSA. It remains unclear which micro-organisms contribute to infertility as a risk factor for infertility because there are no good markers for past gonococcal infection. Other reproductive tract pathogens that have been associated with tubal disease are bacterial vaginosis (BV) related organisms, herpes simplex virus type 2 (HSV-2) and HIV (Gaudoin et al., 1999; Hettmann et al., 2008). The former two have not been examined in relation to infertility in an African population. A few studies in SSA have found a higher prevalence of HIV in infertile women and there is some evidence that HIV has a fertility-reducing effect (Favot et al., 1997; Gray et al., 1998).

The design of cost-effective health interventions aimed at preventing infertility requires identification of modifiable risk factors for infertility in SSA. We conducted a case–control study in Kigali, Rwanda, to examine potential predictors and their population attributable fraction (PAF%) for infertility.

### Methods

#### Subjects and settings

Between November 2007 and May 2009, an infertility research clinic was opened at the Kigali University Teaching Hospital in Rwanda, and infertile women were recruited mainly through word of mouth. To be eligible for participation in the study, women self-reported to be infertile needed to be between 21 and 45 years of age, residing in Kigali, willing to undergo HIV testing and having had sexual intercourse at least once in the last 2 weeks. Refusal to participate in the study did not influence access to further services. For this analysis, infertility was defined as having had regular unprotected intercourse for 1 year or more without conception with at least one regular partner, and included both primary and secondary infertility. Fertile controls were defined as non-pregnant women who recently (between 6 and 18 months ago) delivered. Controls were recruited at the level of the community, as no appropriate control group could be selected at the hospital. A list of all residential neighbourhoods (known as mutungudu) from where the infertile couples originated was compiled (120 mutungudus in total). Fourteen neighbourhoods were randomly selected from this list by blindly hand-picking numbers from a bowl. Community mobilizers in these neighbourhoods visited all families to identify potential eligible candidates and explained that they would receive free cervical cancer screening and treatment if indicated. This service was offered to both cases and controls.

Male partners of the enrolled participants were also asked to participate on a separate occasion, using a written invitation given to the woman at the end of her study visit. The study was approved by the National Ethics Committee of Rwanda, the Ethics Committee of the University Hospital Ghent and the Centre National de Lutte contre le Sida (CNL5) in Rwanda.

#### Statistical analysis

Data collected during interviews and laboratory investigations were single entered, verified and cleaned using MS Access 2000 (Microsoft, Seattle, WA, USA). Intercooled Stata 9.2 (Stata Corporation, College Station, TX, USA) was used for statistical analysis. Socio-demographic characteristics of infertile and fertile women and their partners were compared using \chi^2-tests or Mann–Whitney U-tests. The relationships between selected covariates and infertility were examined by comparing all infertile women (regardless of infertility type) and the subgroups of infertile women with and without tubal factor with fertile women and all infertile men and the subgroups of infertile men with and without male factor with fertile men. Within the infertility relationships, women with and without a tubal factor, and men with and without a male factor were also compared. Women were considered to have tubo-peritoneal infertility if HSG and/or laparoscopy had shown tubal obstruction and/or peritoneal adhesions. Men were considered to have a male factor if their sperm motility and concentration was abnormal according to the new WHO reference values (Cooper et al., 2010). Logistic regression was used to assess associations between each predictor of interest and infertility whereas controlling for age, marital status and educational level. In these initial models, seven measures of sexual behaviour for women and five measures for men were assessed. Engaging in sex before 15 years of age was considered a risk factor for women because PID at a young age is more damaging for the immature genital tract. The median age at first sexual intercourse in urban Rwanda is 20 years for men (Ministry of Health, 2006); we therefore chose the cut-off value of 20 years for men. Ever transactional sex was defined as ever having received money or gifts in exchange for sex. The cut-off values for alcohol use were based on distribution of the answers.
and were at least one and nine units a week for women and men, respectively. All participants were weighed and measured at enrolment and obesity was defined as a body mass index (BMI) more than 25.

Predictors with a moderate association with infertility after controlling for age, education and marital status (P-value of < 0.2) were fitted in a final logistic regression model to assess their independent relationship with tubal and male factor infertility. To reduce the number of covariates, composite variables were constructed for high-risk sexual behaviour. For women, high-risk sexual behaviour was defined as age at first sexual intercourse before 15 years and/or ever had a union dissolution and/or ever engaged in transactional sex; for men, it was defined as age at first sexual intercourse before 20 years and/or ever had a union dissolution. The number of lifetime sexual partners was not included, because we believe that a high number of lifetime partners may be a consequence of infertility as much as a risk factor. The same applies to lack of condom use. PAF% were calculated for selected risk factors using the following formula: \( \text{PAF%} = \frac{\text{p}\text{a}\text{l}\text{e} - \text{p}\text{a}\text{l}\text{e}}{1} \) where p is the proportion of cases that is exposed to risk factor.

**Results**

Of a total of 339 potentially infertile women who presented to the clinic, 312 were confirmed eligible and enrolled. Of 407 fertile women identified in the community, 352 (86%) came to the clinic and 312 were confirmed eligible and enrolled. Of the 55 non-responders, half stated having no time to come to the clinic, one-third were afraid of the physical examinations and the remainder did not state a reason. Educational level and employment did not differ between responders and non-responders. Male partners of 81% of the infertile women (254 partners) and 61% of the fertile women (189 partners) agreed to participate. Twenty-nine women in the infertile group were excluded from the analysis because they tried to conceive for their last pregnancy for more than 12 months, for a final sample size of 283 women and 170 male partners in fertile relationships and 312 women and 254 male partners in infertile relationships.

Women in infertile relationships were more likely than women in fertile relationships to be married, to be older, and to have an occupation and income (Table I). Infertile women without a tubal factor were better educated than fertile women and women with a tubal factor. All unmarried participants in both groups reported to have a steady sexual partner, and in most cases, this partner spend the night with them most of the time. Men in infertile relationships were older, better educated and had a higher income than men in fertile relationships.

All sexual behaviour covariates, except ever use of condoms, were associated with tubal infertility after controlling for age, marital status and educational level (Table II). Non-tubal factor infertility was associated with a history of sexual violence and more than three lifetime sexual partners but not with other sexual behaviour covariates. All measured reproductive tract infections (RTIs) were associated with tubal factor infertility (Table II). Apart from HIV, none of the RTIs was significantly associated with non-tubal infertility (Table II). Alcohol use and being overweight were not associated with infertility. Smoking was associated with tubal infertility but not with non-tubal infertility. Within the group of infertile women all measures of high-risk sexual behaviour, apart from transactional sex and all measured RTIs, with the exception of positive Chlamydia serostatus, were associated with tubal pathology (data not shown). Sexual violence (AOR 2.41; 95% CI 1.36–4.25), positive HIV serostatus (AOR 2.41; 95% CI 1.36–4.25), positive HSV-2 serostatus (AOR 1.67; 95% CI 1.03–2.71) and current BV by Amsel criteria (AOR 1.97; 95% CI 1.12–3.47) were significantly associated with tubal infertility in the final multivariable logistic regression model for women (Table IV).

Male factor infertility was associated with having had a union dissolution, never using condoms, positive HIV and HSV-2 serology, and current urological abnormalities after controlling for age, marital status and educational level (Table III). In the subset analysis of men with normal sperm analysis, infertility was associated with male circumcision and HIV. Lifestyle factors (smoking, alcohol and BMI) and reported STIs were not associated with infertility in men. Within the group of infertile men, no significant associations were found with abnormal semen analysis (data not shown). In the final logistic regression model, infertility was associated with positive HIV serostatus (AOR 2.43; 95% CI 1.31–5.23), positive HSV-2 serostatus (AOR 1.71; 95% CI 1.02–2.87) and urologic abnormalities (AOR 2.32; 95% CI 1.01–5.31) (Table IV).

Positive HSV-2 serostatus carried the greatest PAF% (26%) for tubal infertility, followed by positive HIV serostatus (20%), a history of sexual violence (17%), BV by Amsel criteria (12%), high-risk sexual behaviour (9%), positive Chlamydia serostatus (9%) and lifestyle (9%) (Table V). Positive HSV-2 and HIV serology accounted for the largest PAF% for male factor infertility in men (22 and 13%, respectively).

**Discussion**

We found that a history of sexual violence, HIV infection and HSV-2 infection contribute most to infertility in Rwandan women, especially to tubal factor infertility. In men, HIV and HSV-2 infection were the most important risk factors for male factor infertility. Lifestyle factors could not predict infertility in our population.

In our study, a history of sexual violence contributed more to infertility than other measures of high-risk sexual behaviour. It is the first time that a history of sexual violence is found to be associated with infertility. Women in an infertile relationship had experienced three times more sexual violence during their lifetime than fertile women. Although we did not specifically ask, it is possible that many of these women were raped during the genocide of 1994 in Rwanda. Although the association between a history of sexual violence and tubal factor infertility can easily be explained, the association with non-tubal infertility is somewhat puzzling. This may be due to the fact that tubal pathology was diagnosed using HSG as opposed to the gold standard method laparoscopy; HSG is not a reliable test for tubal patency with only 65% sensitivity and 83% specificity (Crosignani and Rubin, 2000). Therefore, the non-tubal infertility group could have included an unknown number of cases of undiagnosed tubal infertility. In addition, psychological trauma resulting from sexual violence could have led to infertility through anovulation or sexual dysfunction. However, we did not identify an association between past sexual violence and current menstrual irregularities.

The association of HSV-2 with tubal factor infertility but not with non-tubal factor infertility, and its association with tubal pathology within the group of infertile women, suggest that HSV-2 plays a role in tubal pathogenesis. Prior studies in Western countries have
Table I Baseline characteristics of enrolled women and their male partners in fertile and infertile relationships and by infertility diagnosis in Kigali, Rwanda.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fertile relationship (n = 283), n (%)</th>
<th>Infertile relationship (n = 312), n (%)</th>
<th>P-value*</th>
<th>Tubo-peritoneal factor (n = 189), n (%)</th>
<th>P-value*</th>
<th>No tubo-peritoneal factor (n = 90), n (%)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>27 (24–31)</td>
<td>30 (27–35)</td>
<td>&lt;0.001</td>
<td>31 (27–36)</td>
<td>&lt;0.001</td>
<td>30 (26–35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to primary school</td>
<td>213 (75)</td>
<td>225 (72)</td>
<td>0.38</td>
<td>145 (77)</td>
<td>0.72</td>
<td>58 (64)</td>
<td>0.045</td>
</tr>
<tr>
<td>Post-primary school</td>
<td>70 (25)</td>
<td>87 (28)</td>
<td></td>
<td>44 (23)</td>
<td></td>
<td>32 (36)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>170 (60)</td>
<td>135 (43)</td>
<td>&lt;0.001</td>
<td>88 (47)</td>
<td>0.015</td>
<td>32 (36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Married</td>
<td>112 (40)</td>
<td>176 (56)</td>
<td></td>
<td>100 (53)</td>
<td></td>
<td>58 (64)</td>
<td></td>
</tr>
<tr>
<td>Separated, divorced or widowed</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td></td>
<td>1 (0)</td>
<td></td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Not employed</td>
<td>155 (55)</td>
<td>92 (29)</td>
<td>&lt;0.001</td>
<td>55 (29)</td>
<td>&lt;0.001</td>
<td>28 (31)</td>
<td>&lt;0.001</td>
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<tr>
<td>Employed</td>
<td>128 (45)</td>
<td>220 (70)</td>
<td></td>
<td>134 (71)</td>
<td></td>
<td>62 (69)</td>
<td></td>
</tr>
<tr>
<td>Income ($/day)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 USD</td>
<td>159 (56)</td>
<td>98 (33)</td>
<td>&lt;0.001</td>
<td>57 (31)</td>
<td>&lt;0.001</td>
<td>32 (38)</td>
<td>0.008</td>
</tr>
<tr>
<td>&lt; 1 USD</td>
<td>26 (9)</td>
<td>79 (27)</td>
<td></td>
<td>58 (32)</td>
<td></td>
<td>13 (15)</td>
<td></td>
</tr>
<tr>
<td>1–4 USD</td>
<td>88 (31)</td>
<td>85 (29)</td>
<td></td>
<td>44 (24)</td>
<td></td>
<td>31 (37)</td>
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</tr>
<tr>
<td>5 USD or more</td>
<td>10 (4)</td>
<td>34 (11)</td>
<td></td>
<td>23 (13)</td>
<td></td>
<td>8 (10)</td>
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<tr>
<td><strong>Males</strong></td>
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</tr>
<tr>
<td>Age, median (IQR)</td>
<td>31.5 (27–38)</td>
<td>34 (30–40)</td>
<td>0.001</td>
<td>35 (30–41)</td>
<td>&lt;0.001</td>
<td>34 (30–38)</td>
<td>0.07</td>
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<td>Education level</td>
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</tr>
<tr>
<td>Up to primary school</td>
<td>132 (78)</td>
<td>151 (59)</td>
<td>&lt;0.001</td>
<td>84 (58)</td>
<td>&lt;0.001</td>
<td>52 (63)</td>
<td>0.02</td>
</tr>
<tr>
<td>Post-primary school</td>
<td>38 (22)</td>
<td>103 (41)</td>
<td></td>
<td>60 (42)</td>
<td></td>
<td>30 (37)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Single</td>
<td>85 (50)</td>
<td>118 (46)</td>
<td>0.57</td>
<td>68 (47)</td>
<td>0.5</td>
<td>39 (48)</td>
<td>0.72</td>
</tr>
<tr>
<td>Married</td>
<td>85 (50)</td>
<td>135 (53)</td>
<td></td>
<td>75 (52)</td>
<td></td>
<td>43 (52)</td>
<td></td>
</tr>
<tr>
<td>Separated, divorced or widowed</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td></td>
<td>1 (1)</td>
<td></td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Income ($/day)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 USD</td>
<td>2 (1)</td>
<td>1 (0)</td>
<td>0.03</td>
<td>1 (1)</td>
<td>0.14</td>
<td>0 (0)</td>
<td>0.17</td>
</tr>
<tr>
<td>&lt; 1 USD</td>
<td>12 (7)</td>
<td>31 (13)</td>
<td></td>
<td>19 (14)</td>
<td></td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>1–4 USD</td>
<td>120 (71)</td>
<td>138 (58)</td>
<td></td>
<td>83 (60)</td>
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<td>45 (58)</td>
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</tr>
<tr>
<td>5 USD or more</td>
<td>36 (21)</td>
<td>68 (29)</td>
<td></td>
<td>35 (25)</td>
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<td>23 (30)</td>
<td></td>
</tr>
</tbody>
</table>

*For all three columns of P-values: P-values are derived from comparison with women in fertile relationship.
†Sixteen missing values for infertile women and men.
### Table II: Predictors for tubal factor, non-tubal factor and infertility of any cause in Rwandan women.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All fertile women (n = 283), n (%)</th>
<th>All infertile women (n = 312), n (%)</th>
<th>Age, marital status and education adjusted OR (95% CI)</th>
<th>Infertile with tubal factor (n = 189), n (%)</th>
<th>Age, marital status and education adjusted OR (95% CI)</th>
<th>Infertile without tubal factor (n = 90), n (%)</th>
<th>Age, marital status and education adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sexual history</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime sex partners 3 or more</td>
<td>45 (16)</td>
<td>140 (45)</td>
<td>6.01 (3.87–9.31)</td>
<td>98 (52)</td>
<td>7.30 (4.50–11.88)</td>
<td>31 (34)</td>
<td>4.06 (2.22–7.42)</td>
</tr>
<tr>
<td>Ever had a union dissolution&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31 (11)</td>
<td>61 (20)</td>
<td>1.62 (0.97–2.73)</td>
<td>49 (26)</td>
<td>2.05 (1.18–3.55)</td>
<td>7 (8)</td>
<td>0.82 (0.33–2.08)</td>
</tr>
<tr>
<td>Ever transactional sex</td>
<td>16 (6)</td>
<td>26 (8)</td>
<td>2.75 (1.36–5.57)</td>
<td>18 (9)</td>
<td>2.81 (1.29–6.12)</td>
<td>5 (6)</td>
<td>2.38 (0.84–7.94)</td>
</tr>
<tr>
<td>Age at first intercourse &lt; 15</td>
<td>22 (8)</td>
<td>32 (10)</td>
<td>1.81 (0.99–3.31)</td>
<td>24 (13)</td>
<td>2.13 (1.10–4.11)</td>
<td>3 (3)</td>
<td>0.43 (0.12–1.55)</td>
</tr>
<tr>
<td>Age at first intercourse &gt; 30</td>
<td>3 (1)</td>
<td>11 (4)</td>
<td>0.98 (0.26–3.86)</td>
<td>4 (2)</td>
<td>0.54 (0.11–2.68)</td>
<td>4 (4)</td>
<td>2.02 (0.40–10.24)</td>
</tr>
<tr>
<td>Never used condoms</td>
<td>94 (33)</td>
<td>161 (52)</td>
<td>1.67 (0.64–4.14)</td>
<td>84 (44)</td>
<td>1.21 (0.80–1.83)</td>
<td>56 (62)</td>
<td>2.66 (0.73–2.86)</td>
</tr>
<tr>
<td>Ever exposed to sexual violence&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28 (10)</td>
<td>79 (25)</td>
<td>3.02 (1.85–4.91)</td>
<td>54 (29)</td>
<td>3.39 (2.00–5.74)</td>
<td>17 (19)</td>
<td>2.01 (1.01–4.00)</td>
</tr>
<tr>
<td>Past high-risk sexual behaviour&lt;sup&gt;c&lt;/sup&gt;</td>
<td>57 (20)</td>
<td>100 (32)</td>
<td>2.17 (1.43–3.28)</td>
<td>74 (39)</td>
<td>2.50 (1.43–3.28)</td>
<td>15 (17)</td>
<td>1.06 (0.55–2.06)</td>
</tr>
<tr>
<td><strong>Measured RTIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV serology positive&lt;sup&gt;d&lt;/sup&gt;</td>
<td>39 (14)</td>
<td>98 (32)</td>
<td>3.61 (2.30–5.68)</td>
<td>65 (35)</td>
<td>4.01 (2.43–6.61)</td>
<td>20 (22)</td>
<td>2.63 (1.36–5.10)</td>
</tr>
<tr>
<td>HSV-2 serology positive&lt;sup&gt;e&lt;/sup&gt;</td>
<td>115 (41)</td>
<td>180 (59)</td>
<td>2.15 (1.50–2.9)</td>
<td>122 (66)</td>
<td>2.71 (1.77–4.5)</td>
<td>40 (45)</td>
<td>1.27 (0.76–2.13)</td>
</tr>
<tr>
<td>Chlamydia serology positive&lt;sup&gt;f&lt;/sup&gt;</td>
<td>44 (16)</td>
<td>57 (19)</td>
<td>1.80 (1.22–2.88)</td>
<td>38 (20)</td>
<td>2.11 (1.24–3.59)</td>
<td>14 (16)</td>
<td>1.41 (0.70–2.82)</td>
</tr>
<tr>
<td>BV by Amsel criteria</td>
<td>39 (14)</td>
<td>72 (23)</td>
<td>2.45 (1.54–3.90)</td>
<td>48 (25)</td>
<td>2.61 (1.56–4.38)</td>
<td>13 (14)</td>
<td>1.45 (0.71–2.90)</td>
</tr>
<tr>
<td>BV by Nugent criteria&lt;sup&gt;g&lt;/sup&gt;</td>
<td>127 (48)</td>
<td>158 (52)</td>
<td>1.44 (1.01–2.06)</td>
<td>103 (56)</td>
<td>1.68 (1.11–2.54)</td>
<td>35 (40)</td>
<td>0.92 (0.55–1.55)</td>
</tr>
<tr>
<td><strong>Lifestyle factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 25&lt;sup&gt;d&lt;/sup&gt;</td>
<td>66 (24)</td>
<td>87 (31)</td>
<td>1.34 (0.90–1.99)</td>
<td>54 (32)</td>
<td>1.45 (0.92–2.28)</td>
<td>24 (30)</td>
<td>1.18 (0.66–2.10)</td>
</tr>
<tr>
<td>Alcohol (any)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>80 (28)</td>
<td>72 (23)</td>
<td>0.82 (0.55–1.21)</td>
<td>54 (29)</td>
<td>1.06 (0.68–1.63)</td>
<td>12 (13)</td>
<td>0.42 (0.21–0.83)</td>
</tr>
<tr>
<td>Smoker (past and/or now)</td>
<td>24 (8)</td>
<td>54 (17)</td>
<td>2.12 (1.22–3.70)</td>
<td>39 (21)</td>
<td>2.39 (1.32–4.35)</td>
<td>11 (12)</td>
<td>1.65 (0.73–3.73)</td>
</tr>
<tr>
<td>Lifestyle&lt;sup&gt;i&lt;/sup&gt;</td>
<td>136 (48)</td>
<td>166 (53)</td>
<td>1.12 (0.80–1.58)</td>
<td>111 (59)</td>
<td>1.38 (0.93–2.05)</td>
<td>42 (47)</td>
<td>0.91 (0.55–1.49)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Union dissolutions include all separations from previously cohabiting partners and exclude all union dissolutions which were reported to be a consequence of infertility.

<sup>b</sup>Includes sexual coercion by a stranger and/or a family member but not sexual coercion by an intimate partner.

<sup>c</sup>Composite variable for women: age first intercourse before 15 and/or marital dissolutions and/or ever engaged in transactional sex.

<sup>d</sup>HIV: 6 missing values infertiles; HSV-2: 2 missing values fertiles, 8 missing values infertiles; Chlamydia: 7 missing values infertiles; BV: 19 missing values fertiles, 7 missing values infertiles; BMI: 3 missing values fertiles, 32 missing values infertiles.

<sup>e</sup>Cut-off value based on distribution of the answers.

<sup>f</sup>Composite variable combining using alcohol more than 1 unit a day and/or having BMI > 25 and/or ever smoked.

<sup>g</sup>Tubal assessment was completed in 279 of 312 women in infertile relationships with 189 showing tubal pathology.

BV: bacterial vaginosis; BMI: body mass index.
positive HSV-2 serostatus was only weakly associated with abnormal
pathogen in male factor infertility as well. Within the infertile men,
not with non-male factor infertility, suggesting a causal role of this
study, HSV-2 was also associated with male factor infertility but
inflammation facilitates tubal scarring (Cherpes
tract, and whether HSV-2-related genital immune activation and
tates movement of bacteria from the lower to the upper genital
Further research is needed to clarify whether HSV-2 infection facili-
tes tubal obstruction, but its direct effects on PID pathogenesis remain
unclear (Lehtinen et al., 1985; Paavonen et al., 1985; Heinonen and
Meikinnen, 1994; Cherpes et al., 2006; Hettmann et al., 2008).
Further research is needed to clarify whether HSV-2 infection facili-
tates movement of bacteria from the lower to the upper genital tract, and whether HSV-2-related genital immune activation and
inflammation facilitates tubal scarring (Cherpes et al., 2006). In our
study, HSV-2 was also associated with male factor infertility but
not with non-male factor infertility, suggesting a causal role of this
pathogen in male factor infertility as well. Within the infertile men,
positive HSV-2 serostatus was only weakly associated with abnormal
semen analysis, but this may have been due to insufficient statistical
power.

In our study, HIV was consistently associated with all types of infer-
tility in both men and women. The association between infertility and
HIV has predominantly been documented in women but much less in
men (Favot et al., 1997; Ikechebelu et al., 2002; Adeiyun et al., 2008).
Both tubal and non-tubal infertility were significantly associated with
HIV in our study, but the association with tubal infertility was stronger.
Within the infertile women, HIV infection was also significantly associ-
ated with tubal pathology. Positive HIV and HSV-2 serostatus could be
markers for other past STIs known to be tubal pathogens such as C.
trachomatis and G. neisseria. We could not measure past

Table III  Predictors of male factor, non-male factor and infertility of any cause in Rwandan men.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fertile relationship (n = 170), n (%)</th>
<th>Infertile relationship (n = 254), n (%)</th>
<th>Age, marital status and education adjusted OR (95% CI)</th>
<th>Male factor (n = 144), n (%)</th>
<th>Age, marital status and education adjusted OR (95% CI)</th>
<th>No male factor (n = 82), n (%)</th>
<th>Age, marital status and education adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime sex partners 4 or more</td>
<td>72 (42)</td>
<td>133 (52)</td>
<td>1.31 (0.87–2.00)</td>
<td>73 (51)</td>
<td>1.17 (0.72–1.88)</td>
<td>45 (55)</td>
<td>1.54 (0.89–2.68)</td>
</tr>
<tr>
<td>Ever had an union dissolution</td>
<td>16 (9)</td>
<td>55 (22)</td>
<td>2.20 (1.15–4.18)</td>
<td>34 (24)</td>
<td>2.17 (1.08–4.34)</td>
<td>15 (18)</td>
<td>2.16 (0.90–5.20)</td>
</tr>
<tr>
<td>Age at first intercourse &lt; 20</td>
<td>70 (41)</td>
<td>118 (46)</td>
<td>1.32 (0.87–1.98)</td>
<td>62 (43)</td>
<td>1.20 (0.75–1.93)</td>
<td>42 (51)</td>
<td>1.53 (0.88–2.63)</td>
</tr>
<tr>
<td>Circumcised</td>
<td>40 (23)</td>
<td>87 (34)</td>
<td>1.37 (0.86–2.18)</td>
<td>44 (31)</td>
<td>1.14 (0.67–1.94)</td>
<td>33 (40)</td>
<td>1.96 (1.08–3.54)</td>
</tr>
<tr>
<td>Never used condoms</td>
<td>45 (26)</td>
<td>87 (34)</td>
<td>1.51 (0.96–2.36)</td>
<td>55 (38)</td>
<td>1.77 (1.07–2.94)</td>
<td>22 (27)</td>
<td>0.97 (0.52–1.79)</td>
</tr>
<tr>
<td>Past high-risk sexual behaviour</td>
<td>79 (47)</td>
<td>145 (57)</td>
<td>1.48 (0.99–2.22)</td>
<td>78 (54)</td>
<td>1.32 (0.83–2.11)</td>
<td>49 (60)</td>
<td>1.67 (0.97–2.87)</td>
</tr>
<tr>
<td>Reported STIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever had urethral discharge</td>
<td>45 (26)</td>
<td>69 (27)</td>
<td>0.97 (0.61–1.55)</td>
<td>45 (31)</td>
<td>1.15 (0.67–1.95)</td>
<td>18 (22)</td>
<td>0.78 (0.41–1.48)</td>
</tr>
<tr>
<td>Ever had a genital ulcer</td>
<td>41 (24)</td>
<td>43 (17)</td>
<td>0.66 (0.40–1.08)</td>
<td>27 (19)</td>
<td>0.73 (0.41–1.29)</td>
<td>12 (15)</td>
<td>0.59 (0.29–1.20)</td>
</tr>
<tr>
<td>HIV serology positive</td>
<td>13 (8)</td>
<td>55 (22)</td>
<td>3.37 (1.73–6.56)</td>
<td>33 (23)</td>
<td>2.98 (1.43–6.18)</td>
<td>13 (16)</td>
<td>2.56 (1.08–6.07)</td>
</tr>
<tr>
<td>HSV-2 serology positive</td>
<td>59 (35)</td>
<td>129 (51)</td>
<td>2.04 (1.33–3.12)</td>
<td>76 (53)</td>
<td>2.07 (1.27–3.38)</td>
<td>36 (44)</td>
<td>1.53 (0.87–2.70)</td>
</tr>
<tr>
<td>Lifetime factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 (14)</td>
<td>42 (19)</td>
<td>1.26 (0.70–2.26)</td>
<td>23 (18)</td>
<td>1.21 (0.62–2.37)</td>
<td>14 (19)</td>
<td>1.38 (0.65–2.95)</td>
</tr>
<tr>
<td>Alcohol (&gt;9 units/week)</td>
<td>40 (23)</td>
<td>67 (23)</td>
<td>1.20 (0.75–1.92)</td>
<td>41 (28)</td>
<td>1.30 (0.76–2.22)</td>
<td>20 (24)</td>
<td>1.11 (0.58–2.10)</td>
</tr>
<tr>
<td>Smoker (past and/or now)</td>
<td>85 (50)</td>
<td>112 (44)</td>
<td>0.82 (0.54–1.25)</td>
<td>65 (45)</td>
<td>0.81 (0.49–1.32)</td>
<td>37 (45)</td>
<td>0.86 (0.49–1.52)</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>109 (64)</td>
<td>160 (63)</td>
<td>0.89 (0.58–1.37)</td>
<td>91 (63)</td>
<td>0.87 (0.53–1.43)</td>
<td>52 (63)</td>
<td>0.92 (0.52–1.65)</td>
</tr>
<tr>
<td>Urological abnormality</td>
<td>10 (6)</td>
<td>30 (12)</td>
<td>2.00 (0.93–4.28)</td>
<td>21 (15)</td>
<td>2.38 (1.05–5.40)</td>
<td>6 (7)</td>
<td>1.30 (0.45–3.79)</td>
</tr>
</tbody>
</table>

*Union dissolutions include all separations from previously cohabiting partners and excludes all union dissolutions which were reported to be a consequence of infertility.

1Composite variable: had a marital dissolution and/or age first intercourse before 20 years.

2Cut-off value based on distribution of the answers.

3Semen analysis was performed in 226 of 254 men in infertile relations with 144 men diagnosed as having abnormal sperm parameters.

4BMI, body mass index.
G. reesseri infection. However, the association between HIV and tubal infertility remained significant after adjusting for positive Chlamydial antibodies and high-risk sexual behaviour, which could be a marker for gonococcus infection. This supports the current hypothesis that HIV plays a role in tubal pathogenesis (Kamenga et al., 1998; Msisha et al., 2008). All these studies use different diagnostic assays for identification of Chlamydia antibodies, rendering the comparison of results difficult.

The cross-sectional design of our study limits our ability to ascertain temporal relationships between HIV, HSV-2 and infertility. The association between male circumcision and infertility in men is thought to be bidirectional. Anthropological research in SSA has shown that couples with fertility problems are more likely to face extramarital relationships, polygamous unions and divorce, all of which are known risk factors for HIV and HSV-2 infection. In our study population current high-risk sexual behaviour (such as concurrent partners) was also associated with infertility and data on this are described elsewhere (Dhont, unpublished data).

Table IV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women with</th>
<th>Men with abnormal semen analysis</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past high-risk sexual behaviour&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.43 (0.86–2.39)</td>
<td>2.41 (1.57–4.47)</td>
<td>1.67 (1.03–2.71)</td>
</tr>
<tr>
<td>Ever exposure to sexual violence</td>
<td>2.41 (1.36–4.25)</td>
<td>2.43 (1.31–5.23)</td>
<td>1.71 (1.02–2.87)</td>
</tr>
<tr>
<td>Chlamydia serology</td>
<td>1.78 (0.99–3.21)</td>
<td>2.61 (1.49–4.51)</td>
<td>1.97 (1.12–3.47)</td>
</tr>
<tr>
<td>HIV serology</td>
<td>2.41 (1.36–4.25)</td>
<td>2.43 (1.31–5.23)</td>
<td>1.71 (1.02–2.87)</td>
</tr>
<tr>
<td>HSV-2 serology</td>
<td>1.67 (1.03–2.71)</td>
<td>1.71 (1.02–2.87)</td>
<td>1.78 (0.99–3.21)</td>
</tr>
<tr>
<td>Chlamydia serology</td>
<td>1.78 (0.99–3.21)</td>
<td>2.32 (1.01–5.31)</td>
<td>2.61 (1.49–4.51)</td>
</tr>
<tr>
<td>BV (Amsel)</td>
<td>1.97 (1.12–3.47)</td>
<td>2.61 (1.49–4.51)</td>
<td>1.18 (0.76–1.82)</td>
</tr>
<tr>
<td>Lifestyle&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.18 (0.76–1.82)</td>
<td>2.32 (1.01–5.31)</td>
<td>2.61 (1.49–4.51)</td>
</tr>
</tbody>
</table>

<sup>a</sup>AOR, adjusted odds ratio, model includes in addition of all variables listed age, marital status and education.

<sup>b</sup>Composite variable combining for women: age first intercourse before 15 and/or marital dissolution and/or age first intercourse before 20 years. For men: ever had a marital dissolution and/or age first intercourse before 20 years.

<sup>c</sup>Composite variable combining using alcohol more than 1 unit a day and/or having BMI >25 and/or ever smoked. BV, bacterial vaginosis.

Table V

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tubal factor</th>
<th>Male factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past high-risk sexual behaviour&lt;sup&gt;a&lt;/sup&gt;</td>
<td>39%</td>
<td>12%</td>
</tr>
<tr>
<td>Ever exposure to sexual violence</td>
<td>29%</td>
<td>17%</td>
</tr>
<tr>
<td>HIV serology</td>
<td>35%</td>
<td>20%</td>
</tr>
<tr>
<td>HSV-2 serology</td>
<td>66%</td>
<td>26%</td>
</tr>
<tr>
<td>Chlamydia serology</td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>BV (Amsel)</td>
<td>25%</td>
<td>9%</td>
</tr>
<tr>
<td>Lifestyle&lt;sup&gt;b&lt;/sup&gt;</td>
<td>59%</td>
<td>9%</td>
</tr>
<tr>
<td>Urologic abnormalities</td>
<td>15%</td>
<td>8%</td>
</tr>
</tbody>
</table>

PAF = population attributable fractions were calculated using the following formula: Pe(AOR − 1)/AOR, p is proportion of cases that is exposed to risk factor, AOR = adjusted odds ratio.

<sup>a</sup>Composite variable combining for women: age first intercourse before 15 and/or marital dissolution and/or ever engaged in transactional sex; for men: ever had a marital dissolution and/or age first intercourse before 20 years.

<sup>b</sup>Composite variable combining using alcohol more than 1 unit a day and/or having BMI >25 and/or ever smoked.

To further elucidate temporal relationships between infertility and high-risk sexual behaviour, STIs and HIV, longitudinal studies of the reproductive and sexual behaviour and incidence of infections in newly married or cohabiting couples are needed.

Another limitation of this study is the possibility of selection bias.

The infertility study population is a selection of couples who are willing to undergo infertility investigations; they do not necessarily represent all infertile couples in Kigali. This may explain the differences in marital status between the two groups and the differences in education between the men, educational level of women was similar for cases and controls. Married infertile couples might be more motivated to participate in the study than non-married infertile couples since marriage often represents a stronger commitment and a higher expectation to produce children than non-legalized cohabitation. It is not clear how this could have influenced the differences in HIV, HSV-2 and high-risk sexual behaviour in the past between infertile and fertile women. The relationship between socio-economic status and HIV is complex and contradictory results are reported in literature (Wojcicki, 2005; Mshia et al., 2008). The high response rate of fertile women (86%) and the fact that the educational level is the same for responders and non-responders indicates that the selection bias for fertile women is likely to be small. We do not know the response rate of infertile women since they were recruited from the community through
word of mouth from other participants and it is not known how many women heard about the study.

Despite these limitations, our study has several implications. In addition to the promotion of safer sex, provision of STI treatment to rape victims in special gender-based violence clinics has the potential to prevent tubal factor infertility in this group of women. Prevention of HIV and HSV-2 infection are likely to decrease the incidence of male and tubal factor infertility in SSA. Whether long-term antiviral suppression therapy of HIV and HSV-2 can also contribute to the prevention of infertility is not known.

Authors’ roles

The study was conceived and designed by N.D., M.T. and J.W.; N.D., J.V. and C.M. executed the study. N.D. analysed the study data and drafted the article. S.L. and J.W. assisted with data analysis and interpretation of data. S.L., C.M., J.V., J.W. and M.T. revised the article critically.

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References


THE RISK FACTOR PROFILE OF WOMEN WITH SECONDARY INFERTILITY: AN UNMATCHED CASE-CONTROL STUDY IN KIGALI, RWANDA
The risk factor profile of women with secondary infertility: an unmatched case-control study in Kigali, Rwanda

N Dhont, S Luchters, C Muvunyi, J Vyankandwera, L De Naeyer, M Temmerman, J van de Wijgert

Revision submitted to BMC Women’s Health

Secondary infertility is a common, preventable but neglected reproductive health problem in resource-poor countries. This study examines the association of past sexually transmitted infections (STIs) including HIV, bacterial vaginosis (BV) and factors in the obstetric history with secondary infertility and their relative contributions to secondary infertility.

Between November 2007 and May 2009 a research infertility clinic was set up at the Kigali University Teaching Hospital in Rwanda. Cases were defined as sexually-active women aged 21-45 years presenting with secondary infertility (n=177), and controls as multiparous women who recently delivered (n=219).

Participants were interviewed about socio-demographic characteristics and obstetric history using structured questionnaires, and were tested for HIV and reproductive tract infections (RTIs).

Risk factors in the obstetric history for secondary infertility were lack of prenatal care in the last pregnancy, the first pregnancy before the age of 21 years, a history of unwanted pregnancy, a pregnancy with other than current partner, an adverse pregnancy outcome, stillbirth, postpartum infection and curettage. Presence of HIV, herpes simplex virus type 2 (HSV-2), or Treponema pallidum antibodies, and bacterial vaginosis (BV), were significantly more common in women in secondary infertile relationships than those in fertile relationships. The population attributable fractions (PAF%) for obstetric events, HIV, other (STIs), and BV were 25%, 30%, 27%, and 14% respectively.

The main finding of this study is that obstetric events, HIV and other STIs contribute approximately equally to secondary infertility in Rwanda. Scaling up of HIV/STI prevention, increased access to family planning services and improvement of prenatal, obstetric, neonatal and paediatric care are all likely to decrease secondary infertility in sub-Saharan Africa.
Background

In clinical medicine, secondary infertility is usually defined as the inability to conceive despite exposure to pregnancy for one year (2 years in epidemiological studies), after having conceived at least once before [1]. This implies that women with secondary infertility do not necessarily have a living child. Studies looking at prevalence of infertility have all used slightly different definitions making comparison and overall estimates of secondary infertility difficult [2]. Nevertheless, it is well established that primary infertility is much more common than secondary infertility in resource-rich countries but that the reverse is true in sub-Saharan Africa (SSA) [1,3]. In certain African regions, the prevalence of secondary infertility is more than 30% [4]. The high secondary infertility rate in SSA is thought to be due to sexually transmitted infections (STIs) and medical interventions under unhygienic conditions, particularly during delivery or induced abortions [5]. Very few studies have actually examined risk factors for secondary infertility in SSA and little is known about the relative contribution of each factor. In a case-control study in Nigeria, induced abortion, postpartum infection, manual removal of the placenta and prolonged unsupervised labour were associated with secondary infertility [6]. In an analysis of Demographic Health Surveys (DHS) from different Central-African countries risky sexual behaviour such as multiple unions, transactional sex and early age at first intercourse were associated with secondary infertility [7].

Secondary infertility, although not life-threatening, can have severe consequences for the couples involved, especially for the women. If a woman cannot produce a living child in a formal union with a man, she will often be told to leave, and is isolated and stigmatized in the wider community [8-13]. Currently, very few of these women have access to effective infertility treatment. Reproductive technologies are either not available or prohibitively expensive in most SSA countries, although some medical professionals strive to make these techniques more affordable and accessible in SSA in the future [14]. Since most of secondary infertility is preventable, a better knowledge of modifiable risk factors may help to develop interventions targeted at those most at risk.

In order to shed more light on risk factors for secondary infertility in SSA and their relative contribution, we conducted a case control study in Kigali, Rwanda, comparing HIV and other reproductive tract infections (RTIs), past contraceptive behaviour and obstetric history among women in secondary infertile relationships and multiparous fertile women who recently delivered.

Methods

Between November 2007 and May 2009, an infertility research clinic was opened at the Kigali University Teaching Hospital in Rwanda, which is the largest public hospital and the main referral centre for infertility pathology in Rwanda. Women in infertile relationships were recruited mainly through word of mouth. To be eligible for participation, women needed to be between 21 and 45 years of age, residing in Kigali, willing to undergo HIV testing and having had sexual intercourse at least once in the last 2 weeks. Refusal to participate in the study did not influence access to further services. Secondary infertility was defined as having had regular unprotected intercourse for one year or more with at least one regular partner without conception in women who conceived at least once before.
Fertile controls were defined as currently non-pregnant women who recently (between 6 to 18 months ago) delivered. Controls were recruited at the level of the community, as no appropriate control group could be selected at the hospital. A list of all residential neighbourhoods (known as umudugudu) from where the infertile couples originated was compiled (120 umudugudus in total). Fourteen neighbourhoods were randomly selected from this list by blindly hand-picking numbers from a bowl. Community mobilisers in these neighbourhoods visited all families to identify potentially eligible women. The eligibility criteria were the same as for women in infertile relationships, except for fertility status. All participating women were offered free cervical cancer screening and treatment when clinically indicated.

The purpose of the study was explained to potential participants in the local language (Kinyarwanda) and eligibility criteria were checked. All participants provided written informed consent. Socio-demographic characteristics and information on contraceptive practices and obstetric history were elicited in face to face interviews using a structured questionnaire. All female participants received a pelvic examination by the same trained nurse, which was supervised by a gynaecologist. During the speculum exam, vaginal swabs were collected for the preparation of a wet mount, potassium hydroxide testing and pH testing. Saline wet mounts were examined in the study clinic for the presence of clue cells. Thereafter, the study nurse collected blood samples. These were aliquoted, and either tested on site for HIV and syphilis, or frozen and stored at -80°C until further analysis. HIV testing was conducted according to the national algorithm (Determine Rapid HIV-1/2 Test kits (Abbott Laboratories, Abbott Park, IL), followed by Uni-Gold Rapid Test (Trinity Biotech Plc, Ireland) if Determine-positive, and the Capillus HIV-1/HIV-2 Rapid Test (Trinity Biotech Plc, Ireland) if a tiebreaker was needed. *Treponema pallidum*-specific rapid test (SD Bioline Syphilis 3.0) was conducted on site, followed by RPR titration (Syphilis RPR test, Human, Germany) in the National Reference Laboratory of Rwanda. A positive Treponema-specific rapid test with a negative RPR was interpreted as a past, cured infection. Participants were advised to return to the study clinic for test results and, if required, received treatment according to local guidelines. Stored specimens were analysed for HSV-2 antibodies (Herpeselect 2 ELISA IgG, Focus Diagnostics) in the National Reference Laboratory of Rwanda, and for *Chlamydia trachomatis*-specific IgG antibodies by a synthetic-peptide based EIA test (labsystems, Helsinki, Finland) at Ghent University Hospital, Department of Microbiology. All participants were offered HIV counselling and same-day HIV testing; those testing positive were enrolled in an HIV care and treatment clinic at the study site. Women in infertile relationships received a tubal patency test using hysterosalpingography (HSG) in most and laparoscopy in some cases. Their male partners were offered semen analysis.

All women regardless of study group who had reported an unwanted pregnancy in the past were invited for a semi-structured in-depth interview to collect data about the circumstances in which the unwanted pregnancy had occurred.

Data collected during interviews and laboratory investigations were single entered and rigorously verified and cleaned using MS Access 2000 (Microsoft, Seattle, USA). Intercooled Stata 9.2 (Stata Corporation, College Station, Texas, USA) was used for statistical analysis of the data.
The cause of the secondary infertility was determined to be a male factor in some relationships, but a female factor in most. Some female factors may have been missed because investigations to determine the cause of infertility were not complete in all participants. Furthermore, the sensitivity of HSG to detect tubal pathology is only 65% [15]. We therefore included all women in secondary infertile relationships in these analyses, regardless of whether a male or female cause was identified. In analyses including obstetric events as risk factors, we did not consider events that occurred during the last pregnancy or delivery for the fertile women, because it is unclear whether the fertile women were in fact still fertile during the time period since their last pregnancy or delivery. For this same reason, fertile primiparae were excluded. Furthermore, fertile women with a history of trying for the previous pregnancy for more than one year were considered subfertile and were excluded from the analysis. Socio-demographic characteristics of women in infertile and fertile relationships were compared using Chi-squared tests or the Mann-Whitney U-test. The relationship between selected covariates and secondary infertility were examined and controlled for age using logistic regression. RTIs and obstetric events can lead directly to infertility. Their independent associations with secondary infertility were examined in a multivariable logistic regression model. Risk factors were grouped according to the type of infection they represent: endogenous infection (bacterial vaginosis (BV)), iatrogenic infection (a composite variable including a history of curettage post-abortion or postpartum, unsafe abortion, caesarean section, and/or postpartum infection) and STIs (a composite variable including herpes simplex type 2 (HSV-2), syphilis, and/or chlamydial infection). HIV was kept as a separate predictor. Population Attributable Fractions (PAF%) were calculated for selected risk factors using the following formula: pe (AOR-1)/AOR with pe the proportion of cases that is exposed to risk factor.

**Results**

Of 339 women in infertile relationships who presented at the study clinic, 312 were confirmed eligible for the study and enrolled (Figure1). Among these, 177 women had conceived at least once before and were considered to have secondary infertility. Of 407 women in fertile relationships identified in the community, 352 (86%) came to the clinic and 312 eligible women were enrolled. Educational level and occupation did not differ between responders and non-responders. Of the 312 fertile women enrolled in the control group, 29 reported to have tried more than one year for the previous pregnancy and 64 had only had one pregnancy in the past, leaving 219 fertile women for this analysis. In 114 (71%) of the 161 women in secondary infertile relationships who completed infertility investigations a tubo-peritoneal factor was diagnosed on HSG or laparoscopy.

Women in secondary infertile relationships reported a total of 303 pregnancies, and fertile women a total of 625 pregnancies. Women in secondary infertile relationships were more likely to be older and to have had a deceased child than women in fertile relationships (Table 1). Thirteen percent of women in secondary infertile relationships were nulliparous (never carried a pregnancy beyond 24 weeks), 70% had not more than one pregnancy and 44% had no living children.
Table 1: socio-demographic characteristics and reproductive history of cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>cases</th>
<th>controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=177</td>
<td>N=219</td>
<td></td>
</tr>
<tr>
<td>Total number of pregnancies†</td>
<td>303</td>
<td>625</td>
<td></td>
</tr>
<tr>
<td>Pregnancies, median (IQR)</td>
<td>1 (1-2)</td>
<td>3 (2-5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>32 (28-37)</td>
<td>28 (25-32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to primary</td>
<td>135 (76)</td>
<td>175 (80)</td>
<td>0.38</td>
</tr>
<tr>
<td>More than primary</td>
<td>42 (24)</td>
<td>44 (20)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>94 (53)</td>
<td>125 (57)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>83 (47)</td>
<td>93 (42)</td>
<td>0.47</td>
</tr>
<tr>
<td>Separated, divorced or widowed</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (13)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>101 (57)</td>
<td>9 (4)</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>45 (25)</td>
<td>118 (54)</td>
<td></td>
</tr>
<tr>
<td>4 or more</td>
<td>7 (4)</td>
<td>92 (42)</td>
<td></td>
</tr>
<tr>
<td>Living children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>78 (44)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-2</td>
<td>93 (52)</td>
<td>84 (38)</td>
<td></td>
</tr>
<tr>
<td>3 or more</td>
<td>6 (3)</td>
<td>135 (62)</td>
<td></td>
</tr>
<tr>
<td>Ever had a deceased child</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>94 (53)</td>
<td>154 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>yes</td>
<td>83 (47)</td>
<td>65 (30)</td>
<td></td>
</tr>
</tbody>
</table>

† excluding last pregnancy for fertile women

Women in secondary infertile relationships were more likely to have had the first pregnancy before the age of 21 years (aOR = 2.56, CI=1.63-4.02), an unwanted pregnancy (aOR=11.51, CI=5.47-24.20), a pregnancy with someone other than the current partner (aOR=5.68, CI=3.56-9.08), no prenatal care in the last pregnancy (aOR=4.68, CI=1.81-12.12), an adverse pregnancy outcome (aOR=1.89, CI=1.17-3.04), a stillbirth (aOR=7.52, CI=2.97-19.01) a postpartum infection (aOR=11.49, CI=3.31-39.89) or a curettage (aOR=1.71, CI=0.93-3.13) than women in fertile relationships. Very few women reported to ever have had an intrauterine device fitted (five controls and two cases). The only studied obstetrical antecedents that were not associated with secondary infertility were an unattended birth and a caesarean section in the past.
Table 2: Association of obstetrical and reproductive history and reproductive tract infections with secondary infertility

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases N=177 n (%)</th>
<th>Controls N=219 n (%)</th>
<th>Age adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetrical and reproductive history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever IUCD</td>
<td>2 (1)</td>
<td>5 (2)</td>
<td>0.38 (0.07-2.10)</td>
</tr>
<tr>
<td>First pregnancy before age 21 years</td>
<td>97 (55)</td>
<td>92 (42)</td>
<td>2.56 (1.63-4.02)</td>
</tr>
<tr>
<td>unwanted pregnancy</td>
<td>49 (28)</td>
<td>11 (5)</td>
<td>11.51 (5.47-24.20)</td>
</tr>
<tr>
<td>pregnancy with another partner</td>
<td>105 (59)</td>
<td>48 (22)</td>
<td>5.68 (3.56-9.08)</td>
</tr>
<tr>
<td>No prenatal care in last pregnancy</td>
<td>20 (15)</td>
<td>7 (4)</td>
<td>4.68 (1.81-12.12)</td>
</tr>
<tr>
<td>unattended birth</td>
<td>44 (25)</td>
<td>75 (34)</td>
<td>0.81 (0.56-1.18)</td>
</tr>
<tr>
<td>Adverse pregnancy outcome</td>
<td>57 (32)</td>
<td>44 (20)</td>
<td>1.89 (1.17-3.04)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>32 (18)</td>
<td>6 (3)</td>
<td>7.52 (2.97-19.01)</td>
</tr>
<tr>
<td>unsafe abortion</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>caesarean section</td>
<td>30 (17)</td>
<td>27 (12)</td>
<td>1.33 (0.73-2.39)</td>
</tr>
<tr>
<td>postpartum infection</td>
<td>24 (13)</td>
<td>3 (1)</td>
<td>11.49 (3.31-39.89)</td>
</tr>
<tr>
<td>curettage</td>
<td>32 (18)</td>
<td>23 (10)</td>
<td>1.71 (0.93-3.13)</td>
</tr>
</tbody>
</table>

Reproductive tract infections

| BV | 50 (28) | 32 (15) | 2.68 (1.58-4.54) |
| Positive HIV serology | 74 (42) | 35 (16) | 4.10 (2.50-6.72) |
| Positive HSV-2 serology | 121 (70) | 99 (45) | 2.56 (1.65-3.96) |
| Positive Chlamydia serology | 31 (18) | 33 (15) | 1.58 (0.89-2.80) |
| Old treated syphilis | 16 (9) | 8 (4) | 2.85 (1.13-7.18) |

1 excludes dissolutions that were reported to be the consequence of infertility
2 includes miscarriage and ectopic pregnancy
3 includes post-abortion and postpartum curettage
4 women whose last pregnancy was a miscarriage are excluded from analysis, leaving 129 cases and 195 controls

The presence of HIV, HSV-2, or Treponema pallidum antibodies was significantly more common in women in secondary infertile relationships than women in fertile relationships (aOR=4.10, 95%CI=2.50-6.72; aOR=2.56, 95%CI=1.65-3.96; aOR=2.85, 95%CI=1.13-7.18, respectively). The presence of Chlamydia trachomatis antibodies was higher in cases (31/177, 18%) than controls (33/219, 15%) but did not reach statistical significance (p=0.12). Women in secondary infertile relationships were more likely to have a diagnosis of BV than women in fertile relationships (aOR= 2.68, 95%CI=1.58-4.54). The PAF% for obstetric events, HIV, other sexually transmitted infections (STIs), and BV were 25%, 30%, 27%, and 14% respectively. (Table III).
Table 3: Population attributable fractions of direct risk factors for secondary infertility

<table>
<thead>
<tr>
<th>Predictor</th>
<th>pe</th>
<th>AOR</th>
<th>PAF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric events (^1)</td>
<td>0.38</td>
<td>3.03</td>
<td>25</td>
</tr>
<tr>
<td>STIs (^2)</td>
<td>0.74</td>
<td>1.57</td>
<td>27</td>
</tr>
<tr>
<td>Endogenous infections (BV)</td>
<td>0.28</td>
<td>1.95</td>
<td>14</td>
</tr>
<tr>
<td>HIV</td>
<td>0.42</td>
<td>3.58</td>
<td>30</td>
</tr>
</tbody>
</table>

\(^1\) pregnancy complications include postpartum infection, caesarean section, unsafe abortion and/or curettage
\(^2\) STIs include positive HSV-2, Chlamydia and/or syphilis serology
\(^3\) logistic regression model included all listed (composite) variables
\(^4\) PAF is calculated using the following formula: PAF=pe(AOR-1)/AOR, with pe the proportion of cases exposed and AOR is derived from a logistic regression model containing all the listed biological factors and age.

Of the 49 women in infertile relationships and the 11 fertile women who had reported an unwanted pregnancy, 19 and seven women respectively returned for the in-depth interviews. Two of the fertile women had tried for their previous pregnancy for more than one year and are therefore considered subfertile, resulting in 21 women who reported unwanted pregnancies in the infertile and five in the fertile group. Almost all (95%) unwanted pregnancies in women in infertile relationships, and 20% in fertile women were with another partner than the current partner. Age at conception was less than 20 years for half of the women in secondary infertile relationships and for one woman in fertile relationships. In eight women in infertile relationships and in none of the women in a fertile relationship, the unwanted pregnancy was a consequence of rape. Another frequently reported scenario in the group of women in infertile relationships (five cases) was a younger girl having unforced sex with an older man without being aware of the possibility of pregnancy. The unwanted pregnancies in the fertile women were all, apart from one, due to failure to access effective contraception with the current partner. Six women in infertile relationships and no woman in fertile relationships reported a postpartum infection after delivery. Of the women in infertile relationships with a past of unwanted pregnancies, 14 out of 18 (78%) had tubal abnormalities on the HSG.

Discussion

The main finding of this study is that obstetric events, HIV and other STIs contribute approximately equally to secondary infertility in Rwanda. Furthermore, the study indentified some previously unknown obstetric history risk factors for secondary infertility such as a history of no prenatal care during the last pregnancy, early age of first pregnancy, unwanted pregnancies and stillbirths.
Infections acquired during a previous delivery were strongly associated with secondary infertility as reported by other authors. A history of dilatation and curettage, which was weakly associated with secondary infertility in our population, has been associated with pelvic inflammatory disease (PID) but not with infertility in other studies [16]. In our study, we did not find an association between caesarean section and secondary infertility, but this could be due to insufficient statistical power [6,17,18].

A history of stillbirth was strongly associated with secondary infertility in our study. Stillbirths can contribute to infertility through several mechanisms: First, they can be a marker for perinatal or ascending infections during strenuous labour; a history of stillbirth has been associated with PID in previous research [16]. Second, stillbirths and high infant mortality rates create a child deficit which is associated with self-reported fertility impairment [19]. The latter might also explain the association between no prenatal care in the previous pregnancy and secondary infertility in our population. In Rwanda, prenatal care usually involves screening and treatment of syphilis and malaria prophylaxis. These infections are important causes of stillbirths in developing countries[20]. The association between HIV infection and secondary infertility could also be explained by an increased occurrence of stillbirths and infant mortality among infected mothers but the relationship is much more complex.

Associations of infertility with HIV and other RTIs such as HSV-2, Chlamydia and BV in this population are discussed in detail elsewhere[21,22]. In summary, the data from these analyses indicate that HIV and HSV-2 could play a role in tubal pathogenesis. In the opposite direction, infertility can also lead to the acquisition of HIV and other STIs through increased extramarital sex. The fact that secondary infertile women are more likely to be HIV infected and to report lifetime high-risk sexual behaviour than primary infertile and fertile women indicates that this group of women enters a vicious circle of unsafe sex, beginning from the start of sexual activity, leading to a first pregnancy (and often the last), STIs and HIV infection, all of which can impair their fertility.

An interesting finding in our study, and not yet reported, is the strong association of unwanted pregnancies with infertility irrespective of induced abortions. Very few infertile women in our study reported induced abortions despite the large number of reported unwanted pregnancies. In a study in Nigeria, induced abortion and post abortion sepsis were the most important risk factors for secondary infertility [6]. Induced abortions may have been underreported in our study. However, we conducted semi-structured in-depth interviews with 27 out of 63 women reporting an unwanted pregnancy, and only one woman admitted to an induced abortion that she had not reported in her first structured interview. On the one hand unwanted pregnancies could lead to infertility through lack of prenatal and obstetric care. On the other hand, the unsafe sex which has caused the unwanted pregnancy could also have caused the acquisition of HIV/STIs with secondary infertility as a consequence. Previous studies have demonstrated that women experiencing unwanted births are seeking prenatal care less frequently and are more likely to have a pregnancy complication (preterm birth, perinatal deaths and postpartum infections) [23]. We learned from our in-depth interviews that unwanted pregnancies in women in infertile relationships are often a result of unsafe sex (including sexual violence and sex of younger girl with an older man), and are more likely to result in postpartum infections, although the numbers are too small to draw firm conclusions.
The results of our study may not be generalised to the general population of Kigali. We do not know the response rate among women in infertile relationships because they were recruited through word of mouth. However, the response rate of fertile women in the community was high, the educational level of responders and non-responders in each study group was similar, and baseline characteristics (such as educational level and marital status) did not differ between cases and controls. The unit of analysis was individual women, and not pregnancies or deliveries. Since women in fertile relationships had experienced twice as many pregnancies/deliveries than women in infertile relationships, the contributions of pregnancy-related and obstetric events to secondary infertility were likely underestimated. Finally, due to the case-control design of this study, temporal relationships between past STIs and HIV and infertility cannot be ascertained.

Conclusion

Our data suggest that secondary infertility rates in Rwanda could be significantly reduced by improving prenatal, obstetric, neonatal and paediatric care. Furthermore, improving access to family planning, especially for young women, has a role to play. We recommend that educational campaigns focus on the fact that sex without a condom can lead not only to infections and unwanted pregnancies but also to infertility [24].
Competing Interest

None declared

Author’s contributions

ND conceived, designed and executed the study, performed the statistical analysis and drafted the manuscript. SL assisted with data analysis and interpretation of data. CM carried out some of the lab tests. JV assisted with study design and execution of the study. LDN assisted with data analysis. MT assisted with study design and drafting of the manuscript. JvdW assisted with study design, data analysis, interpretation of data and drafting of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

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We thank Rosette Busasa, Ammiel Gasarabwe and the Community Mobilizers for their dedication during data collection, Dr. Gilles Ndabisaya for programming of the database, and other members of the Projet Ubuzima team and the EDCTP microbicides project team for their contributions and support.
Reference List


HIV INFECTION AND SEXUAL BEHAVIOUR IN PRIMARY AND SECONDARY INFERTILE RELATIONSHIPS: A CASE-CONTROL STUDY IN KIGALI, RWANDA
Epidemiology

HIV infection and sexual behaviour in primary and secondary infertile relationships: a case—control study in Kigali, Rwanda

Nathalie Dhont,1,2 Claude Muvunyi,3,4 Stanley Luchters,1 Joseph Vyankandondera,2,5 Ludwig De Naeyer,6 Marleen Temmerman,1 Janneke van de Wijgert7,8

ABSTRACT

Objective To compare the prevalence of sexually transmitted infections (STIs) (including HIV) and of high-risk sexual behaviour in the following three groups: primary infertile relationships, secondary infertile relationships and fertile relationships. Primary infertility is here defined as never having conceived before, secondary infertility as infertility subsequent to having conceived at least once.

Methods Sexually active infertile women aged 21–45 years presenting at an infertility clinic of the Kigali Teaching Hospital, Rwanda and their male partners were invited to participate. Fertile controls who had recently delivered were recruited from the community. In a face-to-face interview, participants were asked about sociodemographic characteristics and their sexual behaviours, and tested for HIV and STIs.

Results Between November 2007 and May 2009, 312 women and 254 partners in infertile relationships and 312 women and 189 partners in fertile relationships were enrolled. Involvement in a secondary infertile relationship was associated with HIV infection after adjusting for sociodemographic covariates for women (adjusted OR = 4.03, 95% CI 2.4 to 6.7) and for men (AOR = 3.3, 95% CI 1.8 to 6.4). Involvement in a primary infertile relationship, however, was not. Secondary infertile women were more likely to have engaged in risky sexual behaviour during their lifetime compared with primary infertile and fertile women. Men in primary and secondary infertile relationships more often reported multiple partners in the past year (AOR = 5.4, 95% CI 2.2 to 12.7, AOR = 7.1, 95% CI 3.2 to 15.8, respectively).

Conclusions Increased HIV prevalence and risky sexual behaviour among infertile couples is driven by secondary infertility. Infertile couples, and especially those with secondary infertility, should be targeted for HIV prevention programmes and their fertility problems should be addressed.

INTRODUCTION

Infertility and HIV infection are affecting a large number of couples world wide with sub-Saharan Africa bearing the largest burden of these two reproductive disorders. It is estimated that in this region 2.5% of adults are living with HIV.1 Primary infertility (never having conceived) is affecting 3–6% of couples, whereas the prevalence of secondary infertility (infertility after having conceived at least once before) is much higher, especially in certain regions, affecting 5–25% of couples.2

A number of studies have shown an association between infertility and HIV infection, focusing mainly on reduced fecundity among HIV-positive women compared with HIV-negative women. HIV-positive women and infertile women with secondary infertility with asymptomatic infection) have lower conception rates and higher rates of pregnancy loss. The lower conception rate is thought to be due to greater susceptibility to pelvic inflammatory disease with resultant tubal factor infertility and to weight loss related anovulation, amenorrhoea, male hypogonadism and impaired spermatogenesis.3–6 However, in one prospective study examining the association between HIV infection and infertility, it was found that in half of the patients the infertility had existed before HIV infection, suggesting that infertility is a risk factor for HIV acquisition.7

Previous studies in sub-Saharan Africa have shown that couples with fertility problems are likely to face extramarital relationships, polygamous unions and divorce, all of which are known risk factors for HIV infection.8–10 Few studies have examined the HIV prevalence and current sexual behaviours in infertile patients, particularly among couples. In Tanzania, HIV infection was threefold higher among infertile women than among fertile controls, and perceived partner infidelity was higher among infertile women.11 Similarly, in Nigeria, HIV infection among women undergoing laparoscopy evaluation for infertility was fivefold higher than HIV prevalence among pregnant women.12

Most HIV transmission in sub-Saharan Africa is thought to be through heterosexual transmission among HIV discordant couples in stable relationships.13–15 Couples in infertile relationships may constitute an important vulnerable group for HIV infection in African society and may fuel the HIV epidemic. Little is known about the association between infertility, risky sexual behaviour and sexually transmitted infections (STIs), including HIV. We therefore examined whether HIV/STI infection and risky sexual behaviour were more common among men and women in primary and secondary infertile relationships than among men and women in fertile relationships in an urban population in Kigali, Rwanda.

MATERIAL AND METHODS

Study population and setting

Between November 2007 and May 2009, an infertility research clinic was opened at the Kigali Teaching Hospital in Rwanda (the largest public hospital in Rwanda), and infertile women were
recruited mainly through word of mouth. Recruitment was
terminated when 312 infertile women were enrolled, as per
protocol. To be eligible for participation, women needed to be
between 21 and 45 years of age, residing in Kigali, willing to
undergo HIV testing and to have had sexual intercourse at least
once in the past 2 weeks. Refusal to participate in the study did
not influence access to further services. Infertility was defined as
failure to conceive after regular unprotected intercourse for
≥1 year and included primary and secondary infertility. Male
partners of primary and secondary infertile women are referred
to as men in primary and secondary infertile relationships,
respectively. In the analyses presented in this paper, infertility
was considered a problem for couples and no distinction was
made between female or male causes of infertility. Fertile
controls were defined as women who delivered between 6 and
18 months prior to the sampling. Other eligibility criteria were
the same as for the infertile women. Controls were recruited from the community,
as no appropriate control group could be selected at the hospital.
A list of all residential neighbourhoods (known as umudugudu)
from where the infertile couples originated was compiled (120
umudugudu in total). Fourteen neighbourhoods were randomly
selected from this list by blindly hand picking numbers from
a bowl. Community mobilisers in these neighbourhoods visited
all families to identify potential eligible candidates.
After inclusion, all cases and controls invited their male
partners to participate on a separate occasion.
All participating women were offered free cervical cancer
screening and treatment when clinically indicated. The study
was approved by the National Ethics Committee of Rwanda,
and the National AIDS Control Program (CNLS) in Rwanda.

Procedures
The purpose of the study was explained to potential participants
in their local language (Kinyarwanda) and eligibility criteria
were checked. All participants provided written informed
consent before the study procedures took place. Women were
interviewed by a female nurse and male partners by a male
medical officer about sociodemographic characteristics, sexual
behaviour and obstetric history using structured questionnaires.
Some of the female participants (30 women) were asked again
about extramarital partners in a follow-up interview when
positive STI results were discussed. Female participants received
a clinical gynaecological examination by the female nurse, and
male participants a genital examination by the male medical
officer; all clinical procedures were supervised by a gynaecologist.
During the speculum examination, clinical signs of STIs were
documented, vaginal pH was measured, specimens for STI
diagnostic tests were collected, and visual inspection with acetic
acid was performed to identify cervical precancerous lesions.
Saline wet mounts were examined at the study clinic for the
presence of motile Trichomonas vaginalis. A second vaginal swab
was placed in 8 ml UTM-RT transport medium (Copan Dia-
agnostics, California, USA) and immediately frozen at −80°C.
The swab was shipped, frozen on dry ice, to Ghent University
Hospital for multiplex PCR for C. trachomatis and N. gonorrhoea
(ABbott Laboratories, Illinois, USA).

After the speculum examination and male genital examina-
tion, blood samples were collected for on-site rapid HIV
testing according to a national algorithm (Determine Rapid
HIV-1/2 Test (Abbott Laboratories), followed by Uni-Cold Rapid
Test (Trinity Biotech, Ireland) if determined to be positive,
and followed by Capillus HIV-1/HIV-2 Rapid Test (Trinity
Biotech Plc, Ireland), if a tiebreaker was needed, and an on-site
Trepomonas-specific rapid syphilis test (SD Bioline Syphilis 3.0,
Standard Diagnostics, Korea). If the rapid syphilis test was
positive, rapid plasma reagin (RPR) titration (Human, Germany)
was carried out in the National Reference Laboratory in Kigali.
A positive Trepomonas-specific rapid test with a positive RPR was interpreted as active or recently treated syphilis, while a positive
Trepomonas-specific rapid test and negative RPR was considered
evidence of old previously treated syphilis. The serum sample
was immediately processed in four aliquots and stored at −80°C
until analysis. One aliquot was analysed for HSV-2 antibodies
(Herpesselect 2 ELISA IgG, Focus Diagnostics, California, USA) in
the National Reference Laboratory. Participants were advised to
return for test results and, if required, received treatment
according to local guidelines. All participants were offered HIV
counselling and same-day testing; those testing positive were
ever in an HIV care and treatment clinic of their choice.
Infertile couples were investigated with a tubal patency test
(hysterosalpingography or laparoscopy) and a semen analysis.

Variables and study measures
Sexual behaviour was assessed with the following indicators:
ever separated, lifetime sexual partners, age at first intercourse,
ever engaged in transactional sex (women only), ever use of
condoms, multiple partners in past year (concurrent partner-
ships and/or more than one partner in the past year), perception
of partner’s fidelity and condom use at last sexual intercourse
(men only). STIs included self-reported STIs (any genital
symptoms within the past year), clinically diagnosed STIs
(genital ulcers/warts/blisters, urethral discharge, cervicitis
and pelvic inflammatory disease) and STIs diagnosed using
laboratory tests (T vaginalis, N gonorrhoeae, C trachomatis
and T pallidum, HIV and herpes simplex virus 2 (HSV-2) serology).
STI laboratory tests among men were limited to T pallidum, HIV
and HSV-2 serology.

Statistical analysis
Data collected during interviews and laboratory investigations
were single entered, verified and cleaned using MS Access
2000 (Microsoft). Intercooled Stata 9.2 (Stata Corporation) was
used for statistical analysis. Sociodemographic, sexual behaviour
and reproductive health characteristics of infertile and
fertile women and their partners were compared using square
tests or Mann–Whitney U tests. crude and adjusted ORs were
calculated for men and women separately to compare HIV
prevalence, sexual behaviour and STI prevalence. Potential
confounding variables among the sociodemographic character-
istics were selected a priori and retained in multivariable models
when they affected the association (OR) between the primary
predictor of interest and the outcome by ≥10%.

As a result, all primary predictors in women were controlled
for age, occupation, income and marital status, in men predictors
were controlled for age, income and education.

RESULTS
Baseline characteristics
At total of 312 female cases and 312 female controls were
recruited. Three hundred and thirty-nine infertile women
presented at the clinic, of whom 312 eligible women were
subsequently enrolled. Community mobilisers identified and
invited 407 fertile women after visiting all families in selected
neighbourhoods. Of these, 55 women were not interested in
participating owing to lack of time, fear of the gynaecological
examinations, or an unknown reason. The remaining 352
women came to the clinic (response rate of 86%). Of these,

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Sexual risk behaviour and STIs in men

Men in primary infertile relationships were more likely to never have used condoms (AOR=2.30, 95% CI 1.57 to 3.35) and men in secondary infertile relationships were more likely to have separated at least once (AOR=2.03, 95% CI 1.07 to 3.84) compared with fertile men (table 3). In men in primary and secondary infertile relationships were more likely to report multiple sexual partners in the past year (AOR=5.34, 95% CI 2.24 to 12.72; AOR=7.11, 95% CI 5.20 to 15.76, respectively) and lack of condom use at last sexual intercourse (AOR=3.91, 95% CI 1.91 to 7.92; AOR=3.03, 95% CI 1.16 to 7.87, respectively) than men in fertile relationships. Of 25 men in an infertile relationship who knew their HIV-positive status before the study, only two reported condom use at last sexual intercourse compared with 11 out of 15 men in a fertile relationship. Only three men (two in a fertile and one in a primary infertile relationship) believed that their female partners had another sexual partner. Prevalence of STIs did not differ between men in primary infertile relationships and men in fertile relationships.

In men, HIV infection was statistically significantly associated with being in a secondary infertile relationship (AOR=2.57, 95% CI 1.58 to 4.16). The reporting of genital symptoms and the presence of any active STI was slightly higher in men in secondary infertile relationships but did not reach statistical significance.

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Table 1  Characteristics of enrolled women and their male partners in fertile and infertile relationships and by infertility type in Kigali, Rwanda

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fertile relationship, n (%)</th>
<th>Primary infertile, n (%)</th>
<th>Secondary infertile, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women N=312</td>
<td>Primary infertile N=135</td>
<td>Secondary infertile N=177</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>28 (24–31)</td>
<td>29 (26–34)</td>
<td>32 (28–37)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to primary school</td>
<td>234 (75)</td>
<td>90 (67)</td>
<td>135 (76)</td>
</tr>
<tr>
<td>Secondary school or more</td>
<td>78 (25)</td>
<td>45 (33)</td>
<td>42 (24)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>185 (59)</td>
<td>41 (30)</td>
<td>94 (53)</td>
</tr>
<tr>
<td>Married</td>
<td>126 (40)</td>
<td>93 (69)</td>
<td>83 (47)</td>
</tr>
<tr>
<td>Separated, divorced or widowed</td>
<td>1 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>170 (54)</td>
<td>45 (33)</td>
<td>47 (26)</td>
</tr>
<tr>
<td>Student</td>
<td>4 (1)</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Cultivator</td>
<td>1 (0)</td>
<td>7 (6)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>115 (37)</td>
<td>59 (44)</td>
<td>98 (55)</td>
</tr>
<tr>
<td>Employed</td>
<td>22 (7)</td>
<td>22 (16)</td>
<td>19 (11)</td>
</tr>
<tr>
<td>Income (US$/day)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>174 (56)</td>
<td>50 (39)</td>
<td>48 (29)</td>
</tr>
<tr>
<td>&gt;0–1</td>
<td>29 (9)</td>
<td>25 (19)</td>
<td>54 (32)</td>
</tr>
<tr>
<td>1–4</td>
<td>97 (31)</td>
<td>35 (27)</td>
<td>50 (29)</td>
</tr>
<tr>
<td>≥5</td>
<td>12 (4)</td>
<td>19 (15)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0 (0)</td>
<td>135 (100)</td>
<td>ND</td>
</tr>
<tr>
<td>1</td>
<td>80 (26)</td>
<td>0 (0)</td>
<td>101 (57)</td>
</tr>
<tr>
<td>2–3</td>
<td>131 (42)</td>
<td>0 (0)</td>
<td>45 (25)</td>
</tr>
<tr>
<td>≥4</td>
<td>101 (32)</td>
<td>0 (0)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Parity ever for HIV†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>3 (1)</td>
<td>20 (15)</td>
<td>29 (16)</td>
</tr>
<tr>
<td>At least once</td>
<td>3 (0) (99)</td>
<td>115 (85)</td>
<td>148 (84)</td>
</tr>
<tr>
<td>Partner participation</td>
<td>189 (60)</td>
<td>121 (90)</td>
<td>133 (75)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fertile relationship, n (%)</th>
<th>Primary infertile, n (%)</th>
<th>Secondary infertile, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men N=189</td>
<td>Primary infertile N=121</td>
<td>Secondary infertile N=133</td>
</tr>
<tr>
<td>Partner age, median (IQR)</td>
<td>32 (28–39)</td>
<td>34 (30–39)</td>
<td>35 (30–41)</td>
</tr>
<tr>
<td>Partner education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to primary school</td>
<td>143 (76)</td>
<td>67 (55)</td>
<td>84 (63)</td>
</tr>
<tr>
<td>Secondary school or higher</td>
<td>46 (24)</td>
<td>54 (45)</td>
<td>49 (37)</td>
</tr>
<tr>
<td>Partner’s occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Student</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Cultivator</td>
<td>4 (2)</td>
<td>5 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>116 (61)</td>
<td>79 (65)</td>
<td>80 (60)</td>
</tr>
<tr>
<td>Employed</td>
<td>66 (35)</td>
<td>36 (30)</td>
<td>49 (37)</td>
</tr>
<tr>
<td>Partner’s income (US$/day)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>18 (10)</td>
<td>13 (12)</td>
<td>19 (15)</td>
</tr>
<tr>
<td>1–4</td>
<td>125 (68)</td>
<td>83 (57)</td>
<td>75 (59)</td>
</tr>
<tr>
<td>≥5</td>
<td>42 (22)</td>
<td>35 (21)</td>
<td>33 (26)</td>
</tr>
<tr>
<td>Partner ever tested for HIV†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>13 (7)</td>
<td>26 (21)</td>
<td>37 (28)</td>
</tr>
<tr>
<td>At least once before</td>
<td>176 (93)</td>
<td>95 (78)</td>
<td>96 (72)</td>
</tr>
</tbody>
</table>

*Six and 10 missing values for primary and secondary infertile women and 10 and six for men in primary and secondary infertile relationships. †One missing value for fertile relationship. z Derived from comparison between primary and secondary infertile relationships.

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Clinical STIs include urethral discharge and genital ulcer; one case missing for fertile men.

Syphilis: two and three cases missing for primary and secondary infertility respectively; HSV-2: three cases missing for fertile relationships, four cases for primary and secondary infertility; HIV: three cases missing for primary and secondary infertility; Chlamydia: 11 cases missing for fertile relationships; Gonorrhoea: 11 cases missing for fertile relationships and one for secondary infertility.

Old treated syphilis

Positive HSV-2 serology

Never used a condom

Multiple partners in past year

Age at first intercourse

Old treated syphilis

Ever separated

Epidemiology

Table 2 Sexual behaviour and sexually transmitted infections (STIs) among women in fertile, primary infertile and secondary infertile relationships

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fertile relationship N = 135</th>
<th>Primary infertile N = 135</th>
<th>Secondary infertile N = 177</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>AOR*</td>
<td>p Value</td>
<td>AOR*</td>
</tr>
<tr>
<td>Sexual behaviours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever separated</td>
<td>39 (12)</td>
<td>25 (18)</td>
<td>2.03 (1.07–3.84)</td>
</tr>
<tr>
<td>Ever separated, not because of childlessness</td>
<td>37 (12)</td>
<td>5 (4)</td>
<td>0.26 (0.09–0.73)</td>
</tr>
<tr>
<td>Age at first intercourse &lt; 20</td>
<td>171 (55)</td>
<td>58 (43)</td>
<td>0.79 (0.3–1.5)</td>
</tr>
<tr>
<td>Three or more lifetime sexual partners</td>
<td>54 (17)</td>
<td>47 (30)</td>
<td>3.01 (1.17–8.16)</td>
</tr>
<tr>
<td>Ever had transactional sex</td>
<td>19 (6)</td>
<td>6 (4)</td>
<td>1.20 (0.4–3.54)</td>
</tr>
<tr>
<td>Never used a condom</td>
<td>106 (34)</td>
<td>92 (68)</td>
<td>3.53 (2.21–5.62)</td>
</tr>
<tr>
<td>Multiple partners in past year</td>
<td>8 (3)</td>
<td>5 (4)</td>
<td>2.82 (0.84–9.46)</td>
</tr>
<tr>
<td>Reported partner’s infertility</td>
<td>19 (6)</td>
<td>23 (17)</td>
<td>4.18 (2.03–8.41)</td>
</tr>
<tr>
<td>STIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital symptoms in the past year</td>
<td>255 (62)</td>
<td>115 (85)</td>
<td>1.10 (0.61–1.97)</td>
</tr>
<tr>
<td>Active syphilis infection</td>
<td>9 (3)</td>
<td>4 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Gonococcus infection</td>
<td>15 (5)</td>
<td>5 (4)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Chlamydial infection</td>
<td>12 (4)</td>
<td>5 (4)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Trichomoniasis infection</td>
<td>15 (5)</td>
<td>4 (3)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Any active STIs</td>
<td>49 (16)</td>
<td>17 (13)</td>
<td>0.94 (0.50–1.75)</td>
</tr>
<tr>
<td>Old treated syphilis</td>
<td>12 (4)</td>
<td>5 (4)</td>
<td>0.70 (0.21–2.82)</td>
</tr>
<tr>
<td>Positive HSV-2 serology</td>
<td>124 (35)</td>
<td>59 (45)</td>
<td>1.26 (0.89–1.99)</td>
</tr>
<tr>
<td>Positive HIV serology</td>
<td>50 (16)</td>
<td>24 (18)</td>
<td>1.63 (0.90–2.96)</td>
</tr>
</tbody>
</table>

AOR* adjusted odds ratio; HSV-2, herpes simplex virus 2.

Table 3 Sexual behaviour and sexually transmitted infections (STIs) among men in fertile, primary infertile and secondary infertile relationships

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fertile relationship N = 195</th>
<th>Primary infertile N = 195</th>
<th>Secondary infertile N = 233</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>AOR*</td>
<td>p Value</td>
<td>AOR*</td>
</tr>
<tr>
<td>Sexual behaviours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever separated</td>
<td>22 (12)</td>
<td>26 (21)</td>
<td>1.64 (0.63–3.31)</td>
</tr>
<tr>
<td>Ever separated, not because of childlessness</td>
<td>21 (11)</td>
<td>26 (21)</td>
<td>1.80 (0.89–3.61)</td>
</tr>
<tr>
<td>Age at first intercourse &lt; 20</td>
<td>79 (42)</td>
<td>53 (44)</td>
<td>1.00 (0.96–1.03)</td>
</tr>
<tr>
<td>Four or more lifetime sexual partners</td>
<td>86 (45)</td>
<td>57 (47)</td>
<td>0.95 (0.81–1.12)</td>
</tr>
<tr>
<td>Never used a condom</td>
<td>47 (25)</td>
<td>49 (41)</td>
<td>2.30 (1.27–3.85)</td>
</tr>
<tr>
<td>No condom use at last sexual intercourse</td>
<td>167 (88)</td>
<td>119 (98)</td>
<td>8.51 (4.16–37.82)</td>
</tr>
<tr>
<td>Multiple partners in past year</td>
<td>9 (5)</td>
<td>19 (16)</td>
<td>5.34 (2.24–12.72)</td>
</tr>
<tr>
<td>Reported partner’s infertility</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>STIs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital symptoms in the past year</td>
<td>13 (7)</td>
<td>13 (11)</td>
<td>1.51 (0.63–3.59)</td>
</tr>
<tr>
<td>Active syphilis infection</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td>1.20 (0.4–3.54)</td>
</tr>
<tr>
<td>Any active STIs</td>
<td>9 (5)</td>
<td>5 (4)</td>
<td>0.70 (0.20–2.44)</td>
</tr>
<tr>
<td>Oral treated syphilis</td>
<td>10 (5)</td>
<td>7 (6)</td>
<td>1.44 (0.52–3.99)</td>
</tr>
<tr>
<td>Positive HSV-2 serology</td>
<td>71 (38)</td>
<td>50 (42)</td>
<td>1.72 (0.77–2.93)</td>
</tr>
<tr>
<td>Positive HIV serology</td>
<td>18 (9)</td>
<td>19 (16)</td>
<td>1.86 (0.90–3.95)</td>
</tr>
</tbody>
</table>

A*Adjusted for female age, occupation, marital status and income in logistic regression model; no other variables are included.

Includes clinical STIs, active syphilis, gonococcus, chlamydia and trichomoniasis infection.

AOR*, adjusted odds ratio; HSV-2, herpes simplex virus 2.

a threefold higher HIV prevalence among infertile women, a higher exposure to STIs in the past, but no difference for current STIs compared with pregnant women. Two studies in Nigeria reported a higher HIV prevalence among infertile women undergoing diagnostic evaluation and among women with tubal infertility compared with the general population. The HIV prevalence of 16% among fertile women in our study agrees with the reported HIV prevalence of 15.4% among

34. doi:10.1136/sti.2010.042879
women attending antenatal clinics in Kigali in 2003.19 The higher HIV prevalence among couples in secondary infertile relationships contrasts with previous reports showing the same or a higher HIV prevalence in primary infertile women compared to fertile women.10,20 Our data suggest that secondary infertile women represent a distinct group of infertile women characterised by a risky sexual behaviour profile, often starting in adolescence, which has predisposed them to a first pregnancy (the majority of them had had only one pregnancy), HIV infection, other STIs and subsequent infertility. It is of interest to note that 55% of the secondary infertile women had their first pregnancy before the age of 21 (marriage before the age of 21 is illegal in Rwanda) and 28% had experienced at least one unwanted pregnancy. These proportions were significantly lower in the fertile women in our study (N Dhont, unpublished data). The profile of secondary infertile women shows that the epidemics of HIV, STIs, unintended pregnancies and (secondary) infertility are closely linked. Primary infertile women do not report a higher-risk sexual behaviour than fertile women, apart from never use of condoms, which is likely to be a result of their infertility, and a higher number of lifetime partners, which is in part related to unstable relationships caused by infertility. It can be hypothesised that it is rather the risky sexual behaviour of their current and/or past sexual partner that has predisposed them to infertility.

We did not find a higher prevalence of any active STI among infertile couples than among fertile controls despite the higher level of reporting recent high-risk sexual behaviour. This might in part be due to the more vigorous treatment-seeking behaviour among women in infertile relationships when facing genital symptoms. Of the women in infertile relationships, 74% had sought treatment for the last STI episode versus 50% for women in fertile relationships. This phenomenon has been described elsewhere.13 Another study in Nigeria did find a higher prevalence of cervical N. gonorrhoeae in secondary infertile women than in primary infertile and fertile women.41 Unfortunately, we could not implement extensive STI testing in male participants.

It should be noted that selection bias may have influenced the results of our study. The infertile study population is a selection of couples who are willing to undergo infertility investigations; they do not necessarily represent all infertile couples in Kigali. Married infertile couples may have been more motivated to participate in this study than non-married infertile couples because marriage often represents a higher expectation to produce children than non-legalised cohabitation. Married women are less likely to report extramarital sex, and over-representation of married women in the infertile group may therefore have resulted in an underestimation of the HIV-risk behaviours in this group. The different participation rates of male partners in all three groups may also have induced a selection bias. It is possible that disproportionately more faithful fertile men participated in the study, which might have led to overestimation of the differences in HIV-risk behaviour between men in fertile and infertile relationships. However, male infidelity was also reported consistently more frequently by infertile women than by fertile women.

Conclusions about the temporality or causality of the relationships between infertility, sexual behaviour and HIV infection cannot be drawn owing to the case-control design of the study and the lack of data on timing of HIV infections (such as CD4+ counts). However, our own observations and other sources of information are in favour of a causal role of infertility in sexual behaviour and HIV infections. Several social science studies have shown that infertility leads to the practice of ‘looking elsewhere for offspring’, especially among men and to a lesser extent women, and to unstable sexual relationships.11 12 22 These behaviours in turn predispose women and men to HIV infection and STIs. A risky sexual behaviour which put women, and to a lesser extent men, at risk for infertility is perpetuated or might be reinforced after they have become infertile, closing a vicious circle of risky sexual behaviour, HIV infection and infertility.

Furthermore, in our study, high-risk male sexual behaviour in the past was only weakly associated with infertility, whereas more recent high-risk behaviour was more strongly associated with infertility, suggesting that their current sexual behaviour could be a consequence of infertility. Finally, we found an association, although not statistically significant, between HIV infection and longer infertility duration (>5 years) after adjusting for age.

Our study has several implications. First, HIV prevention programmes should target infertile couples, especially secondary infertile, as a high-risk group. Voluntary HIV counselling and testing of infertile couples may identify new HIV infections and increase opportunities for HIV care and prevention. Young people should be taught that unsafe sex increases the risk of acquiring HIV and unintended pregnancies, and also can lead to infertility. Second, provision of fertility services (including safe services for women who are already HIV-infected) could reduce high-risk behaviours and reduce HIV transmission. Some fertility services are readily available in developing countries but are underused, and others are currently not available. To increase access, fertility services could be integrated in family planning or women’s health clinics. Finally, more research is needed to determine the prevalence of primary and secondary infertility in different parts of sub-Saharan Africa, and the temporal relationships between infertility, sexual behaviour and HIV infection.

### Key messages
- In men and women, HIV prevalence rates are significantly higher for secondary infertile relationships than for either primary infertile relationships or fertile relationships.
- In women, secondary infertility is associated with a greater lifetime probability of high-risk sexual behaviour than primary infertility and fertility.
- In men, both primary and secondary infertility relationships are associated with a higher rate of reported multiple partners than fertile relationships.
- Infertility in sub-Saharan Africa should be addressed because it generates enormous suffering and also is closely linked to the HIV epidemic and hampers HIV prevention efforts.

---

**Table 4 HIV diagnosis on couple level according to fertility status**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fertile infertile</th>
<th>Primary infertile</th>
<th>Secondary infertile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=189 n (%)</td>
<td>N=119 n (%)</td>
<td>N=132 n (%)</td>
</tr>
<tr>
<td>Both seronegative</td>
<td>155 (82) 0.5</td>
<td>94 (78) 0.5</td>
<td>73 (55) &lt;0.001</td>
</tr>
<tr>
<td>Both seropositive</td>
<td>12 (6) 0.5</td>
<td>14 (12) 0.3</td>
<td>27 (20) &lt;0.001</td>
</tr>
<tr>
<td>Serodiscordant (female +)</td>
<td>16 (9) 0.3</td>
<td>6 (5) 0.3</td>
<td>23 (17) 0.02</td>
</tr>
<tr>
<td>Serodiscordant (male +)</td>
<td>6 (3) 0.3</td>
<td>5 (4) 0.3</td>
<td>9 (7) 0.1</td>
</tr>
</tbody>
</table>

*Only the couples in whom HIV testing was completed are included.

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Epidemiology

Acknowledgements We thank Rosette Bussa, Ammiel Gasarabwe and the Community Mobilisers for their dedication during data collection, Dr Gilles Nolabsaya for programming the database, and other members of the Projet Ubuzima team and the EDCTP microbicides project team for their contributions and support.

Funding This study was funded by a PhD grant from the Flemish Interuniversity Council (VLIR-UOS). The project also received funding from the European and Developing Countries Clinical Trials Partnership (EDCTP) through a project entitled: Preparing for phase III vaginal microbicide trials in Rwanda and Kenya: preparedness studies, capacity building and strengthening of medical referral systems. However, EDCTP cannot accept any responsibility for information or views expressed herein.

Competing interests None.

Patient consent Obtained.

Ethics approval None.

Provenance and peer review Not commissioned; externally peer reviewed.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Rwanda National Ethics Committee and ethics committee of the University Hospital (UH). The study was conceived and designed by ND, MT and JvdW. JV, ND, CM and JV contributed to specimen and data collection. ND and JvdW assisted with data analysis and interpretation of data. CM, LDN, SL and JV revised the article critically. MT and JvdW provided overall supervision and critical revision of the article. Not commissioned; externally peer reviewed.

REFERENCES

RESULTS OF INFERTILITY INVESTIGATIONS AND FOLLOW-UP AMONG 312 INFERTILE WOMEN AND THEIR PARTNERS IN KIGALI, RWANDA
Results of infertility investigations and follow-up among 312 infertile women and their partners in Kigali, Rwanda

Nathalie Dhont, Janneke van de Wijgert, Joseph Vyankandondera, Rosette Busasa, Ammiel Gasarabwe, Marleen Temmerman

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SUMMARY

The objectives of this study were to assess the outcome of infertility investigations and 18 month follow-up of 312 infertile women and their partners in Rwanda. Between November 2007 and May 2009, an infertility research clinic was opened. Infertile couples received basic infertility investigations, available treatment was provided and couples were followed up over an 18 month period. The infertility remained unexplained in 3%, was due to a female factor in 31%, due to a male factor in 16%, and due to a combination of male and female causes in 50% of fully investigated couples (n=224). A tubal factor was found in 69% of women, a male factor in 64% of men. Predictors for tubal infertility in women included a history of high risk sexual behavior, HIV infection, and a history of STI symptoms in the male partner. After 12-18 months of follow up, 40 pregnancies (16%) had occurred in 244 women. Our study shows high rates of tubal and male factor infertility in Rwanda. Pregnancy rates were low after conventional therapy. In order to provide effective and affordable treatment for infertility in resource poor countries the development of low cost assisted reproductive technologies are needed.
INTRODUCTION

Infertility is highly prevalent in sub-Saharan Africa (SSA), affecting 10-30% of couples. Despite this large burden, very few infertility management programs exist. Consequences of infertility in SSA are often severe and include marital problems, divorce, stigmatization and depression.

The management of infertility patients in medical services is often poor due to lack of guidelines and effective treatment. Information is needed on the causes of infertility in SSA to allow for guidelines to be developed. The pattern of infertility in Africa is different from that in other continents, with a higher proportion of infertility caused by tubal occlusion. Data on male causes of infertility are scarce.

Assisted reproductive technologies are only available in a few African centers and most couples are offered some form of conventional treatment consisting mainly of tubal surgery and ovulation induction. However, little is known about pregnancy outcomes after conventional treatment or spontaneously. A study in Nigeria found a cumulative incidence of pregnancy of 40% in 1948 couples followed up for a maximum of 10 years. In Ghana, a cumulative incidence of spontaneous pregnancies of 12% was reported among 1000 infertile patients followed up for 18 months.

Rwanda is a poor, overpopulated and landlocked country belonging to Central Africa and the great lakes region. Virtually, no data exist on causes of infertility in this region. Our study describes the outcome of infertility investigations in 312 women and 254 male partners presenting at a research infertility clinic in Kigali University Teaching Hospital (KUTH) and predictors for tubal infertility. We also examined pregnancy rates, and predictors for pregnancy, during a 12-18 months follow-up period after the initial infertility investigations.
METHODS

Subjects and setting

An infertility clinic was opened specifically for this study at the Kigali University Teaching Hospital between November 2007 and May 2009 and women in infertile relationships were recruited mainly through word of mouth. Recruitment was terminated when 312 women were enrolled, as per protocol. Infertility was defined as failure to conceive after regular unprotected intercourse for one year or more, and included primary and secondary infertility. After inclusion, all women invited their male partners with a written note to participate on a separate occasion. Refusal to participate in the study did not influence access to further services. The infertility clinic continued to offer care to infertile couples after study closure.

The study was approved by the National Ethics Committee of Rwanda, the Ethics Committee of the University Hospital Ghent and the Centre National de Lutte contre le Sida (CNLS) in Rwanda.

Procedures

A detailed medical history was taken in face to face interviews using structured questionnaires. All female participants received a clinical gynecological examination by the same trained nurse, and supervised by a gynecologist. All men received a genital exam by a male medical officer. Thereafter, the study nurse collected blood samples for serial rapid HIV testing on site as per national algorithm.

After the initial study visit, all women were scheduled for hysterosalpingography (HSG). All HSGs were performed by the same gynecologist in the radiology department of KUTH, using a soluble contrast medium between 7th and 10th day of menstrual cycle. All women were given ibuprofen 400 mg half an hour before the procedure and prophylactic Doxycycline was prescribed. They were asked to come back in case of pain, fever and abdominal pain after the HSG. Some women had evidence of tubal pathology on previously performed HSGs and were therefore referred directly for laparoscopy. Women with a history of amenorrhea were further investigated with measurement of prolactine levels and a
progesterone withdrawal test. Women with a positive progesterone withdrawal test and a normal prolactine were considered to have anovulation.

All male partners were referred for a semen analysis after 3-5 days of abstinence. The semen analysis was performed by an experienced lab technician in a private lab and results were interpreted according to the new WHO reference values. Assessment of morphology was not done due to lack of appropriate equipment. Men who reported to have retrograde ejaculation or regular absence of an erection and/or ejaculation were classified as having a male sexual dysfunction that interferes with their fertility.

After the completion of all investigations, the couples were invited for a follow-up appointment in which the findings were discussed in detail. Women with anovulation, but otherwise normal investigations, were prescribed Clomiphene citrate and followed up in the research clinic. Women with tubal pathology were referred for laparoscopic surgery in KUTH, which is covered by the community based health insurance (patients only pay 10%). As resources of this community based health insurance are limited, we chose to use strict referral criteria including absence of significant male factor, no living children with current partner, no more than 3 living children with a previous partner and age under 43. HIV positive patients were only referred if both partners were tested and aware of each other’s HIV status and if both of them were followed in a HIV care and treatment program.

In cases of oligozoospermia split ejaculation was advised.

Between 12 and 18 months after enrolment all infertile women were contacted by phone to find out about the occurrence of pregnancy. An attempt was made to record reasons for missed visits and non-participation of male partners throughout the study.
RESULTS

Baseline characteristics

A total of 312 infertile women were enrolled in the study and 254 (81%) male partners accepted to participate. A tubal assessment was completed in 266 women and semen analysis in 226 men, resulting in complete assessment in 224 couples. Women whose male partners refused to participate in the study or refused to undergo semen analysis indicated that having children outside their official union (reported by 26 of 78 women) and an unstable union (reported by 11 of 78 women) were important reasons for nonparticipation of their male partner. Some male participants experienced difficulty producing a semen sample through masturbation, and a special condom had to be used to collect the sample during intercourse in 50 cases.

Median age for women was 30 years (inter quartile range (IQR)=27-35) and for men 34 years (IQR=30-40). Fifty seven percent of women and men had secondary infertility. About half of the participants had infertility duration of more than five years. The majority of women (73%) had sought care for their infertility before, whereas very few of men had (22%). Thirty two percent of women and 22% of men tested positive for HIV. For both men and women half of the HIV infections were newly diagnosed cases.

Female investigations

The menstrual history in 312 women revealed amenorrhea in 27 (9%) and oligomenorrhea in 34 (11%) cases (Table 1). Six of the 23 women with amenorrhoea who underwent the progesterone withdrawal test were diagnosed with anovulatory amenorrhoea. Two hundred and sixty six women underwent a tubal assessment: 260 women through HSG and six women through laparoscopy (Table 1). Of these, 80 (31%) had normal tubes and 186 (69%) had evidence of tubo-peritoneal pathology (unilateral in 15% and bilateral in 54% of women). One third of women had a hydrosalpinx, which was bilateral in most cases.
Five women were diagnosed with pelvic inflammatory disease (PID) after HSG with one case requiring hospitalization.

**Male investigations**

Ten percent of the men were diagnosed with sexual dysfunction (Table 1). Of the 226 men who completed a semen analysis, 82 (36%) had normal motility and concentration, 47 (21%) had mild oligozoospermia, 7 (3%) had severe oligozoospermia, 12 (5%) has asthenozoospermia, 64 (28%) had oligoasthenozoospermia and 14 (6%) were found to have azoospermia. Of the 21 men with either azoospermia or severe oligozoospermia, eight men claimed to have fathered children before, mostly with another partner.

**Couple diagnosis**

The infertility remained unexplained in six out of 226 couples (3%), was due to a female factor in 70 couples (31%), due to a male factor in 35 couples (16%), and due to a combination of male and female causes in 113 couples (50%).

**Treatment**

After these initial infertility investigations, 213 couples were seen for medical follow-up. Seventy eight women were referred for laparoscopic surgery in KUTH, nine women were prescribed Clomiphene citrate, and three men were referred to an urologist for sexual dysfunction. Ten women had become pregnant after HSG and 21 were lost to follow-up during further ongoing investigations. For 90 couples, including cases with male factor infertility, women with amenorrhea and negative progesterone withdrawal test and women with tubal factor not eligible for laparoscopic surgery (see criteria mentioned above) we did not prescribe specific treatment.
Table 1: Infertility investigations in 312 women and 254 male partners

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Menstrual history, n=312</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>226 (80)</td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>27 (9)</td>
</tr>
<tr>
<td>oligomenorrhoea</td>
<td>34 (11)</td>
</tr>
<tr>
<td><strong>Tubal assessment, n=266</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>80 (31)</td>
</tr>
<tr>
<td>Unilateral adhesions/phimosis</td>
<td>14 (5)</td>
</tr>
<tr>
<td>Unilateral cornual block</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Bilateral cornual block</td>
<td>29 (11)</td>
</tr>
<tr>
<td>Unilateral distal block</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Bilateral distal block</td>
<td>13 (5)</td>
</tr>
<tr>
<td>Unilateral hydrosalpinx</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Bilateral hydrosalpinx</td>
<td>75 (29)</td>
</tr>
<tr>
<td>Combination adhesions and tubal block</td>
<td>23 (8)</td>
</tr>
<tr>
<td>Total unilateral</td>
<td>42 (15)</td>
</tr>
<tr>
<td>Total bilateral</td>
<td>144 (53)</td>
</tr>
<tr>
<td><strong>Uterine assessment, n=268</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>208 (77)</td>
</tr>
<tr>
<td>Filling defect</td>
<td>30 (11)</td>
</tr>
<tr>
<td>Ashermann</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Congenital</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>7 (3)</td>
</tr>
<tr>
<td><strong>MALE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sexual function, n=254</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>229 (90)</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>25 (10)</td>
</tr>
<tr>
<td><strong>Semen analysis, n=226</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>82 (36)</td>
</tr>
<tr>
<td>Azoospermia</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Mild oligozoospermia</td>
<td>47 (21)</td>
</tr>
<tr>
<td>Severe oligozoospermia</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Asthenozoospermia</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Oligoasthenozoospermia</td>
<td>64 (28)</td>
</tr>
</tbody>
</table>

1 266 HSG and 6 laparoscopies resulted in 266 tubal assessments (6 HSG showed very little uterine fill because of Ashermann and no conclusion could be reached on status of tubes) in 2 women cervical/vaginal stenosis did not allow HSG and they are categorised among miscellaneous uterine abnormalities.
2 includes large or deformed cavities, uterovesical fistula, cervical stenosis
3 includes the men who reported to have rarely or never an erection, orgasm and/or ejaculation and those who report consistent ejaculation before penetration
4 mild oligozoospermia = concentration > 5 million/ml, severe oligozoospermia = concentration of 5 million/ml or less
Of the 78 women who were referred for laparoscopy, 37 women underwent the procedure. Women sometimes had to wait for a laparoscopy appointment for more than a year due to lack of well-trained staff or equipment failure. 27 women underwent laparoscopic surgery (adhesiolysis and/or salpingostomy), which resulted in tubal patency in 14 women (6 unilateral and 8 bilateral).

**Predictors for tubal infertility**

Women who were married or had more than primary school education were less likely, and women in a polygamous union were more likely, to be diagnosed with a tubal abnormality (Table 2). Self-reporting of gynecological symptoms did not predict a tubal abnormality, but a self-reported history of sexually transmitted infections (STIs) in the male partner did. Women who had been pregnant in the past, ever experienced sexual violence, reported coitarche before 20 years, and were HIV positive were also more likely to be diagnosed with a tubal abnormality.

**Pregnancy**

An attempt was made to contact all 312 women after 12-18 months to find out about the occurrence of a pregnancy; 244 women (78%) could be reached. Forty of these women (16%) reported a history of pregnancy in the year following the first study visit. Thirteen of these women became pregnant spontaneously before the HSG was done, 10 pregnancies occurred after treatment (four after laparoscopic surgery, three after Clomiphene citrate, one after IVF, one after split ejaculation, one after weight loss), and 17 were spontaneous pregnancies after HSG. Younger women (age 30 or below) and women with an infertility duration of less than 5 years had a significantly higher chance of becoming pregnant (Table 3).
Table 2: Predictors for tubal abnormality among 266 women in infertile relationship

<table>
<thead>
<tr>
<th>Predictor</th>
<th>No of women (%)</th>
<th>Percent tubal abnormality</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>266</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Socio-demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>151 (57)</td>
<td>64</td>
<td>0.52</td>
<td>0.30-0.91</td>
</tr>
<tr>
<td>Ever divorced or separated</td>
<td>84 (32)</td>
<td>88</td>
<td>4.62</td>
<td>2.24-9.55</td>
</tr>
<tr>
<td>Education more than primary</td>
<td>72 (27)</td>
<td>60</td>
<td>0.53</td>
<td>0.30-0.93</td>
</tr>
<tr>
<td>In polygamous union</td>
<td>24 (9)</td>
<td>92</td>
<td>5.23</td>
<td>1.20-22.81</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever experienced vaginal discharge</td>
<td>188 (71)</td>
<td>72</td>
<td>1.35</td>
<td>0.77-2.37</td>
</tr>
<tr>
<td>Ever had a genital ulcer</td>
<td>44 (16)</td>
<td>68</td>
<td>0.91</td>
<td>0.45-1.82</td>
</tr>
<tr>
<td>Ever experienced acute abdominal pain</td>
<td>30 (11)</td>
<td>63</td>
<td>0.71</td>
<td>0.32-1.58</td>
</tr>
<tr>
<td>Complains of chronic abdominal pain</td>
<td>83 (31)</td>
<td>71</td>
<td>1.08</td>
<td>0.61-1.91</td>
</tr>
<tr>
<td>Complains of dyspareunia</td>
<td>107 (40)</td>
<td>69</td>
<td>0.94</td>
<td>0.55-1.60</td>
</tr>
<tr>
<td>Partner ever had STI</td>
<td>59 (22)</td>
<td>86</td>
<td>3.40</td>
<td>1.53-7.55</td>
</tr>
<tr>
<td>Partner circumcised</td>
<td>111 (42)</td>
<td>66</td>
<td>0.71</td>
<td>0.42-1.21</td>
</tr>
<tr>
<td>Normal menses</td>
<td>220 (83)</td>
<td>75</td>
<td>3.19</td>
<td>1.66-6.34</td>
</tr>
<tr>
<td><strong>Obstetric history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever had pregnancy before</td>
<td>146 (55)</td>
<td>76</td>
<td>1.90</td>
<td>1.12-3.23</td>
</tr>
<tr>
<td>Ever had adverse obstetric event(^1)</td>
<td>47 (18)</td>
<td>80</td>
<td>2.01</td>
<td>0.92-4.40</td>
</tr>
<tr>
<td><strong>Sexual history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever sexual violence</td>
<td>70 (26)</td>
<td>80</td>
<td>2.03</td>
<td>1.44-4.20</td>
</tr>
<tr>
<td>coitarche &lt;20 yrs</td>
<td>154 (58)</td>
<td>78</td>
<td>2.46</td>
<td>1.05-3.91</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV(^2)</td>
<td>82 (31)</td>
<td>78</td>
<td>1.84</td>
<td>1.00-3.37</td>
</tr>
<tr>
<td><strong>Ultrasound</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspicion hydrosalpinx(^3)</td>
<td>44 (17)</td>
<td>91</td>
<td>5</td>
<td>1.72-14.53</td>
</tr>
</tbody>
</table>

\(^1\) includes post partum infection, caesarean section or stillbirth \(^2\) n=264 \(^3\) n=257

Table 3: Predictors of pregnancies at 1 year follow up in 244 women in an infertile relationship

<table>
<thead>
<tr>
<th>Predictor</th>
<th>N (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 or less</td>
<td>27/122 (22)</td>
<td>0.001</td>
</tr>
<tr>
<td>More than 30</td>
<td>13/122 (11)</td>
<td></td>
</tr>
<tr>
<td><strong>Infertility duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years or less</td>
<td>28/116 (24)</td>
<td>0.002</td>
</tr>
<tr>
<td>More than 5 years</td>
<td>12/128 (9)</td>
<td></td>
</tr>
<tr>
<td><strong>Infertility diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7/50 (14)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6/34 (18)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>9/85 (10)</td>
<td>NS</td>
</tr>
<tr>
<td>Unexplained</td>
<td>1/6 (17)</td>
<td></td>
</tr>
<tr>
<td>Not finished</td>
<td>17/69 (25)</td>
<td></td>
</tr>
<tr>
<td><strong>Infertility type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>17/112 (15)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>23/132 (17)</td>
<td></td>
</tr>
<tr>
<td><strong>HIV diagnosis woman</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>27/172 (16)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive</td>
<td>11/68 (16)</td>
<td></td>
</tr>
</tbody>
</table>

NS=non significant \(^1\) 2 missing values
DISCUSSION

Our study found a high prevalence of tubal factor and male factor infertility, among urban infertile couples in Rwanda. Pregnancy rates were low after conventional therapy. Predictors for tubal infertility in women included a history of rape, early age first intercourse, HIV infection, and a history of STI symptoms in the male partner.

The prevalence of tubal occlusion in our study is similar to the prevalence found in other African countries, which ranges from 50% to 82.5% of women complaining of infertility \(^{6,7,10,11}\). Data on male factor infertility in SSA are scarce, but the few available sources indicate that it is not uncommon. A male factor was found in 82% of men in infertile relationships in South Africa and in 45% in Ghana \(^6,7\).

Comparison of semen analysis results is difficult due to lack of standardization between different laboratories.

The cumulative incidence of pregnancy in our study (16%) was much lower than the 40% reported by Orhue et al in Nigeria \(^6\). It is likely that the two study populations differ considerably, making comparison difficult. The study in Nigeria covered a period of 10 years, their rates of tubal infertility (47% of women) were much lower and their rates of idiopathic infertility much higher (20% of couples). The low pregnancy rate after tubal macrosurgery confirms findings from other countries \(^12\).

We encountered many problems during the investigation of infertile couples. Due to prolonged periods of radioscopy equipment failure the time lag between the initial visit and the HSG appointment was often considerably long, explaining why 12 women became pregnant before the HSG. A high proportion of men had difficulties producing a semen sample. A large proportion of infertile couples did not complete all medical follow-up procedures after infertility diagnosis. There are possibly many causes for the lost to follow-up among these couples. The investigations were offered free of charge, but the treatments were not free of charge. Furthermore, many couples experienced relationship problems
because of infertility. Finally, many patients found out about their positive HIV serostatus in our study, and this may have influenced their reproductive choices and their willingness to continue with treatment. This underscores the importance of comprehensive pre- and post-HIV test counseling.

A few limitations need to be considered when interpreting our study findings. The study population is urban and the results are not necessarily applicable to the whole population of Rwanda. However, a study in Tanzania showed that infertility diagnoses among urban women do not differ significantly from those in rural women. The selection of infertile couples was through the women, and it is therefore possible that male factor infertility was underestimated. The study was not designed to examine pregnancy rates or treatment success: the number of couples fully examined was relatively small and the number treated even smaller. Finally, the results of the semen analysis need to be interpreted with caution since data on morphology are lacking and there are no laboratories offering standardized semen analysis methods.

Few infertile couples in SSA can be treated effectively without assisted reproductive technologies (ART) and the majority of these will need IVF/ICSI. The current cost of ART prohibits its widespread use in resource poor countries. There is some hope that these techniques can be offered at a much lower cost in the future. However, we believe that infertility management in resource-poor countries can be improved even without ART. On the primary care level, the main focus should be on history-taking and counseling (with emphasis on the need to involve male partners) and some basic investigations such as syphilis and HIV testing can be performed. In the district hospitals, tubal assessment and semen analysis should be included in the infertility diagnostic workup simultaneously and treatment should not be started until these assessments have been completed. Investment in radioscopy equipment and training courses in standardized semen analysis for lab technicians can improve the quality of the diagnostic tools available. On the tertiary referral level, a unit dedicated to infertility is needed to provide these
patients with the specialized care they need. Investment in laparoscopy and hysteroscopy equipment and training is called for. For many women, HSG is a painful experience and it carries a risk for PID. Therefore, it could be argued that it might be appropriate to refer certain women, including those ones with secondary infertility—especially if there was an adverse obstetric event, HIV, previous history of sexual violence and/or early age at first sex—straight for laparoscopic assessment, if readily available.

Above all, there is an urgent need for political willingness to put infertility care on the public health agenda. Prevention of infertility through prevention of STIs, better management on all levels of healthcare through a systematic and dedicated approach and the provision of low cost ART will all contribute considerably to alleviate the suffering of infertile couples in SSA.
AKNOWLEDGMENTS

This study was funded by a PhD grant from the Flemish Interuniversity Council (VLIR-UOS) and by the European and Developing Countries Clinical Trials Partnership (EDCTP) through a project entitled: “Preparing for Phase III vaginal microbicide trials in Rwanda and Kenya: Preparedness studies, capacity building, and strengthening of medical referral systems”. EDCTP cannot accept any responsibility for information or views expressed herein. The project also received funding from the “Walking Egg npo”, Genk 2000.

CONFLICT OF INTEREST

None declared.


GENDER DIFFERENCE AND FACTORS ASSOCIATED WITH TREATMENT-SEEKING BEHAVIOUR FOR INFERTILITY IN RWANDA
Gender differences and factors associated with treatment-seeking behaviour for infertility in Rwanda

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BACKGROUND: This study examines perceptions of infertility causes, treatment-seeking behaviour and factors associated with seeking medical care in an urban infertile population in Rwanda, as well as the response of health providers.

METHODS: Between November 2007 and May 2009 a hospital based survey was conducted among 312 women and 254 male partners in an infertile relationship.

RESULTS: Infertility causes based on a medical diagnosis were mentioned by 24% of women and 17% of men. Male infertility awareness was low in both sexes with 28% of men and 10% of women reporting male-related causes. Seventy-four per cent of women and 22% of men had sought care for their infertility in the past. Seeking treatment in the formal medical sector was associated with higher income, being married and infertility duration of more than 5 years in both sexes. In women, higher education and being nulliparous and in men blaming oneself for the infertility was also associated with seeking formal medical care. Participants reported a wide array of treatments they received in the past, often including ineffective or even harmful interventions.

CONCLUSION: Health authorities should invest in improving information, education and counselling on issues pertaining to causes and treatments of infertility, and in drawing up guidelines for the management of infertility at all levels of health care.

Key words: infertility / treatment-seeking behaviour / resource-poor countries / gender / Rwanda

Introduction

Infertility is highly prevalent in sub-Saharan Africa, affecting up to one-third of couples in certain areas, but has not received the attention it deserves due to limited resources, policies aimed at reducing population growth and the high cost of modern infertility treatment (Larsen, 2000; Vayena et al., 2002; Abouighar, 2005; Bovin et al., 2007; Ombelet et al., 2008). The inability to conceive has severe consequences for couples, especially for women, in countries where female identity, social status and security depend on the ability to produce offspring (Gerrits, 1997; Sundby, 1997; Dyer, 2002; van Balen and Bos, 2009). Although it is unlikely that modern assisted reproductive technologies at current cost will become available in the public services of resource-poor countries, at least in the medium term, a call has been made by several authors to improve information, education and counselling on causes of and treatments for infertility and to draw up guidelines for the management of infertility at all levels of healthcare (Sundby et al., 1998; van Balen and Gerrits, 2001; Folkvord et al., 2005). In order to do this, information about prevailing perceptions and treatment-seeking behaviour is needed.

Previous research in Mozambique and Gambia has shown that many infertile couples engage in prolonged and relentless care-seeking often without the desired result (Gerrits, 1997; Sundby et al., 1998). In most developing countries, the formal medical sector has very little to offer to these couples and often ineffective treatments without prior systematic investigations are tried out with limited success. As a result, some patients consult both the formal medical and traditional health-care sector draining their already scarce resources. Men are culturally often not construed as infertile and therefore absent themselves from seeking treatment for infertility (Upton, 2002; Barden-O’Fallon, 2005a, b; Folkvord et al., 2005).
Most of the research on infertility in Africa has been anthropological and mainly conducted in Western or Southern Africa. There are virtually no data on treatment-seeking behaviour for infertility and prevailing perceptions on its causes in the East-African region. Furthermore, we know very little about the factors associated with seeking care in the formal medical sector for both men and women, and very few descriptions of the response of health-care providers have been reported. Detailed knowledge of these factors could assist in developing the appropriate strategy for helping infertile couples in some African countries.

We therefore conducted a survey among 312 infertile women and 254 male partners presenting themselves for infertility investigations at a research clinic in Kigali, Rwanda. We obtained a detailed history from each participant including where and when they had sought care for infertility, the interventions they received and their perception of the causes of infertility. Associations between care-seeking in the formal medical sector and selected factors (socio-demographics, reproductive history, relationship/ household characteristics and perceptions) were analysed. Perceptions and treatment-seeking behaviour were compared between both sexes.

Materials and Methods

Study population and setting

Between November 2007 and May 2009, an infertility research clinic was opened at the Kigali University Teaching Hospital (KUTH) in Rwanda, which set out to offer a basic package of infertility investigations, free of charge, to 300 couples. Initially, study participants were recruited among women attending the gynaecological consultations at KUTH and the district hospital of Muhima, the largest secondary referral hospital for gynaecological problems in Kigali. Recruited women spread the word of the research clinic, which resulted in two-thirds of the enrolled participants being recruited through word of mouth. To be eligible for participation, women needed to be between 21 and 45 years of age, residing in Kigali, willing to undergo HIV testing and having had sexual intercourse at least once in the last 2 weeks. Refusal to participate in the study did not influence access to further services. Infertility was defined as having had regular unprotected intercourse for 1 year or more without conception with at least one regular partner. After inclusion, all women invited their male partners with a written note from the research clinic to participate on a separate occasion.

The study was approved by the National Ethics Committee of Rwanda and the Ethics Committee of the Ghent University Hospital.

Study measurements and variables

The purpose of the study was explained to potential participants in their local language (Kinyarwanda) and eligibility criteria were checked. All participants provided written informed consent before study procedures took place. Women were interviewed by a female nurse and male partners by a male medical officer about socio-demographic characteristics, reproductive history and their perception of causes of infertility using a structured questionnaire. The question about what participants thought had caused their infertility was open-ended and categorized after data collection. Belief in poisoning, bewitching or demons was categorized as traditional beliefs and belief in God’s will or God’s punishment as religious beliefs. The category medical causes applied when one of the following terms was used by the participant: ovulation disorders, abnormal tubes, semen abnormalities, abnormal menses, myomias, hormonal problems, post-partum or post-operative complications and advancing age. Lifestyle factors include sexual behaviours, alcohol and stress. All medical concepts, which remained vague such as ‘some disease’ or which were clearly fabricated by the participant such as ‘too many hormones’, ‘blood incompatibility’ were categorized under own medical construct. Participants were asked to report on the investigations and treatments received for each medical visit in the past.

Statistical analysis

Data collected during interviews and laboratory investigations were entered once, verified and cleaned using MS Access 2000 (Microsoft, Seattle, USA). Intercooled Stata 9.2 (Data Corporation, College Station, TX, USA) was used for statistical analysis. Differences between proportions and medians were compared using Chi-squared tests (test for trend in case of ordered exposure categories) and Mann–Whitney U-tests, respectively. Variables with a moderate association with the outcome (P-value less than 0.2) in bivariate analysis were selected and retained in multivariable models when they were significantly associated or affected the association (odds ratio (OR)) between the other predictors and the outcome with 10% or more.

Results

Demographic characteristics

Of a total of 339 potentially infertile women who presented to the clinic, 312 were confirmed eligible and enrolled. Male partners of 81% of the infertile women (254 partners) agreed to participate. The median age was 30 years (inter quartile range (IQR) = 27–35 years) for the infertile women and 34 years (IQR = 30–40 years) for the infertile men (data not shown). Twenty-eight per cent of the infertile women and 41% of the infertile men had received more than primary education. Seventy per cent of the infertile women and 100% of the infertile men was employed at the time of the survey. Sixty-seven per cent of women and 21% of men were earning less than 1.25 USD a day, and 9% of women and 22% of men were earning more than five USD a day.

Perception of causes of infertility

When asked what they perceive as the cause of their infertility, 25% of women mentioned traditional or religious beliefs, 25% named a cause based on a medical diagnosis, 6% blamed HIV/STIs, 11% fabricated their own medical concept and the remaining had either no idea (30%), blamed contraceptives (4%) or diverse lifestyle factors (2%) (Table I). Men were less likely than women to mention traditional beliefs (11% versus 18%, P = 0.025), were less likely to construct their own medical concepts (5% versus 11%, P = 0.02) and more likely to say I don’t know (48% versus 30%, P < 0.001) than women. Fifty-three per cent of the women blamed only themselves for the infertility versus 14% of males (P < 0.001). When indicating a female cause of infertility, men often mentioned that they had children in another relationship.

Characteristics of treatment-seeking behaviour in the past

Table II lists the different features of fertility treatment-seeking behaviour for participating women and men. Of the 312 women and the 254 men, 227 (73%) and 56 (22%) had sought care for their infertility,
women this was six times their monthly income (data not shown). Income on infertility investigations and treatment and for 25% of once, whereas 43% reported to have done so for infertility. Half the resulted the traditional healer for a general medical problem at least compared with men. Fifteen per cent of women reported to have con-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female (n = 308), n (%)</th>
<th>Male (n = 252), n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional beliefsa</td>
<td>55 (18)</td>
<td>28 (11)</td>
<td>0.025</td>
</tr>
<tr>
<td>Religious beliefsb</td>
<td>25 (8)</td>
<td>17 (7)</td>
<td>0.54</td>
</tr>
<tr>
<td>Medical cause</td>
<td>73 (24)</td>
<td>44 (17)</td>
<td>0.07</td>
</tr>
<tr>
<td>STI/HIV</td>
<td>20 (6)</td>
<td>13 (5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Contraceptives</td>
<td>13 (4)</td>
<td>7 (3)</td>
<td>0.36</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>6 (2)</td>
<td>8 (3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Medical concept constructed by participant</td>
<td>34 (11)</td>
<td>14 (5)</td>
<td>0.02</td>
</tr>
<tr>
<td>No concept</td>
<td>93 (30)</td>
<td>122 (48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The person perceived as having the problem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>self is cause</td>
<td>163 (53)</td>
<td>35 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>partner is cause</td>
<td>14 (5)</td>
<td>130 (52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>both are cause</td>
<td>15 (5)</td>
<td>35 (14)</td>
<td>0.002</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>116 (38)</td>
<td>52 (21)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Answers were given to an open-ended question: “What, according to you, is the cause of infertility in your relationship?” and were afterwards categorized. Multiple responses were possible.

Belief that infertility is caused by poisoning, bewitching and demons.

Belief that infertility is caused by God’s will or punishment.

respectively (Table II). Eleven per cent (24/227) of these women and 5% (3/56) of these men had only consulted a traditional healer; the remaining women and men had visited the formal medical sector (private, public and non-governmental not-for-profit organization (NGO)). Forty per cent of women and 47% of men first sought help in the public sector. Twenty-five per cent of women and 7% of men had consulted the traditional healer first (P = 0.003). Women started looking for help after a shorter time interval (median of 2 versus median of 3 years, P = 0.002), they paid more visits (median of 4 versus median of 2 visits, P < 0.001), sought help more frequently from different sources (P < 0.001) and paid more frequently at least one visit to the traditional healer (43% versus 14%, P < 0.001), compared with men. Fifteen per cent of women reported to have consulted the traditional healer for a general medical problem at least once, whereas 43% reported to have done so for infertility. Half the infertile women who had sought care spent twice their monthly income on infertility investigations and treatment and for 25% of women this was six times their monthly income (data not shown).

Predictors of treatment-seeking among infertile women

Independent predictors for seeking care in the formal medical sector for women were: higher education (adjusted odds ratio (AOR): 4.04, 95% CI: 1.89–8.64), higher income (AOR: 2.14, 95% CI: 1.20–3.82), being married (AOR: 2.00, 95% CI: 1.16–3.42), being nulliparous (AOR: 2.78, 95% CI: 1.30–5.95) and being in an infertile relationship for at least 5 years (AOR: 1.96, 95% CI: 1.11–3.49) (Table III).

Predictors of treatment-seeking among infertile men

For the men in an infertile relationship, having a higher income (AOR: 5.65, CI: 1.34–23.82), being married (AOR: 4.51, CI: 1.95–10.42), having infertility for at least 5 years (AOR: 3.22, CI: 1.41–7.33) and blaming oneself for the infertility (AOR: 3.61, CI: 1.76–7.43) were associated with seeking care in the formal medical sector (Table IV).

Treatments offered by formal medical sector

Of the 203 women who consulted the formal medical sector, 25% reported to never having received any tubal investigations (either by hysterosalpingography (HSG) or by laparoscopy). Women mentioned having received a wide variety of treatments in the formal medical sector, mostly medical treatments including oral tablets, injections, suppositories and vaginal tablets. Clomiphene citrate was the most popular medical treatment followed by some kind of hormonal treatment, which includes steroids, contraceptives, estrogens and progesterogens. Women often received a cocktail of drugs including antibiotics, female hormones, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids. Some women reported receiving injections into the uterus. Half the men received medical treatments, mostly testosterone or clomiphene citrate. Twenty per cent of women had undergone surgery as treatment for their infertility including tubal surgery, myomectomy and ovarian cystectomy. In most cases surgery was performed through laparotomy. Twenty-five per cent of women received clomiphene citrate at least once. Of the 57 women who had received clomiphene citrate in the past, the majority (49/57, 84%) reported a regular menstrual cycle, and 30% of these women we diagnosed a bilateral tubal block on the hysterosalpingography/laparoscopy performed in the research clinic.

Discussion

Sex differences in the perception of causes of infertility, in treatment-seeking behaviour and in the factors associated with seeking modern medical care for infertility were identified. A wide variation of causes was reported by men and women for their infertility. Traditional beliefs (poisoning, bewitching, etc.) and religious beliefs (God’s will) were often cited the cause of infertility, though more by women than men. Only a quarter of the participants named explanations based on a medical diagnosis and often they constructed their own medical concept, despite the fact that the majority (65%) of women had previously been exposed to modern medical healthcare. These findings complement existing research on this subject from other sub-Saharan countries (Sundby, 1997; Dyer et al., 2002a, b; Richards, 2002). In-depth interviews with infertile women in South Africa highlighted the discrepancy between biomedical information rendered by patients and their personal concept on this information (Dyer et al., 2002a, b).

In a region where infection-related causes of infertility dominate, there is very little awareness of the link of infertility with high-risk sexual behaviour and sexually transmitted infections (STIs). In our population, very few men and women thought that their infertility could be caused by STIs including HIV. The same was noted by Barden-O’Fallon among women and men in rural Malawi (Barden-O’Fallon, 2005a, b).
Both men and women are unlikely to attribute infertility to the male partner, partly explaining why only 22% of men had ever sought care for infertility. These results are in keeping with reports from other African countries with the exception of South Africa where male infertility awareness was unexpectedly high (Fiander, 1990; Sundby, 1997; Sundby et al., 1998; Dyer et al., 2004). Free and easy access to a referral hospital with an organized and welcoming research team might have positively influenced the high participation rate of male partners in our study (81%).

The gender differences, which we found in perceptions towards infertility and in treatment-seeking behaviour indicate that in Rwandese society the woman is blamed, not only by her partner but also by herself, for the couple’s difficulty with childbearing. She carries the greatest burden of stigmatization and suffering caused by infertility. Educational campaigns need to make an effort to reach both women and men to address these issues.

In addition to the public services, the private sector and the traditional healer are both important alternative sources of first help. It has been demonstrated repeatedly that traditional healers attract people to come to them for infertility treatment (Sundby et al., 1998; Barden-O’Fallon, 2005a, b; Folkvord, 2005; Stekelenburg et al., 2005). Care is often sought from both the traditional and the formal health sector, as is also the case in our population (Dyer et al., 2002a, b). These findings indicate the need to involve healthcare staff from both formal and informal sectors when investing in education of infertile couples and the community about infertility.

The analysis of factors associated with seeking formal medical treatment suggests that in addition to factors related to reproductive history, educational level, income and perceptions are predicting treatment-seeking behaviour. A similar finding was reported from a study in Malawi where educated women were more likely to seek treatment for infertility (Barden-O’Fallon, 2005a, b). In our study, we also found that men who blame themselves for infertility are four times more likely to have consulted medical services. A significant limitation of this study is that the study design cannot ascertain whether these men are more likely to seek care or whether their perception has changed after contact with the medical services.

Rwanda is a poor and overpopulated country with 77% of its population living under the poverty threshold of 1.25 USD a day. Management of infertility is not a priority for the public health sector. Basic infertility investigations such as HSG and semen analysis are not widely available and often of poor quality. None of the hospitals has a unit dedicated to infertility. Laparoscopic surgery is only available in the capital. The curative health-care services in the public sector are provided with a 10% co-payment fee, the rest is paid by the community-based health insurance. However, the need to travel long distances to access infertility investigations adds considerably to the cost. The finding in our study that infertile men and women with higher income are more likely to seek care indicates that financial constraints play a role in treatment-seeking behaviour for infertility.

Our study findings were obtained from urban couples, willing to undergo infertility investigations and may therefore not be
generalized to the country level. It is possible that findings on perception towards infertility and treatment-seeking behaviour for infertility are quite different among a community-based sample of rural infertile couples. The socio-economic status of infertile women in our study is not different from the general female population in Kigali whereas the socio-economic status of the infertile men seems higher than the general male population in Kigali (DHS 2005).

There is some hope that in the future assisted reproductive techniques could be made more affordable but further research is necessary to understand the factors influencing treatment-seeking behaviour in Rwanda.

### Table III: Predictors of having sought care in formal medical sector for women (n = 312).

<table>
<thead>
<tr>
<th>Socio-economic characteristics</th>
<th>Per cent having sought medical care in formal sector</th>
<th>Crude odds ratio</th>
<th>95% CI</th>
<th>Adjusted odds ratioa</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21–29</td>
<td>60.3</td>
<td>1.43</td>
<td>0.84–2.29</td>
<td>1.60</td>
<td>0.87–2.91</td>
</tr>
<tr>
<td>30 and above</td>
<td>68.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to primary</td>
<td>56.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than primary</td>
<td>87.4</td>
<td>5.33</td>
<td>2.69–10.58</td>
<td>4.04</td>
<td>1.89–8.64</td>
</tr>
<tr>
<td><strong>Religion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Muslimb</td>
<td>64.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>75.0</td>
<td>1.68</td>
<td>0.69–4.09</td>
<td>NI</td>
<td></td>
</tr>
<tr>
<td><strong>Income</strong>c</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 dollar/day</td>
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<tr>
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<td>2.00</td>
<td>1.16–3.42</td>
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<tr>
<td><strong>Polygamous union</strong></td>
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<td>At least one</td>
<td>64.1</td>
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<td>Parity</td>
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<td>51.0</td>
<td>3.54</td>
<td>2.16–5.79</td>
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<td>Never had a pregnancy &gt;28 weeks</td>
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<td>72.8</td>
<td>2.84</td>
<td>1.73–4.66</td>
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<td>0.79–3.60</td>
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<td><strong>Duration infertility</strong></td>
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<td></td>
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<td></td>
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<td>58.8</td>
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<td>1.07–2.75</td>
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<tr>
<td>Blames partner only</td>
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<td>Blames self for infertility</td>
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<td>0.68–1.74</td>
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</table>

NI, variables not selected for inclusion into final regression model.

aVariables with a moderate association with the outcome (P-value less than 0.2) were selected and retained in final regression model when they were significantly associated or affected the association (odds ratio (OR)) between the other predictors and the outcome with 10% or more. Final model included age, education, marital status, income, parity, living children and duration infertility. Infertility type was not included since it is collinear with parity.

bIncludes all other religions and non-believers.

c16 missing values, n = 296.

d4 missing values, n = 308.
needed in how to implement simplified methods of infertility diagnosis and treatment in developing countries (Ombelet, 2009). Health authorities could in the meantime invest in improving information, education and counselling on causes and treatments of infertility.

In order to prevent inappropriate treatments, guidelines for the management of infertility at all levels of healthcare should be drawn up and included in the curriculum of doctors, nurses and midwives. In health-care centres, the main focus should be on history taking and counselling (with emphasis on need to involve men) and some basic investigations such as syphilis and HIV testing can be performed. If a real problem of infertility (1 year of regular unprotected intercourse without conception) exists, the couple needs to be referred

### Table IV

Predictors of having sought care in formal medical sector for men (n = 254).

<table>
<thead>
<tr>
<th>Socio-economic characteristics</th>
<th>Per cent having sought medical care in formal sector</th>
<th>Crude odds ratio</th>
<th>95% CI</th>
<th>Adjusted odds ratio×</th>
<th>95% CI</th>
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<td><strong>Age</strong></td>
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<td>0.91–4.66</td>
<td>1.01</td>
<td>0.36–2.82</td>
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<td><strong>Education</strong></td>
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<td>Up to primary</td>
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<td>More than primary</td>
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<td>Muslim</td>
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<td>0.11–1.27</td>
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<td>0.81–9.54</td>
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<td>At least one</td>
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<td>1.03</td>
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<tr>
<td>Primary</td>
<td>30.9</td>
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<td>0.96–4.90</td>
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<td>Duration infertility</td>
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<td>5 years or more</td>
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<td>1.30–4.61</td>
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<tr>
<td>Blames partner only</td>
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<tr>
<td>Blames self for infertility</td>
<td>40.0</td>
<td>4.19</td>
<td>2.21–7.92</td>
<td>3.61</td>
<td>1.76–7.43</td>
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</table>

NI, variables not selected for inclusion into final regression model.

*Variables with a moderate association with the outcome (P-value less than 0.2) were selected and retained in final regression model when they were significantly associated or affected the association (odds ratio (OR)) between the other predictors and the outcome with 10% or more. Final model included age, income, marital status, infertility type, pregnancy with current partner, duration infertility and perception. n = 236.

bIncludes all other religions and non-believers.

c18 missing values, n = 236.

d2 missing values, n = 252.
to the district hospital for HSG and semen analysis. After completing the investigations, the couple should receive comprehensive information on the findings and possible treatment. In our experience, couples appreciate the information, even if no treatment can be offered as understanding the problem often helps them to accept it.

All this can prevent exploitation, potentially damaging practices and waste of the savings and can alleviate the stigmatization and enormous suffering of the infertile patient.

The link between high-risk sexual behaviour, HIV/STIs and infertility deserves special attention. Currently family planning or HIV/AIDS prevention programmes promote dual protection against unintended pregnancies and HIV/STIs. Other authors have already suggested that, since infertility is one of the most feared conditions in sub-Saharan Africa, extending the concept of dual protection to include the safeguarding of fertility (‘triple protection’) could be viewed as a unique selling point (Brady, 2003).

Authors’ roles

The study was conceived and designed by N.D., M.T. and Jvd.W. N.D., J.V., G.A., N.D. analysed the study data and drafted the article. S.L. and Jvd.W. assisted with data analysis and interpretation of data. W.O. assisted with interpretation of data. S.L., W.O., A.G., J.V., Jvd.W. and M.T. revised the article critically.

Acknowledgements

We thank Rosette Busasa and the Community Mobilizers for their dedication during data collection. Dr. Gilles Ndabishya for programming of the database, and other members of the Projet Ubuzima team and the ECDCPT microbicides project team for their contributions and support.

Funding

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Dyer SJ, Abrahams N, Mokoena NE, van der Spuy ZM. ‘You are a man because you have children’: experiences, reproductive health knowledge and treatment-seeking behaviour among men suffering from couple infertility in South Africa. Hum Reprod 2004;19:960–967.


‘MAMA AND PAPA NOTHING’: LIVING WITH INFERTILITY AMONG AN URBAN POPULATION IN KIGALI, RWANDA
BACKGROUND: Not being able to procreate has severe social and economic repercussions in resource-poor countries. The purpose of this research was to explore the consequences of female and/or male factor infertility for men and women in Rwanda.

METHODS: Both quantitative and qualitative methods were used. Couples presenting with female and/or male factor infertility problems at the infertility clinic of the Kigali University Teaching Hospital (n = 312), and fertile controls who recently delivered (n = 312), were surveyed about domestic violence, current and past relationships and sexual functioning. In addition, five focus group discussions were held with a subsample of survey participants, who were either patients diagnosed with female- or male-factor fertility or their partners.

RESULTS: Domestic violence, union dissolutions and sexual dysfunction were reported more frequently in the survey by infertile than fertile couples. The psycho-social consequences suffered by infertile couples in Rwanda are severe and similar to those reported in other resource-poor countries. Although women carry the largest burden of suffering, the negative repercussions of infertility for men, especially at the level of the community, are considerable. Whether the infertility was caused by a female factor or male factor was an important determinant for the type of psycho-social consequences suffered.

CONCLUSIONS: In Rwanda, as in other resource-poor countries, infertility causes severe suffering. There is an urgent need to recognize infertility as a serious reproductive health problem and to put infertility care on the public health agenda.

Key words: infertility / marriage / resource-poor countries / psychological effects / social attitudes
This work was part of a larger study offering infertility investigations to 312 infertile couples and examining predictors of infertility (Dhont et al., 2010b). The focus of the main study was to determine the causes and risk factors for infertility in Rwanda. The focus of this sub-study was to explore the consequences of infertility in Rwanda, with special emphasis on the differences of experiences between men and women, and between infertility caused by a male or female factor.

Materials and Methods
A quantitative survey and qualitative focus group discussions (FGDs) were conducted in order to gain a better understanding of the socio-cultural consequences of infertility.

Quantitative study
The survey was an integrated part of a larger case–control study; the study participants and procedures have been described elsewhere (Dhont et al., 2010b). In brief, an infertility clinic was opened specifically for this study at the Kigali University Teaching Hospital between November 2007 and May 2009, and women in infertile relationships were recruited mainly through word of mouth. Recruitment was terminated when 312 women were enrolled, as per the protocol. Infertility was defined as failure to conceive (irrespective of the underlying cause) after regular unprotected intercourse for 1 year or more, and included primary and secondary infertility. Refusal to participate in the study did not influence access to further services. The infertility clinic continued to offer care to infertile couples after study closure.

Fertile controls were defined as non-pregnant women who recently (between 6 and 18 months ago) delivered and were recruited at the hospital. From this list, 14 neighbourhoods were randomly selected by blindly hand-picking numbers from a bowl. Community mobilizers in these neighbourhoods invited all potential eligible candidates to participate in the study.

After inclusion, all cases and controls invited their male partners to participate in a separate occasion.

The study was approved by the National Ethics Committee of Rwanda, the Ethics Committee of the University Hospital Ghent and the National AIDS Control Program (CNLS) in Rwanda.

The purpose of the study was explained to the study participants in the local language (Kinyarwanda) and eligibility criteria were checked. All participants provided written informed consent before study initiation. A female nurse interviewer addressed the women and a male medical officer addressed the male partners. A structured questionnaire was administered during a face-to-face interview including questions about socio-demographic characteristics, current and past relationships, domestic violence and sexual functioning. Most questions had been field-tested by studies previously conducted in Rwanda; a few questions were study-specific. All questions had fixed-choice response alternatives. Before asking the questions on sexual functioning, the concepts of sexual desire, sexual arousal, sexual activity and sexual stimulation were uniformly explained to all the respondents.

After the first study visit, all women in an infertile relationship were offered hysterosalpingography and/or laparoscopy. Their male partners were offered semen analysis. After the completion of these investigations, the infertile couples were invited back to the clinic to discuss the findings and, if appropriate, were referred for further treatment (in most cases, laparoscopic surgery or ovulation induction). This is when the couples were told whether their infertility was most likely caused by a female factor, a male factor, or both, or that a cause could not be determined.

Clinical follow-up of treatment was provided free of charge in the study clinic, but patients had to pay for medications and operative procedures.

Data collected during interviews were single entered, verified and cleaned using MS Access 2000 (Microsoft, Seattle, WA, USA). Intercooled Stata 9.2 (Stata Corporation, College Station, TX, USA) was used for statistical analysis. Characteristics of infertile and fertile women and their partners were compared using chi² tests or tests for trend.

Qualitative study
For each FGD, 7–10 participants were selected from different diagnostic groups: one FGD with women and a second FGD with men from infertile couples diagnosed with female factor only, a third FGD with women and a fourth FGD with men from infertile couples diagnosed with male factor only. This specific group assignment served two purposes: to encourage participants to speak more freely and to explore the effect of a gender-specific infertility diagnosis on the experience of infertile couples. A fifth FGD included a mixture of men and women in infertile relationships irrespective of the cause of the infertility. The five FGDs included a total of 21 female and 20 male participants and were held in the local language, Kinyarwanda. FGD participants provided separate informed consent for FGD participation. A discussion guide was developed based on the current knowledge of consequences of infertility, which included questions about relationships with the partner and in-laws, experiences in the community, economic aspects, issues related to continuing the family line and relationships with ancestors, and emotional status. In addition, in each group, the effect of the gender-specific infertility diagnosis, which is received during the course of the study, on their relationship was discussed. In the FGDs with men or women from couples with diagnosed male infertility, we also explored the attitudes towards donor insemination. The role of religion did not figure in the interview guide but emerged as a very important cross-cutting theme. Qualitative FGD data on marital relationships and economic aspects were complemented with the data from the quantitative survey. FGD data were also complemented with medical chart notes that were recorded by study staff during follow-up visits with the infertile couples after the infertility investigations and treatments.

All discussions were tape-recorded, transcribed verbatim in Kinyarwanda and translated from Kinyarwanda into English. The transcripts and the medical chart notes were then coded and analyzed using Nvivo 8 (QSR International, Melbourne, Australia).

Results
Baseline characteristics
Of a total of 339 women in potentially infertile couples who presented at the study clinic, 312 were confirmed as eligible and enrolled. Of 407 fertile women identified in the community, 352 (86%) came to the clinic and 312 were confirmed as eligible and enrolled. Male partners in 81% of the infertile couples (254 partners) and 61% of the fertile couples (189 partners) agreed to participate. The median ages of infertile and fertile women were 30 years (inter quartile range (IQR) 27–35) and 28 years (IQR 24–31), respectively (P < 0.001). Regarding education, 28% of women in infertile relationships and 25% of the fertile women had attended secondary school (P = 0.41). The median ages of men in infertile relationships and those of fertile men were 34 years (IQR 30–40) and 32 years (IQR 28–38), respectively (P = 0.006). Regarding education, 41% of men in infertile relationships...
and 24% of the fertile men had attended secondary school (P < 0.001).

FGD participants were from a mixed socio-economic background and had been dealing with their infertility for variable periods of time (Table I).

### Consequences infertility

#### Relationship with partner and in-laws

Although some couples seem to be able to cope with the burden of infertility and to maintain loving relationships, most FGD participants agreed that ‘without children there can be no peace at home’, or, ‘there can be no love’.

The threat of divorce was almost exclusively mentioned by women. Some of them had already divorced from a previous partner because of childlessness, as became clear from the quantitative data. Of the 312 women in infertile relationships, 94 (30%) had experienced separation from at least one previous partner (referred to as union dissolution) compared with 39 of the 312 fertile women (12%) (Table II). Men in infertile relationships had also experienced more union dissolutions in the past than fertile men (58/254, 23% versus 22/189, 12%), but only three of the men in infertile relationships attributed this separation to childlessness.

Many female FGD participants testified of emotional as well as physical abuse by their partner related to infertility. In the survey on domestic violence, all aspects of abuse were reported more frequently by women in infertile relationships than by women in fertile relationships: ever been beaten (23 versus 16%, P = 0.015), ever been hurt physically (14 versus 1%, P < 0.001), ever been threatened (17 versus 6%, P < 0.001) and ever been chased (27 versus 15%, P < 0.001; Table II). A higher educational level of both men and women was associated with significantly less domestic violence (data not shown). Some of the male FGD participants stated that they also suffered from verbal abuse by their wife, such as accusations of being the cause of infertility.

### Table I Baseline characteristics of male and female participants of the FGDs.

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<tr>
<th></th>
<th>Women (n = 21)</th>
<th>Men (n = 20)</th>
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<tr>
<td>Age, median (IQR)</td>
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<td>34.5 (30–40)</td>
</tr>
<tr>
<td>Occupation</td>
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<td>1–3 years</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3–5 years</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5–8 years</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>More than 8 years</td>
<td>10</td>
<td>7</td>
</tr>
</tbody>
</table>

*Three missing data for women and one for men.

### Table II Relationship characteristics and domestic violence according to fertility status and gender.

<table>
<thead>
<tr>
<th></th>
<th>Females of Fertile couples (n = 312), n (%)</th>
<th>Females of Infertile couples (n = 312), n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever union dissolution</td>
<td>39 (12)</td>
<td>94 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever domestic violence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever beaten</td>
<td>49 (16)</td>
<td>73 (23)</td>
<td>0.015</td>
</tr>
<tr>
<td>Ever hurt physically</td>
<td>2 (1)</td>
<td>44 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever threatened</td>
<td>20 (6)</td>
<td>54 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever chased</td>
<td>47 (15)</td>
<td>84 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever sexual coercion</td>
<td>8 (3)</td>
<td>37 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partner has other partner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>262 (84)</td>
<td>130 (42)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>31 (10)</td>
<td>115 (37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>19 (6)</td>
<td>67 (21)</td>
<td></td>
</tr>
<tr>
<td>Extramarital partners at present or last year</td>
<td>3 (1)</td>
<td>9 (3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Polygamous union</td>
<td>14 (4)</td>
<td>28 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sexual intercourse more than 3 times/week</td>
<td>45 (14)</td>
<td>113 (36)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Males of Fertile couples (n = 189), n (%)</th>
<th>Males of Infertile couples (n = 254), n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever union dissolution</td>
<td>22 (12)</td>
<td>58 (23)</td>
<td>0.002</td>
</tr>
<tr>
<td>Partner has other partner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>125 (66)</td>
<td>187 (74)</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>62 (33)</td>
<td>66 (26)</td>
<td>0.19</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (1)</td>
<td>1 (0)</td>
<td></td>
</tr>
<tr>
<td>Extramarital partners at present or last year</td>
<td>6 (3)</td>
<td>41 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sexual intercourse more than 3 times/week</td>
<td>26 (14)</td>
<td>95 (37)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
In the patrilineal society of Rwanda, it is the task of the woman to provide her husband’s family with offspring. Harassment and pressure by the in-laws is almost exclusively exercised by the family of the man. They often abuse the woman, abstain from visiting her or refuse her inheritance of any property. They may encourage the man to leave her or to seek extramarital sex. Both men and women suffered from these pressures and often tried to resist them. Many FGD participants said that if it were not for the in-laws, they would have a good and loving relationship as a couple, despite the infertility.

During the FGDs, both men and women mentioned extramarital sex as a means to resolve the infertility, but only in general terms, and not as something that they had tried personally. Most informants seemed to agree that this is more common among men than women. One man said that looking for a child with another partner is the ‘solution [that] the majority [of men] try first’. When a child is produced outside the relationship, separation can follow or the second wife and her child(ren) may come to live in a polygamous union, often causing conflicts and abuse of the infertile wife. In the quantitative survey, very few women in both groups reported extramarital partners but a majority of women in infertile relationships were either not sure about their partner’s fidelity or reported that their partners were unfaithful (Table II). In contrast, the men in both fertile and infertile relationships rarely accused their partner of being unfaithful. The proportion of men in infertile relationships reporting extramarital partners in the previous year was higher than that for men in fertile relationships (41/254, 16% versus 6/189, 3%; P < 0.001). Although polygamous unions are not common in Rwanda, 28 out of 312 (9%) women in infertile relationships reported to be in a polygamous union, which is significantly more than that for fertile women (14/312, 4%).

**Economic consequences**

Social security is linked to marital stability for women. The FGDs revealed that husbands sometimes refuse to buy food or clothes for partners with whom they are in an infertile relationship, arguing that ‘they don’t have any child to give him in return’. Women who are chased away can lose their home, properties and right to utilize the land, which traditionally belongs to the man and his family.

Both male and female FGD participants expressed on many occasions the fear that they would ‘reach old age with no child to help us’. Male FGD participants also mentioned that they are less motivated to work or ‘start new projects’ because of their childlessness.

Many FGD participants said that they were ‘burdened’ with children from relatives and this is confirmed by the quantitative data: 48% (151/312) of women in infertile relationships fostered at least one child compared with 24% (74/312) of the fertile women (P < 0.001). For some male FGD participants, especially those with a better socio-economic status, fostering was not a burden but a source of pride, giving them the opportunity to prove their usefulness to society. However, they emphasized that it does not replace having children of their own.

**Experiences in the community**

Both men and women in infertile relationships testified of major suffering caused by their community. In fact, some FGD participants said that they would be able to cope with their infertility if it was not for the stigmatization they suffered from the wider community. Only one female and one male FGD participant said that they never experienced any negative consequences of their infertility in the community. Accusation of witchcraft and bringing bad luck to the community (women only), not being invited to birth ceremonies, being referred to as ‘that barren woman’ or being called impotent (men only), finding ‘few people to collaborate with’ or ‘having no word to say in society’ were all mentioned many times during the FGDs. One woman said: ‘In fact, people with infertility are isolated more than people living with HIV/AIDS.’ Another woman spoke about this incident: Me, on New Year’s evening, I had gone out with my husband, then women in our neighbourhood called my husband: ‘Hey, “papa nothing”’ where are you going with “mama nothing”?’

On the other hand, some male FGD participants expressed the idea that infertile couples can benefit Rwandese society by taking care of relatives and non-relatives.

**Continuity of family lines**

The men who participated in the FGD worried a lot about the lack of children to continue the family line. Remaining childless means ‘cutting short the family growth’ and also implies that ‘the dead ancestors cannot be replaced’. They often fear that after their death ‘their properties will be eaten by outsiders’. The women were not concerned about their own family but about the family of the man to whom the children would have belonged. They were blamed by their husbands and in-laws for ‘finishing the family’. Both female and male FGD participants worried about the day of their funeral in which the children play an important role. Some referred on several occasions to the tradition of burying childless people by placing a charcoal in their hand or at the tip of their genitals. It seemed a dreadful prospect to them, although no-one knew exactly the significance of this ritual and most thought that this tradition no longer exists.

**Emotional status**

Both men and women agreed that children are the most important thing in life and that, without them, it is very difficult to lead a fulfilling and happy life. Many participants said that they would give up all their possessions in exchange for a child. The women more than the men, and the women with diagnosed infertility more than the women without a female factor expressed, often in tears, feelings of depression and of being valueless and useless. The words said, painful and difficult recurred many times when describing their situation.

Some men expressed the need to produce a child in order to feel or to be regarded as ‘a man’. But several men, especially those found with male factor infertility, refuted this idea when they said ‘children are not the only thing that makes someone a man’.

**Sexual functioning**

Infertile couples engage more often in sexual intercourse than their fertile counterparts as is shown by the quantitative survey data (Table II). About 36% of infertile couples have sexual intercourse over three times per week compared 14% of fertile couples (P < 0.001). One of the male FGD participants explained that infertile couples have more sex hoping to increase their chances of conception. Women in infertile relationships are more frequently coerced to have sex with their partner than were women in fertile relationships (37/312, 12% versus 8/312, 3%; P < 0.001; Table II).

When surveyed about sexual desire, sexual arousal and frequency of orgasm, women in infertile relationships scored significantly lower
Table III  Sexual functioning according to fertility status and gender.

<table>
<thead>
<tr>
<th>Females of...</th>
<th>Fertile couples (n = 312), n (%)</th>
<th>Infertile couples (n = 312), n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual desire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>8 (3)</td>
<td>15 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>154 (49)</td>
<td>78 (25)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>130 (42)</td>
<td>143 (46)</td>
<td></td>
</tr>
<tr>
<td>Low/very low</td>
<td>20 (6)</td>
<td>76 (24)</td>
<td></td>
</tr>
<tr>
<td>Sexual arousal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>52 (17)</td>
<td>25 (8)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>171 (55)</td>
<td>105 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate</td>
<td>85 (27)</td>
<td>135 (43)</td>
<td></td>
</tr>
<tr>
<td>Low/very low</td>
<td>4 (1)</td>
<td>47 (16)</td>
<td></td>
</tr>
<tr>
<td>Orgasm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>14 (4)</td>
<td>13 (4)</td>
<td></td>
</tr>
<tr>
<td>Most of the time</td>
<td>200 (64)</td>
<td>80 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>A few times/never</td>
<td>98 (31)</td>
<td>214 (68)</td>
<td></td>
</tr>
<tr>
<td>I don’t know</td>
<td>0 (0)</td>
<td>5 (2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Males of...</th>
<th>Fertile couples (n = 189), n (%)</th>
<th>Infertile couples (n = 254), n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual desire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td>23 (17)</td>
<td>23 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High</td>
<td>119 (63)</td>
<td>92 (36)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>38 (20)</td>
<td>125 (49)</td>
<td></td>
</tr>
<tr>
<td>Low/very low</td>
<td>9 (5)</td>
<td>14 (6)</td>
<td></td>
</tr>
<tr>
<td>Erection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>175 (93)</td>
<td>219 (86)</td>
<td>0.034</td>
</tr>
<tr>
<td>Most of the times</td>
<td>8 (4)</td>
<td>18 (7)</td>
<td></td>
</tr>
<tr>
<td>Sometimes/a few times</td>
<td>6 (3)</td>
<td>17 (6)</td>
<td></td>
</tr>
<tr>
<td>Orgasm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>179 (95)</td>
<td>235 (92)</td>
<td>0.33</td>
</tr>
<tr>
<td>Most of the times</td>
<td>8 (4)</td>
<td>9 (3)</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>2 (1)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>A few times/never</td>
<td>0 (0)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Ejaculation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>180 (95)</td>
<td>234 (92)</td>
<td>0.16</td>
</tr>
<tr>
<td>Most of the times</td>
<td>8 (4)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>0 (0)</td>
<td>7 (3)</td>
<td></td>
</tr>
<tr>
<td>A few times/never</td>
<td>1 (0)</td>
<td>7 (3)</td>
<td></td>
</tr>
</tbody>
</table>

than did fertile women (Table III). Sexual desire and frequency of erection was also lower in men in infertile relationships compared with their fertile counterparts (Table III).

Some FGD participants thought ‘sex is useless’ because of their incapacity to produce children.

Role of religion

The word God was mentioned 139 times during the five FGDs. Children are often seen, not only as a ‘gift or a blessing from God’, but also as ‘a command of God’ and being childless can imply that one is cursed or may not go to heaven.

God was a source of consolation for many informants; religion helped them to accept their fate since they believed that ‘God provides children’. Furthermore, praying to God helped them to cope with the situation, certain churches have special prayer groups for infertile couples.

For many couples, ‘being a good Christian’ means tolerating each other despite the infertility, illustrated by the following interview extract: ‘On my side, as we are Christians and the word of God encourages us to tolerate each other in all situations; our relationship has never been affected by this problem’.

Experiences with female factor infertility

During the study, many couples received the results of their infertility investigations in each other’s presence. Some experiences clearly differed between couples diagnosed with female factor infertility and couples with male factor infertility. Emotional abuse by the partner, including threat of divorce, was mentioned by all but two of the eight female FGD participants with diagnosed female infertility. The wives of men with diagnosed male infertility also reported abuse but this abuse generally stopped after the male factor diagnosis. One woman reported that she was abandoned by her partner immediately after they received the results of female factor infertility. Two women with female factor diagnosis said that they planned to leave their husbands ‘to live alone and to never marry again’. Another woman had encouraged her partner to father children outside marriage, and offered to take care of such extramarital children.

None of the male partners of women with a diagnosed female infertility said that they had abandoned their wives but they referred to it in general terms. One man said: ‘Once you know that the woman is the one with a problem, you cannot continue to live with her, and you have to separate’. Other men said that they were pressurized by family to abandon their wives: one man was threatened to be disowned by his family if he did not. Several men also said to be relieved to know they were normal’ and added that this diagnosis had confirmed their suspicion.

Experiences with male factor infertility

Most FGD participants, women and men alike, admitted that they ‘did not know that the man could be responsible for infertility’, and in most cases, the woman had been blamed by her partner, his in-laws and the wider community. Several men had been ‘shocked’ by the male factor diagnosis.

None of the infertile men reported abuse or threats of divorce by their female partner. Instead, most of them felt that, despite the...
infertility, one should stick together and continue to love each other. One woman had been pressurized by her father to leave ‘that useless man’ after it was found that her husband was infertile. Both men and women agreed that a woman will rarely leave a man because of male factor infertility, although it does happen occasionally. One woman had asked for a divorce in court after finding out that her husband was infertile. One man thought that women might ‘try their luck outside’ instead of divorcing. One man with a diagnosed infertility problem said that ‘knowing he has a problem’ has stopped him from ‘trying with other women’.

Although a man can bring children in the household from another woman, a man cannot accept to raise a child from another man. In keeping with this, none of the FGD participants (male and female alike) could accept donor insemination as a possible treatment for male infertility. It was seen as adultery by some; others considered it as contrary to their religion and many disliked the fact of not knowing the ‘father’ and preferred to get a child from a relative or a friend (women) or to go for adoption (men). One woman told us in private that she got pregnant from a neighbour after she found out that her husband had a semen abnormality, but she pretended that the child was her husband’s.

### Discussion

The negative social implications of infertility that we observed in Rwanda seem similar to those observed in other developing countries in Asia and Africa. They are most likely the consequence of a low socio-economic status and a strong behavioural norm to reproduce (Dyer et al., 2002). In Rwanda, as in other developing countries, women carry the largest burden of the suffering but the negative implications of infertility for men should not be underestimated. In our study, at the level of the community, the men suffered as much as the women, as has also been reported in South Africa and Bangladesh (Nahar et al., 2000; Dyer et al., 2004). Some of the male FGD participants with a higher socio-economic status perceived themselves as being very useful to society despite their infertility, through their jobs and their ability to take care of family members. Furthermore, women with higher education or with a highly educated partner were less likely to report domestic violence. Lower levels of perceived stigma and infertility-related stress among infertile women with higher education was also noted in Ghana (Donkor and Sandall, 2007).

This study showed that a gender-specific diagnosis can impact on the couples’ relationship. Infertile women were more likely to face abuse or divorce than female partners of infertile men. In contrast, infertile men did not expect to be abandoned by their wives. This was also reported by Horbst in a study of infertile men in Mali (Horbst, 2010). A study in Taiwan showed that wives with a diagnosed female infertility had higher levels of distress and marital and sexual dissatisfaction than either their husbands and wives with an infertile male partner (Lee et al., 2001). Considering the negative consequences of a female factor diagnosis for women, the question arises whether it is ethical to offer gender-specific diagnosis without the possibility of effective treatment. This applies also to the diagnosis of male factor infertility in the face of which women could be enticed to look for a child outside marriage as was illustrated by the case of one study participant (Mariano, 2004). On the other hand, increasing the awareness of male factor infertility has the potential of relieving the burden from women and motivating the men to seek care (Dhont et al., 2010a). The men who participated in our research accepted the diagnosis of male infertility, often after an initial phase of disbelief, and in some cases, their behaviour changed towards less abuse of their partner and less extramarital sex.

Another interesting finding in this study is the overwhelmingly negative attitudes expressed by all participants towards donor insemination. This is in keeping with the findings from field research in Mali where women were open to insemination with the partners’ gametes but not to insemination with donor sperm (Horbst, 2010).

It has been documented before that religious beliefs shape perceptions of infertility and can offer consolation. Our findings indicate that Christian faith can also inspire certain infertile couples to stay with their partner and maintain a good relationship despite the childlessness. In Nigeria, the Charismatic Christian movement encourages husbands to shield their wives from the pressures of extended kin (Pearce, 1999).

Problems with sexual functioning can be a cause of infertility, especially in the case of an erectile and/or ejaculation dysfunction in the male. However, since sexuality and reproduction are closely linked, it is more likely that infertility has consequences for the sexual functioning of a couple (Audu, 2002). In Nigeria, sexual dysfunction was found to be common among infertile Nigerians. Women, on the other hand, were more likely to seek care (Dhont et al., 2010a). The men who participated in our study were infertile. One man thought that women might ‘try their luck outside’ instead of divorcing. One man with a diagnosed infertility problem said that ‘knowing he has a problem’ has stopped him from ‘trying with other women’.

In conclusion, we found that the psycho-social consequences suffered by infertile couple in Rwanda are severe and similar to those found in other resource-poor countries, that women carry the largest burden of suffering but that the negative repercussions are also considerable for men and that a diagnosis of female factor versus male factor infertility may have different consequences, especially for women. Access to and quality of infertility care in Rwanda should be improved to address these problems.

### Authors’ roles

The study was conceived and designed by N.D., M.T., G.C. and J.W., N.D. and A.G. executed the study. N.D. analysed the study data and drafted the article. J.W. and G.C. assisted with data analysis and interpretation of data. J.W., M.T., G.C. and A.G. revised the article critically.

### Acknowledgements

We thank Rosette Busasa and the Community Mobilizers for their dedication during data collection, Dr Gilles Ndlubusa for...
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Funding

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Horbit V. Male perspectives on infertility and assisted reproductive technologies (ART) in sub-Saharan context. FIV&V in ObGyn 2010; Monograph:22–27.


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KEY FINDINGS

Risk factors and determinants of infertility (papers 1-2-3)

In the first two papers modifiable risk factors for infertility in Rwanda were examined. **In the first paper**, it was found that among exposures measured, HSV-2 and HIV infection were the most important determinants of infertility for both men and women. For women, sexual violence was the third most important determinant. All variables related to STIs and risky sexual behaviour were stronger associated with tubal factor infertility than non tubal factor infertility. This pattern was not observed for male factor infertility. Finally, lifestyle factors cannot predict infertility in Rwanda.

**A second paper** looked at women with secondary infertility only and identified some previously unknown obstetric history predictors for secondary infertility such as lack of prenatal care during the last pregnancy, unwanted pregnancies and stillbirths. A history of unwanted pregnancies was strongly associated with secondary infertility despite the fact that few women reported an induced abortion. Obstetric events, HIV infection and other STIs all contribute equally to secondary infertility.

**A third paper** looked at the association between high risk sexual behaviour and HIV with primary and secondary infertility. Women in secondary infertile relationships have the highest HIV prevalence (43%) followed by men in secondary relationships (27%) of all groups (primary and secondary infertile and fertile men and women).

Secondary infertile women are more likely to have engaged in high risk sexual behaviour in the past than primary infertile and fertile women.

In men both primary and secondary infertile relationships are associated with a higher rate of reported multiple partners over the last year than fertile relationships. The association of infertility with other elements in the lifetime sex history was less strong in men.

Infertility investigations and follow-up (paper 4)

Our study found a high prevalence of tubal factor (70%) and male factor infertility (64%), among urban infertile couples in Rwanda. Pregnancy rates (16%) were low after conventional therapy. Predictors for tubal infertility in women included a history of rape, early age first intercourse, HIV infection, and a history of STI symptoms in the male partner. Younger women (age 30 or below) and women with an infertility duration of less than 5 years had a significantly higher chance of becoming pregnant.

Treatment seeking behaviour (paper 5)

A wide variation of causes was reported by men and women for their infertility. Poisoning, bewitching and God’s will were often cited, though more by women than men. Only one in four of the participants gave explanations based on a medical diagnosis and often they constructed their own medical concept,
despite the fact that the majority of women had previously been exposed to modern health care. There is very little awareness of the link of infertility with high risk sexual behaviour and STIs. Both men and women are unlikely to attribute infertility to the male partner. Women looked for care earlier, more often and from different sources. Participants reported a wide array of treatments they received in the past, often including ineffective or even harmful interventions.

Socio-cultural consequences (paper 6)

The psycho-social consequences suffered by infertile couples in Rwanda are severe and similar to those reported in other resource-poor countries. Although women carry the largest burden of suffering, the negative repercussions of infertility for men, especially at the level of the community, are considerable. Whether the infertility was caused by a female factor or male factor was an important determinant for the type of psycho-social consequences suffered.

LIMITATIONS

Selection bias

The infertile study population is a selection of urban couples who are willing to undergo infertility investigations; they do not necessarily represent all infertile couples in Kigali. The ‘snow ball sampling’, although could also have introduced a bias. One can presume that there is a selection bias towards the more ‘connected’ women or less isolated women. Furthermore the women had to be trying for pregnancy with a partner for at least 1 year, which excludes infertile women who are separated and are not involved in a relationship at the moment. It is however unclear how this could have affected the associations with sexual behaviour and HIV/STIs. Married infertile couples may have been more motivated to participate in this study than non-married infertile couples because marriage often represents a higher expectation to produce children than non-legalized cohabitation. Married women are less likely to report extramarital sex, and overrepresentation of married women in the infertile group may therefore have resulted in an underestimation of the HIV risk behaviours in this group.

The different participation rates of male partners in all three groups may also have induced a selection bias. It is possible that disproportionately more faithful fertile men participated in the study which could have overestimated the differences in HIV risk behaviour between men in fertile and infertile relationships.

Furthermore, the selection of infertile couples was through the women, and it is therefore possible that male factor infertility was underestimated.

Finally, the fertile women are not a representation of all fertile women in the population since currently pregnant and postpartum women are excluded.
Study design cannot ascertain causal relationships

Conclusions about the temporality or causality of the relationships between infertility, sexual behaviour, and HIV/STIs cannot be drawn due to the case-control design of the study and the lack of data on timing of HIV infections (such as CD4+ counts). For certain variables such as age at first intercourse it is clear that it happened before the infertility. Other variables such as multiple partners in the last year are happening in a point of time after the establishment of fertility problem. However, this doesn't mean that this behaviour is a consequence of infertility since it could be perpetuation of a behavioural pattern which was present before or could have been the cause of the infertility.

Urban population

The study population was entirely urban and the results cannot be extrapolated to the rural community. In Rwanda, the prevalence of high risk sexual behaviour and HIV infection are different in the rural areas [143]. It is also possible that findings on perception towards infertility and treatment seeking behaviour for infertility are quite different among rural infertile couples. The results of the infertility investigations are unlikely to be very different in a rural community since a study in Tanzania showed that infertility diagnoses among urban women do not differ significantly from those in rural women [32].

Limitations related to resources

Due to financial and logistic restraints we lacked the means to perform important tests such as gonococcal serology, laparoscopic evaluation of tubo-peritoneal status in all infertile women, hormonal assays (prolactine, FSH, etc...) and semen morphology, all of which would have contributed to a more comprehensive picture of the aetiology and risk factors of infertility in Rwanda and to a better differentiation between male and female factor.

CONTRIBUTION TO THE FIELD, DISCUSSION AND RECOMMENDATIONS

Implications for prevention of infertility

It is widely accepted that combating infections has a central role to play in the prevention of infertility in SSA [15,25,66,75,154]. As there has been little research into the etiologic agents of these infections it had been generally presumed that CT and NG are the main culprits. This is the first study in SSA to combine clinical data on infertility diagnosis with data on HIV and HSV-2 serology, enabling us to generate some hypotheses concerning the role of these pathogens in female factor infertility and to a lesser extent their role in male factor infertility. The association of these infections with tubal factor infertility remains significant after controlling for sexual behaviour and other RTIs. Although we cannot exclude residual confounding- we did not measure past gonococcal infections for instance-, our findings suggest that HIV and HSV-2 play, if not a causal role, at least a facilitating role in tubal pathogenesis. This
hypothesis is endorsed by some published studies. There are several studies examining the effect of HIV upon PID. A study in Ivory Coast found that tubo-ovarian mass on ultrasound was significantly more frequent among HIV-seropositive women than HIV seronegative women [110]. Another laparoscopic study in Nairobi found a 2.8 fold increased odds of tubo-ovarian abscess among HIV seropositive subjects [155]. In both studies the severity of PID was related to advanced immune suppression. A few US studies found that HIV positive women with acute PID more often failed medical therapy, required change in therapy, required surgical interventions or required longer hospitalization [156-159]. A study in Spain did a HSG in all HIV infected women without evidence of infertility, coming for preconception counselling and found that one in four of these women had evidence of tubal damage, which was considerably higher than the reported prevalence in sub fertile but HIV-negative women [160]. Another study in the US found that 38% of HIV-infected women had histological endometritis, none of whom had NG or CT [161]. It is also possible that post partum infections are more common in HIV infected women but existing studies report conflicting results [162,163].

The effect of HSV-2 upon PID or tubal damage is limited to a few studies. One prospective study found that positive HSV-2 serology was associated with endometritis and with fallopian tube obstruction and co-infection with HSV-2 increased the likelihood of other pathogens such as NG, CT and BV to be associated with endometritis [164]. One study in Hungarian found that the HSV-2 seropositivity among women attending infertility clinics was significantly higher than the seroprevalence among pregnant women [165].

In our study, HIV and HSV-2 antibodies were also associated with male factor infertility and less strong (HIV) or not (HSV-2) with non male factor infertility, and the association remained significant after controlling for sexual behaviour, suggesting a role of these viruses in male infertility. Virtually nothing is known about the effect of HSV-2 on male infertility. *Herpes simplex* virus has been isolated from the male genital tract and some studies found an association with abnormal semen parameters and the isolation of this virus in the semen, others did not [61,166-169]. The effect of HIV on semen parameters is also a matter of controversy. Most studies report a negative effect of HIV on sperm parameters with a positive association between blood CD4 cell count and sperm concentration, motility and morphology [111,113-116]. On the other hand a longitudinal cohort study of 55 asymptomatic untreated HIV-infected men showed that semen quality remained stable during 96 weeks [47]. All of these studies were performed in Western countries. In SSA, one study in South-Africa showed an association between HIV infection, leucocytosperma and impaired semen motility [170].

Although the exact mechanism remains to be elucidated, some of the cited evidence in addition to our findings point to an active role of HIV and HSV-2 in PID and/or tubal damage and male factor infertility. We can therefore conclude that **not only the prevention of bacterial RTIs but also the prevention of HIV and HSV-2 have the potential to prevent an important amount of infertility cases in SSA.** Whether long-term antiviral suppression therapy of HIV and HSV-2 can also contribute to the prevention of infertility is not known.

Sexual violence emerged as a strong predictor for infertility in Rwanda, stronger than other measures of high risk sexual behaviour. It is quite possible that we are measuring here the consequences of the 1994
civil war which has made many rape victims. We did not record systematically the circumstances and timing of the sexual violence acts but we know that some, but not all, cases happened during the war. SSA is a region with high levels of sexual violence, especially in conflict affected countries. Among Ugandese victims of war related sexual violence one quarter of women reported to suffer from infertility [171]. Prevention of sexual violence and better post rape care will contribute to the prevention of infertility in SSA, especially in areas where sexual violence is highly prevalent.

As our findings suggest that 25% of cases of secondary infertility in Rwanda could be attributed to pregnancy related complications, improved obstetric care has an important role to play. Our study is the first to examine obstetric and sexual behavioural risk factors and RTIs in a group of secondary infertile women. It had been estimated before that 70% of pelvic infections are attributable to STIs and 30% to infections associated with abortion and unsafe delivery practices [15]. Our study findings also show that not only infertility but also the high stillbirths and infant mortality rates contribute to childlessness in SSA. Hence, improved neonatal and paediatric care will also have an impact on the rates of infertility and/or childlessness.

Finally efforts to prevent infertility should join hands with efforts to prevent HIV and unintended pregnancies. The safe sex messages used in family planning and HIV programs should teach that unsafe sex does not only increase the risk of acquiring HIV and unintended pregnancies, but can also lead to infertility. Since infertility is seen as one of the worst conditions a woman and a couple can face, there is a potential here to add a unique selling point to the existing campaigns.

Implications for infertility care in SSA

*Diagnostic work up*
A basic diagnostic work-up of infertile couples should include medical history, physical examination, detection of ovulation, semen analysis and assessment of tubal function. Some of these are readily available on primary care level (health centres), others need referral to secondary care level (district hospitals) or tertiary care level (university hospitals). Guidelines for the management of infertility on all levels of healthcare should be developed and included in the curriculum of doctors, nurses and midwives. In health care centres the main focus should be on history taking and counselling (with emphasis on need to involve men) and some basic investigations such as syphilis and HIV testing can be performed. If a real problem of infertility (1 year of regular unprotected intercourse without conception) exists the couple needs to be referred to the district hospital for HSG and semen analysis. After completing the investigations, the couple should receive comprehensive information on the findings and possible treatment. In our experience, couples appreciate the information, even if no treatment can be offered as understanding the problem often helps them to accept it. It is not clear how counsellors can deal with the potential negative effects on a couple’s relationship of a gender specific diagnosis. Sensitive counselling is needed but in the end only effective treatment of the infertility will be able to nullify most of these consequences.
Although most of these diagnostic tools are available, their performance is hampered by a lack of well trained personnel. **Investment in radioscopy equipment and training courses in standardized semen analysis for lab technicians** can improve the quality of the diagnostic tools available [172]. **On the tertiary referral level, a unit dedicated to infertility** is needed to provide these patients with the specialized care they need. Some authors advocate for ‘one stop infertility clinics’ in which all these procedures are provided by a small team of well trained health providers within a short period of time [75].

**Treatment**

In infertility there are two fundamentally different ways of treating patients. One is based on etiological treatment and the other is based on the enhancement of conception rates. The latter makes use of artificial reproductive technologies (ART) such as intrauterine insemination (IUI), in-vitro-fertilisation (IVF) and intracytoplasmatic sperm injection (ICSI). As a general rule etiological treatment should be tried first but often this is not successful. Etiological treatment is most successful in treating anovulation [173]. Etiological treatments for tubal infertility have proven less successful, especially in SSA where tubal damage is often severe and microsurgery or laparoscopic surgery is not readily available [174-176]. For male factor infertility conventional andrology has not much to offer as an etiological treatment. Varicocele treatment has proven to be inefficient and the benefit of alternative treatments such as vitamins, antioxidants and carnitine remains unproven [173]. **As tubal factor and male factor infertility are the most prevalent diagnostic groups in SSA, few infertile couples can be treated effectively without assisted reproductive technologies (ART) and the majority of these will need IVF/ICSI.**

The current cost of ART prohibits its widespread use in resource poor countries. There is some hope that these techniques can be offered at a much lower cost in the future [134]. However, we believe that infertility management in resource-poor countries can be improved even without ART. **Guidelines for the management of infertility will prevent inappropriate treatments.** These guidelines should include fertility awareness counselling in case of unexplained infertility and use of Clomiphene Citrate in case of anovulation. As intrauterine adhesions, myomas and polyps are not uncommon in these settings **hysteroscopic surgery** has the potential to treat a considerable number of cases. It remains a matter of debate whether tubal surgery has a place in treating post inflammatory tubal damage in SSA. In many cases the severity of the tubal damage precludes high success rates even when endoscopic surgery is performed by highly trained specialists [174-176].

**Implications for HIV programs**

There is an urgent need to address the challenges associated with HIV and infertility in SSA which bears the major burden worldwide of both conditions.

**Voluntary HIV counselling and testing of infertile couples may identify new HIV infections and increase opportunities for HIV care and prevention.**

**The link between HIV and infertility represent an opportunity and indeed an obligation to put infertility services in place.** Treating infertility in HIV negative couples will prevent them from looking for children in multiple relationships and therefore will reduce the risk of becoming HIV infected. Providing
infertility services to couples with at least one partner infected can prevent HIV transmission to the uninfected partner, transmission from mother to child and transmission to other sexual partners. Some fertility services are readily available in developing countries but are underutilized, and others are currently not available. Some authors argue that HIV/AIDS related funds could be used to put such services in place since the funds available for infertility are scarce[98]. An important prerequisite for addressing the reproductive needs of HIV positive couples is to acknowledge that some will desire children and that this desire is, in principle, legitimate. At present their fertility needs are not addressed and patients do not receive the advice and input they require. Treatment with antiretroviral therapy has prolonged the potential of survival for HIV infected patients and has decreased the risk of mother to child transmission. Therefore, the arguments for excluding HIV infected infertile couples from infertility treatment need to be reviewed. In fact it can even be argued that all couples with HIV should be offered infertility investigations and this should happen preconceptionally, not after 12-24 months of trying. There is enough evidence to assume that many of them will have infertility factors which can prolong the time to achieve fertilization, increasing the risk of sexual transmission to their partner [177]. Furthermore, from the study on uptake of implants among postpartum HIV-infected mothers (see addendum) we can conclude that the integration of family planning services in HIV care has the potential to increase the uptake of contraceptives among HIV infected couples.

Implications for family planning programs

The concept of family planning is widely understood as the provision of contraceptives to prevent unplanned, unintended or unwanted pregnancies [178]. However helping people to plan families should also imply helping those who have difficulties in achieving pregnancies. This would be a more balanced approach to family planning. According to some authors the fear and experience of infertility could be an important factor in women’s decisions to use or reject contraception [80]. Family planning services offering infertility care might be more acceptable to the population. For this reason and to make infertility care more accessible, there is an urgent need to implement the integration of infertility care in existing family planning programs.

Implications for reproductive health programs

All of the previous discussions point to the urgent need for a more holistic approach towards reproductive health services in SSA. From the risk profile of infertile women, and especially secondary infertile women, we can conclude that what protects people from STIs, HIV and unintended pregnancies will protect them from infertility. In other words all these reproductive health problems go hand in hand and share the same structural pathway (figure 1). Family planning and sexually transmitted disease control services have generally been implemented through vertical programs administered by separate departments in government ministries. Recently a call has been made by several international health organisations to increase the linkage between these services. In 2009, WHO, the United Nations Population Fund (UNFPA), the International Planned Parenthood Federation (IPPF), United Nations AIDS
(UNAIDS, and the University of California, San Francisco published a systematic review of the literature, examining the evidence on linking reproductive health and HIV services. A majority of studies showed improvements in indicators of health as well as in overall quality of services, providing further support for fast-tracking integration [179]. Many international organisations are endorsing now the need for more integration of reproductive health services [179-184]. The five core aspects of reproductive health, essential in accelerating progress towards meeting internationally agreed targets, according to WHO, are:

- Improving pregnancy related care
- Providing high-quality services for family planning including infertility services
- Eliminating unsafe abortions
- Combating STIs including HIV, RTIs and cervical cancer
- Promoting sexual health

Sexually active men and women of reproductive age presenting themselves for one of these services should be screened for other reproductive health needs or problems as they are likely to concur. From a purely practical point of view this approach makes even more sense. A comprehensive reproductive health history taking will provide a picture of the reproductive health needs of the woman, man or couple involved. During the same genital exam screening for STIs and precancerous cervical lesions can be performed and if needed IUCDs or vaginal contraceptive rings can be inserted. Nurses familiar with one aspect of reproductive health such as prenatal care can be easily trained in the other aspects. An additional advantage of these integrated services is the avoidance of stigma related to STI en HIV clinics.
Context of poverty, low education, gender-power inequalities

- Transactional sex
- Concurrent partners
- Multiple unions
- No condom use
- Early age at first sex
- Gender based violence

INFERTILITY AND CHILDLESSNESS

STIs/HIV and unintended pregnancies

Limited access to and bad quality of Health info and care

High value of children

war

Figure 1: structural pathway
PERSPECTIVES FOR FUTURE RESEARCH

This research could be considered as a first exploration of different aspects of infertility in resource-poor countries and it is therefore not surprising that more questions than answers were generated. The ideas for future research presented here are only the tip of the iceberg.

At present the temporal relationships between infertility and sexual behaviour and HIV remain unclear. **A large prospective cohort study** of newly married couples could shed more light on this question. The same prospective design could also examine more closely the etiological role in tubal damage of different micro-organisms including viral agents such as HIV and HSV-2. The direct effects of HIV and HSV-2 on PID pathogenesis remain unclear and further research is needed to clarify whether these infections facilitate movement of bacteria from the lower to the upper genital tract or whether genital immune activation and inflammation related to these infections facilitate tubal scarring or whether immune suppression caused by HIV infection modifies the immune response of the host. Prevention of tubal disease will only be possible if we have a better understanding of the pathogenesis involved.

We looked at HIV prevalence in infertile couples but the reverse **looking at the prevalence of infertility in HIV infected couples** would be as interesting. A small study in Spain examined fertility in non-infertile couples in which the woman was HIV infected and found a high prevalence of tubal occlusions (28%) and semen alterations [160]. There are many reasons to assume that the situation in SSA is worse.

Another issue worth looking into is **how the diagnosis of HIV impacts on the relationship and child wish of infertile couples and vice versa**. It is already known that the diagnosis of HIV can have an impact on sexual behaviour, relationships with the intimate partner and reproductive choices [125,185]. On the other hand many HIV positive couples continue to want children, especially with the advent of anti retroviral therapy and the hope for a better and longer live [96,186]. HIV infection results in a profound clash with fertility aspirations, with couples often told that responsible behaviour is to practise safe sex by using condoms [187]. Understanding this interplay of reproductive ill health will help to manage both problems.

There is an urgent need for **pilot studies looking into how infertility care can be integrated into existing reproductive health programs**. Regarding prevention of reproductive ill health, it would be interesting to study the impact of making infertility more visible in safe sex campaigns on the sexual behaviour. The specific health care structure in each country will represent different opportunities for integration. In the case of Rwanda, HIV care and family planning has benefited from a lot of attention recently and the achievements are quite impressive [188]. There is also an ongoing effort to link family planning and HIV care in Rwanda. If policymakers could be convinced of the importance of infertility care it would be a tremendous opportunity to add basic infertility care to these services.

Finally, as stated before, making ART accessible to infertile couples in SSA has the potential of relieving most of the suffering caused by infertility. Currently a group of researchers is looking into the possibility of making IVF more affordable through the use of alternative stimulation protocols and laboratory
procedures. The results are promising and pilot studies will be executed in due course in the developing and developed world [134,135].

FINAL REMARKS

Ultimately, the biggest challenge will consist of putting infertility care on the public health agenda and changing its present ‘Cinderella’ status. It will be hard to refute the idea that the capacity to reproduce is central to reproductive health. In that sense infertility and childlessness represent the most fundamental reproductive health problem one can have. But ironically, it is exactly the problem of reproductive failure that has been overlooked in reproductive health programs. When searching the websites of international organisations who provide reproductive health care programs in Africa it appears that reproductive health equals family planning for most. Due to overpopulation and the urgent need of many countries to decrease the fertility rate, the issue of infertility is not regarded as a problem. Refusing to provide care to infertile couples is not a justifiable way to curb population growth. First population growth can be restricted much more effectively by, among others, educating women, providing contraception and safe abortion [189,190]. Second, referring to children of others to explain refusal to assist infertile couples demonstrates a serious misconception of what it means to want a child [190]. Third, family planning programs accepting infertile couples might be much more accepted and accessed by the people in resource-poor countries.

The devastating effects of infertility on the life of affected couples and especially women have been documented extensively. This and the high prevalence of infertility should be enough to convince policymakers and donor communities of the need to invest in infertility care. Unfortunately in developing countries decision making on public health priorities is not necessarily driven by the needs of the people involved. More likely, international funding and economic motives of the governments are dictating this agenda. It could be argued that for most couples in SSA having offspring is more important than limiting offspring and also more important than the acquisition of material goods such as electricity and running water. This is illustrated by the many testimonies of infertile couples in which they state they would give up all their possessions in order to have a child. If the immense suffering caused by infertility cannot convince maybe the emerging evidence that infertility is associated with HIV infection could help to draw the attention of policymakers. Although care should be taken not to double stigmatize infertile couples.

Anyhow, we will probably have to wait a bit before seeing the issue of infertility appear on the agenda of international and national public health authorities. But there is some hope...Lately the problem of infertility in developing countries has been receiving more attention. Many authors have made a call in international peer reviewed journals and conferences for increased access to infertility care [14,16,75,131,133-137,191,192]. The European Society of Human Reproduction and Embryology (ESHRE) formed a special task force dedicated to the problem of infertility in developing countries. The
following statement is posted on their website: ‘After a fascinating period of more than 25 years of IVF, we must admit that only a small part of the world population benefits from these new reproductive technologies. Optimising a concurrent infertility treatment-, family planning- and perinatal care-programme is probably one of the most important challenges for third world countries in the near future.’

In the chapter on fertility regulation in the three yearly report by the International Federation of Gynaecology and Obstetrics (FIGO) the right to assisted reproductive technology was debated in two papers [133,135]. In the report of the WHO meeting on ‘Medical, ethical and social aspects of assisted reproduction’, several authors drew the attention to the problem of infertility in developing countries [193]. The WHO bulletin of December 2010 contained two articles on infertility in Africa [194].

I hope this thesis can be part of a momentum created by these researchers and medical health specialists, which can ultimately lead towards the recognition of infertility as a public health problem and a more balanced approach towards reproductive health.
EXECUTIVE SUMMARY

BACKGROUND

Infertility is highly prevalent in sub-Saharan Africa (SSA), affecting up to one third of couples in certain areas, but has not received the attention it deserves due to limited resources, policies aimed at reducing population growth and the high cost of modern infertility treatment. Existing data indicate that for SSA infection is the leading cause of infertility. Knowing the modifiable risk factors and their relative contribution to infertility can guide the design of cost-effective prevention measures. The bidirectional link between infertility and HIV deserves special attention because of its important consequences for HIV and reproductive health programs. Few studies have examined the HIV prevalence and sexual behaviours in infertile patients, particularly among couples. In order to improve information, education and counselling on causes and treatments of infertility and to develop guidelines for the management of infertility at all levels of healthcare, knowledge on prevailing perceptions and treatment-seeking behaviour is needed. The inability to conceive has severe consequences for the couples, especially for women, in countries where female identity, social status and security depend on the ability to produce offspring. Initiatives to make infertility care accessible in resource-poor settings are gaining momentum. Mapping the socio-cultural consequences of infertility in these settings is necessary to achieve this goal as few data exist on the socio-cultural consequences of infertility in East-Africa.

The general objective of this work was to study the clinical, epidemiological and socio-cultural aspects of infertility in Rwanda. More specifically we examined predictors and determinants for different types of infertility (female and male factor, primary and secondary infertility) and their relative contribution, including HIV and other reproductive tract infections (RTIs), past sexual and contraceptive behaviour, obstetric history and lifestyle factors. Secondary objectives included the evaluation of 1) perceptions of infertility causes, treatment-seeking behaviour and factors associated with seeking medical care as well as the response of health providers, 2) consequences of female and/or male factor infertility for men and women and 3) the outcome of infertility investigations and 18 month follow-up of infertile women and their partners in Rwanda.

METHODS

Between November 2007 and May 2009 sexually-active women aged 21-45 year presenting with infertility problems at the infertility clinic of the Kigali University Teaching Hospital (n=312), and fertile controls who recently delivered (n=312) were surveyed together with their male partners in an unmatched case-control study. Participants were interviewed about socio-demographic characteristics,
medical history, obstetric history, sexual behaviours, sexual functioning and were tested for HIV and RTIs. Infertile couples received also basic infertility investigations and were followed up over an 18 month period. In addition five focus group discussions were held with selected infertile participants.

RESULTS

Among the STIs examined, HSV-2 and HIV infection were the most important determinants of infertility for both men and women. For women sexual violence in the past was the third most important determinant. All variables related to STIs and risky sexual behaviour were stronger associated with tubal factor infertility than non tubal factor infertility. This pattern was not observed for male factor infertility. Finally, lifestyle factors cannot predict infertility in Rwanda.

Some previously unknown obstetric history predictors were identified for secondary infertility such as lack of prenatal care during the last pregnancy, unwanted pregnancies and stillbirths. A history of unwanted pregnancies was strongly associated with secondary infertility despite the fact that very few women reported an induced abortion. Obstetric events, HIV infection and other STIs all contribute equally to secondary infertility in Rwanda.

In contrast with previous reports, we found a higher HIV prevalence among couples in secondary and not primary infertile relationships with at least one HIV infected partner in 45% of these couples. Women in secondary infertile relationships were more likely to report high risk sexual behaviour in the past including in the last year and at present than primary infertile and fertile women. Men in both primary and secondary infertile relationships reported more frequently concurrent partners over the last year than fertile men.

After performing basic infertility investigations in 224 urban infertile couples, we found a high prevalence of tubal factor (70%) and male factor infertility (64%). Pregnancy rates (16%) were low after conventional therapy. Predictors for tubal infertility in women included a history of rape, early age first intercourse, HIV infection, and a history of STI symptoms in the male partner. Younger women (age 30 or below) and women with an infertility duration of less than 5 years had a significantly higher chance of becoming pregnant.

When asked about the cause of their infertility, only one in four of the participants named explanations based on a medical diagnosis, often they constructed their own medical concept and cited witchcraft or God as the cause of their infertility, despite the fact that the majority (65%) of women had previously been exposed to modern medical health care. There is very little awareness of the link of infertility with high risk sexual behaviour and sexually transmitted infections (STIs). Both men and women are unlikely to attribute infertility to the male partner. Women looked for care earlier, more often and from different sources and were more likely to visit traditional healers then men. Participants reported a wide array of treatments they received in the past, often including ineffective or even harmful interventions.
The investigation of the psycho-social consequences of infertility in Rwanda demonstrated severe suffering, similar to what is reported in other resource-poor countries. Although women carry the largest burden, the negative repercussions of infertility for men, especially at the level of the community, are considerable. Whether the infertility was caused by a female factor or male factor was an important determinant for the type of psycho-social consequences suffered.

**DISCUSSION AND CONCLUSIONS**

The main limitations of this study are 1) the study population is a selection of infertile couples willing to undergo infertility investigations and of male partners willing to participate (selection bias), 2) the cross-sectional study design is unable to ascertain temporal relationships between infertility and most of the measured exposures and 3) study population is entirely urban 4) limited resources restricted the scope of infertility investigations and treatment.

Despite these limitations we can draw some important conclusions and make some recommendations. In addition to the prevention of bacterial STIs, the prevention of HIV and HSV-2 has the potential to prevent an important amount of cases of tubal factor infertility in SSA. Reduced sexual violence and better post rape care has a role to play in infertility prevention, especially in areas with high prevalence of this behaviour. The study on secondary infertility indicated that improved obstetric, neonatal and paediatric care will also have a considerable impact on the rates of infertility and/or childlessness. Finally, efforts to prevent infertility should join hands with efforts to prevent HIV and unintended pregnancies. The safe sex messages used in family planning and HIV programs should teach that unsafe sex does not only increase the risk of acquiring HIV and unintended pregnancies, but can also lead to infertility.

The high HIV prevalence among infertile couples indicate that voluntary HIV counselling and testing of infertile couples may identify new HIV infections and increase opportunities for HIV care and prevention. On the other hand, the link between HIV and infertility represent an opportunity and indeed an obligation to put infertility services in place.

The study of perceptions and treatment-seeking behaviour of infertile couples identified a need to improve information, education and counselling on causes and treatments of infertility. Our experience with infertility investigations learned that investment in radioscopy equipment and training courses in standardized semen analysis for lab technicians can improve the quality of the diagnostic tools available. The results from both these studies indicated that guidelines for the management of infertility on all levels of healthcare should be drawn up and included in the curriculum of doctors, nurses and midwives to avoid unnecessary or harmful treatments and to improve counselling on infertility. Since pregnancy rates are low with conventional therapy a call for affordable IVF in resource-poor countries was made. Overall, we can conclude that there is an urgent need for a more holistic approach towards reproductive health services in SSA, one that recognises the importance of reproductive failure and one that provides an integrated package of different services.
ACHTERGROND

Onvruchtbaarheid is zeer wijd verspreid in sub-Sahara Afrika (SSA); tot een derde van de paren is aangetast in bepaalde gebieden. Dit probleem heeft niet de aandacht gekregen die het verdient om verschillende redenen: de beperkte middelen, het beleid gericht op vermindering van de bevolkingsgroei en de hoge kosten van de moderne onvruchtbaarheidsbehandeling. Het onvermogen om zwanger te worden heeft ernstige gevolgen voor de koppels, vooral voor vrouwen, in landen waar vrouwelijke identiteit, sociale status en zekerheid afhangen van het vermogen om nakomelingen te verwekken.

De bestaande gegevens wijzen erop dat voor SSA infectie de belangrijkste oorzaak is van onvruchtbaarheid. De kennis van beïnvloedbare risicofactoren en hun relatieve bijdrage tot onvruchtbaarheid kan het ontwerpen van kosten-effectieve preventiemaatregelen sturen. De bidirectionele link tussen onvruchtbaarheid en HIV verdient speciale aandacht omwille van zijn belangrijke gevolgen voor HIV en reproductieve gezondheidsprogramma’s. Slecht enkele studies hebben de HIV-prevalentie en seksueel gedrag in onvruchtbare vrouwen onderzocht; gegevens over de mannelijke partner zijn er niet.

Om informatie over de oorzaken en behandelingen van onvruchtbaarheid te verbeteren en het opstellen van richtlijnen voor het beleid bij onvruchtbaarheid op alle niveaus van de gezondheidszorg te bevorderen, is inzicht in de heersende opvattingen over onvruchtbaarheid en de behandelingen die hiervoor worden opgezocht nodig. Initiatieven om vruchtbaarheidsbehandelingen toegankelijk te maken in ontwikkelingslanden verkeren momenteel in een stroomversnelling. Om dit doel te bereiken is het noodzakelijk om de sociaal-culturele gevolgen van onvruchtbaarheid in deze landen in kaart te brengen want gegevens hierover in de regio van Oost-Afrika zijn schaars.

De algemene doelstelling van dit werk was de klinische, epidemiologische en sociaal-culturele aspecten van onvruchtbaarheid in Rwanda te bestuderen. Meer specifiek hebben we voorspellende en bepalende factoren voor verschillende vormen van onvruchtbaarheid (vrouwelijke en mannelijke factor, primaire en secundaire onvruchtbaarheid) onderzocht. Deze factoren omvatten de rol van van HIV en andere infecties van de voortplantingsorganen (RTI’s), het seksueel en anticonceptieve gedrag, de verlokskundige geschiedenis en levensstijl. Secundaire doelstellingen zijn de evaluatie van 1) percepties van de oorzaken van onvruchtbaarheid en factoren in verband met het zoeken van medische of alternatieve hulp, alsmede het antwoord van de gezondheidszorg, 2) gevolgen van vrouwelijke en / of mannelijke onvruchtbaarheid voor mannen en vrouwen en 3) de resultaten van onvruchtbaarheidsonderzoeken en 18 maanden follow-up van de onvruchtbare vrouwen en hun partners in Rwanda.
METHODEN

Tussen november 2007 en mei 2009 werden seksueel actieve vrouwen tussen 21 en 45 jaar die zich aanboden met onvruchtbaarheid op de infertilitétsconsultatie van de Kigali University Teaching Hospital (n = 312), en vruchtbare controles die onlangs bevallen waren (n = 312) ondervraagd samen met hun mannelijke partners in een unmatched case-control studie. De deelnemers werden geïnterviewd over socio-demografische kenmerken, medische geschiedenis, verloskundige geschiedenis, seksueel gedrag, seksueel functioneren en ze werden getest op HIV en RTI’s. Onvruchtbare paren werden tevens onderzocht om de oorzaak van de onvruchtbaarheid te kennen en werden gevolgd over een periode van 18 maanden. Ook werden vijf focusgroepgesprekken gevoerd met deelnemers geselecteerd uit de onvruchtbare paren.

RESULTATEN

Uit ons onderzoek bleek dat van de onderzochte STIs, HSV-2 en HIV-infectie de belangrijkste determinanten van onvruchtbaarheid zijn voor zowel mannen als vrouwen. Voor vrouwen was seksueel geweld in het verleden de derde meest belangrijke factor. Alle variabelen met betrekking tot SOA en riskant seksueel gedrag waren sterker geassocieerd met tubaire factor infertiliteit dan infertiliteit in vrouwen met normale tuba. Hetzelfde patroon werd niet waargenomen voor een mannelijke factor.Ten slotte bleek dat factoren ivm leefstijl onvruchtbaarheid in Rwanda niet konden voorspellen. Sommige voorheen onbekende elementen uit de verloskundige geschiedenis, zoals het ontbreken van prenatale zorg tijdens de laatste zwangerschap, ongewenste zwangerschappen en doodgeborenen waren geassocieerd met secundaire onvruchtbaarheid. Een geschiedenis van ongewenste zwangerschappen was sterk geassocieerd met secundaire onvruchtbaarheid, ondanks het feit dat zeer weinig vrouwen een abortus provocatus gemeld hadden. Obstetrische problemen, HIV-infectie en andere SOAs dragen allemaal evenveel bij tot secundaire onvruchtbaarheid.

In tegenstelling met vorige studies, vonden we een zeer hoge HIV-prevalentie in onvruchtbare paren met secundaire onvruchtbare relaties waarbij in 45% van deze koppels tenminste één partner geïnfecteerd is. Vrouwen in secundair onvruchtbare paren vermelden frequenter hoogrisico seksueel gedrag zowel in het heden als in het verleden vergeleken met vruchtbare controles en primair onvruchtbare vrouwen. Mannen in onvruchtbare relaties meldden vaker gelijktijdige partners het afgelopen jaar dan vruchtbare mannen.

Het onvruchtbaarheidsonderzoek in 224 stedelijke onvruchtbare paren toonde een hoge prevalentie van tubaire (70%) en mannelijke oorzaken van onvruchtbaarheid (64%) in Rwanda. Er kwamen weinig zwangerschappen (16%) tot stand na conventionele therapie. Voorspellers voor tubaire factor onvruchtbare vrouwen omvatten een geschiedenis van verkrachting, de eerste geslachtsgemeenschap op jonge leeftijd, HIV-infectie, en een geschiedenis van SOA symptomen in de mannelijke partner. Jongere vrouwen (leeftijd 30 of lager) en vrouwen met een onvruchtbaarheidsduur van minder dan 5 jaar hadden een significant hogere kans om zwanger te worden.
Ondervraagd over de oorzaak van hun onvruchtbaarheid kon slechts een op de vier van de deelnemers een medische diagnose formuleren; vaak verzinnen ze hun eigen zogezegde medische diagnose of zochten een verklaring in hekserij of God, ondanks het feit dat de meerderheid (65%) van de vrouwen eerder waren blootgesteld aan moderne medische gezondheidszorg. Zeer weinig deelnemers brachten hun onvruchtbaarheid in verband met een hoogrisico seksueel gedrag en SOAs. Onvruchtbaarheid werd slechts zelden toegeschreven aan de mannelijke partner in beide geslachten. Vrouwen zochten medische hulp eerder, vaker en uit verschillende bronnen en waren meer geneigd een traditionele heler te raadplegen dan mannen. Deelnemers rapporteerden een breed scala van behandelingen die zij ontvingen in het verleden, waaronder vaak ineffectieve of zelfs schadelijke interventies.

Het onderzoek naar de psycho-sociale gevolgen van onvruchtbaarheid in Rwanda legde een immens lijden bloot, vergelijkbaar met dat in andere arme landen. Hoewel vrouwen de grootste last dragen, zijn de negatieve gevolgen van onvruchtbaarheid ook bij mannen aanzienlijk, vooral op het niveau van de gemeenschap. Of de onvruchtbaarheid veroorzaakt werd door een vrouwelijke of mannelijke factor bepaalde in belangrijke mate de aard van de psycho-sociale gevolgen.

DISCUSSIE EN CONCLUSIES

De belangrijkste beperkingen van dit onderzoek zijn: 1) de studie populatie is een selectie van onvruchtbare paren die bereid zijn onderzoeken te ondergaan en van mannelijke partners die bereid zijn om deel te nemen (selectie bias), 2) de cross-sectionele design is niet in staat om temporele relaties vast te stellen tussen de onvruchtbaarheid en de meerderheid van de geregistreerde blootstellingen en 3) de onderzoekspopulatie is volledig stedelijk 4) de beperkte financiële middelen beperkten de middelen voor diagnosis and behandeling van onvruchtbaarheid.

Ondanks deze beperkingen kunnen we een aantal belangrijke conclusies trekken en een aantal aanbevelingen doen.

Naast de preventie van bacteriële infecties heeft de preventie van HIV en HSV-2 het potentieel om een belangrijk deel van de gevallen van onvruchtbaarheid in SSA te voorkomen. Het voorkomen van seksueel geweld en een betere zorg na verkrachting kunnen een aanzienlijke rol spelen in de preventie van infertilité, in het bijzonder in de landen waar dit vaak voorkomt. De studie over secundaire onvruchtbaarheid geeft aan dat een verbetering van de obstetrische, neonatale en pediatrische zorg ook een impact zal hebben op de prevalentie van onvruchtbaarheid en / of kinderloosheid. Ten slotte moeten inspanningen om onvruchtbaarheid te voorkomen in hand gaan met de inspanningen om HIV en ongewenste zwangerschappen te voorkomen. De veilige- seks boodschappen die de gezinsplanning en HIV-programma’s in de wereld sturen kunnen de aandacht erop vestigen dat onveilige seks niet alleen het risico op HIV en ongewenste zwangerschappen verhoogt, maar ook kan leiden tot onvruchtbaarheid. De hoge HIV-prevalentie bij onvruchtbare koppels betekent dat vrijwillige HIV-counseling en HIV-tests in deze groep de mogelijkheid biedt om nieuwe HIV-infecties op te sporen en de kans voor HIV-zorg en preventie kan verbeteren. De link tussen HIV en
onvruchtbaarheid is een uitnodiging en zelfs een verplichting om infertiliteitszorg te integreren in de reproductieve gezondheidszorg.

Uit het onderzoek naar de onvruchtbare paren en de behandelingen die ze zoeken volgt dat er een grote nood is aan informatie, opvoeding en counseling over oorzaken en behandelingen van infertiliteit. Onze ervaring met onvruchtbaarheidsonderzoek in Rwanda leerde ons dat investering in radioscopie apparatuur en opleiding in gestandaardiseerde sperma-analyse voor laboranten onmisbaar is om de kwaliteit van de zorg te verbeteren.

Omdat conventionele behandelingen van onvruchtbaarheid weinig resultaat opleveren is het noodzakelijk te investeren in een betaalbare hedendaagse behandeling van infertiliteit voor patiënten in arme landen. Ondertussen kunnen richtlijnen voor het opvolgen van onvruchtbaarheid op alle niveaus van de gezondheidszorg worden opgesteld en opgenomen in het curriculum van de artsen, verpleegkundigen en verloskundigen om onnodige of schadelijke behandelingen te voorkomen en de counseling rondom onvruchtbaarheid te verbeteren.

Over het algemeen kunnen we concluderen dat er een dringende behoefte is aan een meer holistische benadering van de reproductieve gezondheidszorg in SSA, die het belang van onvruchtbaarheid erkent en die een geïntegreerd pakket van verschillende diensten levert.
RESUME

CONTEXTE

L'infertilité est très répandue en Afrique sub-saharienne (ASS), qui touche jusqu'à un tiers des couples dans certaines régions, mais n'a pas reçu l'attention qu'il mérite en raison de ressources limitées, les politiques visant à réduire la croissance de la population et le coût élevé du traitement moderne d'infertilité. Les données existantes indiquent que l'infection à ASS est la principale cause d'infertilité. Connaître les facteurs de risque modifiables et leur contribution relative à l'infertilité peuvent guider la conception des mesures de prévention efficace. Le lien bidirectionnel entre l'infertilité et le VIH mérite une attention particulière en raison de ses conséquences importantes pour le VIH et les programmes de santé reproductive. Peu d'études quantitatives ont examiné la prévalence du VIH et des comportements sexuels chez les patients infertiles, en particulier chez les couples. Afin d'améliorer l'information, l'éducation et le conseil sur les causes et les traitements de l'infertilité et d'élaborer des lignes directrices pour la gestion de l'infertilité à tous les niveaux des soins de santé, il est nécessaire d'étudier les perceptions sur les causes d'infertilité et la façon dont ces couples tentent de résoudre leur infertilité. L’incapacité de concevoir a des conséquences graves pour les couples, en particulier pour les femmes, dans les pays où l’identité féminine, le statut social et de la sécurité dépendra de la capacité de produire une descendance. Les initiatives visant à rendre les soins d’infertilité accessibles dans les milieux pauvres en ressources gagnent du terrain. Illustrations des conséquences socioculturels de l’infertilité dans ces milieux est nécessaire pour atteindre cet objectif. Très peu de données existent sur les conséquences socioculturelles de la stérilité en Afrique de l’Est.

L’objectif général de ce travail était d’étudier les aspects cliniques, épidémiologiques et socioculturels de l’infertilité au Rwanda. Plus précisément, nous avons examiné les prédicteurs et les déterminants des différents types de stérilité (facteurs féminins et masculins, stérilité primaire et secondaire) et leur contribution relative, y compris le VIH et autres infections génitales, le comportement sexuel et la contraception, les antécédents obstétricaux et des facteurs de style de vie. Les objectifs secondaires comprenaient l’évaluation de 1) la perception des causes d’infertilité, les demandes de traitement et des facteurs liés à la recherche de soins médicaux ainsi que la réponse des prestataires de santé, 2) les conséquences de l’infertilité masculine ou féminine chez les hommes et les femmes et 3) le résultat des investigations d’infertilité et 18 mois de suivi parmi des femmes infertiles et leurs partenaires au Rwanda.

METHODES

Entre Novembre 2007 et mai 2009, les femmes sexuellement actives âgées de 21 à 45 années présentant des problèmes d’infertilité à la clinique d’infertilité de l'Hôpital universitaire de Kigali (n =
et les contrôles fertile qui a récemment livré (n = 312) ont été étudiées en collaboration avec leurs partenaires masculins dans une étude cas-témoins inégalée. Les participants ont été interrogés sur les caractéristiques sociodémographiques, antécédents médicaux, les antécédents obstétricaux, les comportements sexuels, le fonctionnement sexuel et ont été testés pour le VIH et infections. Les couples infertiles ont reçu également des investigations pour déterminer la cause de leur infertilité et ont été suivis sur une période de 18 mois. En outre, cinq groupes de discussion ont eu lieu avec des participants choisis infertiles.

RÉSULTATS

Parmi les ISTs examinées, le HSV-2 et le VIH ont été les déterminants les plus importants de l'infertilité chez les hommes et les femmes. Pour des femmes la violence sexuelle dans le passé a été le troisième facteur déterminant le plus important. Toutes les variables liées aux IST et comportements sexuels à risque étaient plus forts associés à l'infertilité tubaire qu'à l'infertilité non-tubaire. La même tendance n'a pas été observée pour l'infertilité masculine. Enfin, les facteurs de style de vie ne peuvent pas prédire l'infertilité au Rwanda.

Certains facteurs prédictifs dans les antécédents obstétricaux, jusque-là inconnus, ont été identifiés pour l'infertilité secondaire comme une histoire d'absence de soins prénataux au cours de la dernière grossesse, les grossesses non désirées et les mort-nés. Une histoire de grossesses non désirées a été fortement associée à l'infertilité secondaire malgré le fait que très peu de femmes ont signalé un avortement provoqué. Des événements obstétricaux, l'infection au VIH et autres ISTs contribuent également à une stérilité secondaire au Rwanda.

En contraste avec les rapports précédents, nous avons constaté que la prévalence du VIH dans les couples infertiles est entraînée par les relations avec infertilité secondaire avec au moins un partenaire séropositif de 45% de ces couples. Les femmes avec infertilité secondaire sont plus susceptibles de signaler un comportement sexuel à risque élevé dans le passé, y compris l'année dernière et à l'heure actuelle que les femmes avec infertilité primaire et les femmes fertiles. Les hommes dans une relation d'infertilité primaire et secondaire ont indiqué plus souvent des partenaires sexuels simultanées au cours de l'année dernière que les hommes fertiles.

Après avoir effectué des investigations d'infertilité dans 224 villes couples infertiles, nous avons constaté une forte prévalence du facteur tubaire (70%) et de l'infertilité masculine (64%). Les taux de grossesse (16%) ont été faibles après un traitement conventionnel. Les prédicteurs de la stérilité tubaire chez les femmes sont l'histoire du viol, de rapports sexuels avant 15 ans, l'infection à VIH et des antécédents de symptômes d'IST dans le partenaire masculin. Les femmes plus jeunes (moins de 30 ans) et les femmes avec une durée d'infertilité de moins de 5 ans avaient une chance significativement plus élevée de devenir enceinte.

Interrogé sur la cause de leur infertilité, seulement un sur quatre des participants ont nommé des explications fondées sur un diagnostic médical, souvent, ils ont construit leur propre concept médical et cité sorcellerie ou dieu comme la cause de leur infertilité, malgré le fait que la majorité (65%) des femmes avaient déjà été exposées à des soins médicales modernes. La liaison de l'infertilité à un
comportement sexuel à risque élevé et les infections sexuellement transmissibles (IST) est très peu connue. Les hommes et les femmes ne sont pas susceptibles d’attribuer l’infertilité au partenaire masculin. Les femmes ont cherché des soins tôt, plus souvent et de différentes sources et sont plus susceptibles de visiter les guérisseurs traditionnels que les hommes. Les participants ont signalé un large éventail de traitements dont ils ont bénéficié dans le passé, y compris souvent des interventions inefficaces, voire nuisibles. L’enquête sur les conséquences psycho-sociales de la stérilité au Rwanda a démontré de graves souffrances, semblables à ce qui est rapporté dans d’autres pays pauvres en ressources. Bien que les femmes portent le fardeau le plus lourd, les répercussions négatives de l’infertilité chez les hommes, en particulier au niveau de la communauté, sont considérables. Que l’infertilité a été causée par un facteur féminin ou facteur masculin était un facteur déterminant pour le type de conséquences psycho-sociales souffert.

DISCUSSION ET CONCLUSIONS

Les principales limites de cette étude sont 1) la population d’étude est une sélection de couples infertiles disposées de se soumettre à des investigations d’infertilité et des partenaires masculins disposés à participer (biais de sélection), 2) la méthodologie transversale n’est pas en mesure de déterminer les relations temporelles entre l’infertilité et la plupart des expositions mesurées 3) la population étudiée est entièrement urbaine et 4) les moyens limités ont empêché d’exécuter une diagnostique et thérapie plus avancée.

Malgré ces limites, nous pouvons tirer quelques conclusions importantes et faire des recommandations. En plus de la prévention des IST d’origine bactérienne, la prévention du VIH et HSV-2 a le potentiel de prévenir un nombre important de cas de stérilité en ASS. Réduction de la violence sexuelle et des meilleurs soins post viol ont un rôle à jouer dans la prévention de l’infertilité, en particulier dans les zones à forte prévalence de ce comportement. L’étude sur la stérilité secondaire a indiqué que l’amélioration des soins obstétriques, pédiatriques et néonatals aura également un impact considérable sur le taux de stérilité et / ou l’infécondité. Enfin, les efforts visant à prévenir l’infertilité devraient joindre leurs mains avec les efforts visant à prévenir les grossesses non désirées et le VIH. Les messages éducatifs utilisés dans la planification familiale et les programmes VIH doivent enseigner que les rapports sexuels non seulement augmentent le risque de contracter le VIH et les grossesses non désirées, mais peuvent aussi conduire à l’infertilité.

La forte prévalence du VIH chez les couples infertiles indique que le dépistage volontaire du VIH parmi les couples infertiles peut identifier de nouvelles infections à VIH et accroître les possibilités pour les soins et la prévention du VIH. D’autre part, le lien entre le VIH et l’infertilité représente une opportunité et même l’obligation de mettre en place des services de l’infertilité.

L’étude des perceptions et des comportements à la recherche de traitement des couples infertiles a mise en évidence la nécessité d’améliorer l’information, éducation et conseil sur les causes et les traitements de l’infertilité. Notre expérience avec les investigations de l’infertilité nous ont appris que l’investissement dans l’équipement de radioscopie et des cours de formation dans l’analyse du sperme pour les techniciens de laboratoire peuvent améliorer la qualité des outils de diagnostic disponibles. Les
résultats de ces deux études ont indiqué que les lignes directrices pour la gestion de l’infertilité à tous les niveaux des soins de santé doit être établi et inclus dans le curriculum des médecins, infirmières et sages-femmes à mesure d’éviter les traitements inutiles ou nuisibles et d’améliorer les conseils sur l’infertilité. Les souffrances causées par l’infertilité peuvent être réduites par l'information, l'éducation et le consulting. Comme les taux de grossesse sont faibles avec la thérapie conventionnelle un appel à la FIV abordable dans les pays pauvres en ressources a été faite.
Dans l'ensemble, nous pouvons conclure qu’il ya un besoin urgent d’une approche plus holistique des services de santé reproductive en ASS, qui reconnait l'importance de l'échec de la reproduction et qui offre un ensemble intégré de services différents.
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>AOR</td>
<td>Adjusted Odds Ratio</td>
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<tr>
<td>ART</td>
<td>Artificial Reproductive Technologies</td>
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<td>BV</td>
<td>Bacterial Vaginosis</td>
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<td>CI</td>
<td>Confidence Intervals</td>
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<tr>
<td>CNLS</td>
<td>Centre National de Lutte contre le SIDA</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>CT</td>
<td><em>Chlamydia trachomatis</em></td>
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<tr>
<td>DHS</td>
<td>Demographic and Health Survey</td>
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<tr>
<td>EDCTP</td>
<td>European and Developing Countries Clinical Trial Partnership</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked Immunosorbent Assay</td>
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<tr>
<td>ESHRE</td>
<td>European Society for Human Reproduction and Embryology</td>
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<tr>
<td>FGD</td>
<td>Focus Group Discussion</td>
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<tr>
<td>FIGO</td>
<td>International Federation for Gynecology and Obstetrics</td>
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<tr>
<td>FP</td>
<td>Family Planning</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HPV</td>
<td>Human Papillomavirus</td>
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<td>HSV-2</td>
<td>Herpes Simplex Virus-2</td>
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<td>HSG</td>
<td>Hysterosalpingography</td>
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<td>IAS</td>
<td>International Aids Society</td>
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<td>ICRH</td>
<td>International Centre for Reproductive Health</td>
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<td>ICSI</td>
<td>Intra Cytoplasmatic Sperm Injection</td>
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<td>IPPF</td>
<td>International Planned Parenthood Federation</td>
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<tr>
<td>IUCD</td>
<td>Intra-uterine Contraceptive Device</td>
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<td>IUUI</td>
<td>Intra Uterine Insemination</td>
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<td>IVF</td>
<td>In Vitro Fertilisation</td>
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<td>KUTH</td>
<td>Kigali University Hospital</td>
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<td>MOH</td>
<td>Ministry of Health</td>
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<tr>
<td>NG</td>
<td><em>Neisseria gonorrhoea</em></td>
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<td>NGO</td>
<td>Non-governmental Organisation</td>
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<td>NI</td>
<td>Not Included</td>
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<td>ONAPPO</td>
<td>National Office of Population</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PAF</td>
<td>Population Attributable Fraction</td>
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<td>Pap</td>
<td>Papanicolaou</td>
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<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>PID</td>
<td>Pelvic Inflammatory Disease</td>
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And last but not least: Ludwig, my husband. Thank you for taking me to Africa, for believing in me and for your loving support. Dank je, schat. Dido, Jura and Zadie, my darling daughters. Thank you for bringing joy and laughter everyday and for teaching me what is essential in life. My parents, thank you for your loving support from the very first day of my life.
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ADDENDUM
IMPROVED ACCESS INCREASES POSTPARTUM UPTAKE OF CONTRACEPTIVE IMPLANTS AMONG HIV-POSITIVE MOTHERS IN RWANDA
Improved access increases postpartum uptake of contraceptive implants among HIV-positive women in Rwanda

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ABSTRACT

Background Long-acting reversible contraceptives (LARCs) and sterilisation are the most cost-effective methods of contraception but are rarely used in sub-Saharan Africa partly due to limited access.

Study design HIV-positive pregnant women attending two urban clinics in Rwanda were followed prospectively in a perinatal HIV transmission cohort study. Women attending one clinic were referred to public family planning (FP) services for all contraceptive methods (Site A) and women attending the other clinic (Site B) were offered implants and intrauterine devices (IUDs) on-site.

Results Fifty three percent of the pregnant women reported an intention to use a LARC or to be sterilised after delivery. The uptake of implants was significantly higher at Site B (38%) than at Site A (6%). The IUD uptake was extremely low at both sites (2%). Twenty-eight of the 39 women at Site B who had intended to start using a LARC actually did so as compared to only one of 23 at Site A.

Conclusion When access to LARC was provided, a substantial number of HIV-positive women started using hormonal implants, but not IUDs, in the postpartum period. HIV and FP services should consider improving access to implants to reduce the number of unintended pregnancies.

KEYWORDS Long-acting reversible contraceptives (LARCs); Sterilisation; HIV infection; Postpartum; Unmet need; Family planning; Access; Rwanda

INTRODUCTION

In sub-Saharan Africa, a region with a generalised HIV epidemic, a quarter of all pregnancies are thought to be unintended and the unmet need for contraception exceeds 30% in some countries1. Contraceptive use by HIV-positive women can prevent HIV-positive births and reduce unsafe abortions and maternal and child mortality2. The unmet need for contraception among HIV-positive women is not known but there is some evidence that it is higher than for women in general3,4. A recent survey in Rwanda among HIV-positive...
women who participated in a prevention of mother-to-child transmission (PMTCT) programme found that only 45% were using a modern method of contraception, although 92% did not wish to have any more children. HIV is often diagnosed during pregnancy but the opportunity to initiate contraception postpartum is usually missed. However, there is increasing awareness about the need to link provision of effective family planning (FP) to HIV services.

Long-acting reversible contraceptives (LARCs, such as intrauterine devices [IUDs] and hormonal implants), and female and male sterilisation, are more cost-effective than short-acting methods (e.g., injectables and combined oral contraceptives [COCs]): they are less dependent on user adherence, have lower discontinuation rates, and a longer duration of action. However, in most African countries, short-acting methods are more often used. In Rwanda, current contraceptive prevalence among married women is 27% for any modern method and among these women only one in ten resorts to a LARC or sterilisation. Among women currently not using contraceptives but intending to use a modern method in the future one in five would prefer a LARC or sterilisation. This suggests that there is a substantial unmet need for LARCs and sterilisation in Rwanda. Hubacher and colleagues estimated that, if 20% of the 17.6 million African users of short-acting methods switched to hormonal implants, over 1.8 million unintended pregnancies could be prevented over a five-year period. However, in most developing countries, access to LARCs and sterilisation is limited. In 2001, one or more LARCs were available in only 10% of FP services in Rwanda. Little is known about the unmet need for LARCs and sterilisation among HIV-positive pregnant women, and the impact of increased access to LARCs in the postpartum period on their uptake. We investigated this in a cohort of HIV-positive women participating in a PMTCT study.

**Material and Methods**

Between May 2005 and January 2007, all HIV-positive pregnant women entering the PMTCT programme from 28 weeks of gestation onwards in four government-run health facilities were invited to participate in the AMATA study. The AMATA study was a non-randomised prospective cohort study that aimed at determining the efficacy of two postnatal mother-to-child HIV transmission interventions (formula feeding vs. breastfeeding with maternal antiretroviral therapy). Contraceptive choices were evaluated in two of the four health facilities (both urban sites). Women were seen at study enrolment during pregnancy and post-delivery at week 6, month 3, 6, 7 and 9. Follow-up of mother-infant pairs was discontinued if the infant died. This study was approved by the National Ethics Committee of Rwanda. All women signed an informed consent form in the local language before participating.

All women at both study sites were invited to FP counselling sessions by trained nurses before delivery. No particular method of contraception was given priority but it was emphasised that the use of condoms alone is not the most effective method for preventing pregnancy. Contraception was discussed again at each follow-up visit. Women at one study site (Site A) were referred to public FP services for all their contraceptive needs. At these public services, short-acting methods were usually available, but LARCs were only occasionally available due to the absence of qualified staff and stock-outs. Women attending the other study site (Site B) were offered hormonal implants (Norplant or Jadelle) and IUDs on site and were referred to the adjacent public FP services for short-acting contraceptive methods. For sterilisation women at both study sites were referred to the adjacent district or university hospital. At Site B, implants were made available free of charge and IUDs for a small fee. At public FP services, a small fee is charged for injectables, IUDs and implants but pills and condoms are free of charge. Nurses at Site B were trained in the implant insertion technique, and in pre-and post-insertion counselling, in several hands-on sessions. An on-site doctor was trained in inserting IUDs.

Face-to-face interviews based on a structured questionnaire were used to collect baseline characteristics at enrolment and to assess contraception use at each of their follow-up visits. Supplementary questionnaires on contraceptive and reproductive intentions were administered at enrolment and nine months postpartum to all women who enrolled in the study after February 2006. Out of 411 women 219 women and 273 women answered the supplementary questionnaire at enrolment and at the end of follow-up, respectively. Of the 219 women who answered the question concerning the method they intended to use...
after delivery, 205 provided data on contraceptive use at the end of follow-up.

Data were entered using Microsoft Access software (Microsoft, Seattle, USA), and analysed with Stata version 10 (StataCorp, Texas, USA). In our analyses, modern methods of contraception included condoms, COCs, injectables, IUDs, hormonal implants and tubal occlusion. Short-acting methods included condoms, COCs and injectables; LARCs included hormonal implants and IUDs. The \( \chi^2 \) test was used to compare proportions between the two study sites and logistic regression to determine the association between study site and contraceptive uptake.

We measured unmet need for LARCs and sterilisation by comparing the intention to use these methods and the subsequent use. Unmet need has been measured linking women’s preference for additional children and their current contraceptive behaviour.\(^{12}\) A criticism that may apply to this method is that it does not take into consideration women who use a contraceptive method but want to switch to a different one.

RESULTS

From May 2005 to January 2007, 411 women were enrolled in the study. Nine women were lost to follow-up before delivery, 13 women delivered a stillborn, five newborns died within 48 hours and one woman died in childbirth. Postpartum follow-up of 29 women was discontinued before any data on contraception use were gathered. Therefore, 354 women (179 in Site A and 175 in Site B) provided data on contraceptive use. All but eight (346) completed follow-up until nine months postpartum: one was lost to follow-up at 6 weeks and seven withdrew at 3, 6 or 7 months. Baseline characteristics of the women enrolled after February 2006 did not differ from those of all 411 women (data not shown).

The two study sites differed significantly from each other in only three features (Table 1). More women at Site A than women at Site B had at least one living child (81% vs. 69%) and more reported that the index pregnancy was unintended (69% vs. 53%). However, fewer women at Site A than at Site B reported an intention to use a LARC or to submit to sterilisation (47% vs. 59%). Only three women could not name a modern method of contraception, and 51% had used a modern method of contraception in the past. Most of these methods were short-acting ones: 23% injectables, 24% condoms and 18% COCs. Seven women had used a LARC in the past (five had used an implant and two an IUD).

The overall postpartum uptake of modern contraception (measured at the 9 month visit) was 84% and did not differ significantly between the two sites (Table 2). However, the uptake of implants among the women at Site B (38%) was significantly higher than at Site A (6%). The IUD uptake was low at both sites: 3% at site B and 0.5% at site A. The uptake of injectables was higher at Site A (64%) than at Site B (27%). Women attending Site B (with on-site access to LARCs) were 10.2 times more likely to start using implants (95% confidence interval [CI] 5.0–20.8) than those attending Site A. When adjusting for maternal age and having at least one living child at enrolment, the adjusted OR for uptake of implants was 11.8 (95% CI 5.7–24).

Of the 23 women at Site A who intended to use a LARC, only one did so in the postpartum period; the need for such modality of contraception was unmet in nearly all cases (Table 3). The LARC uptake at Site B was proportionally much more important as nearly three out of four of the women who expressed an interest in using one postpartum did so. The uptake of tubal occlusion among women who intended to be sterilised was extremely low at both sites (3 out of 27 at Site A and 1 out 21 at Site B). The uptake of short-acting methods among women who had expressed a desire to use one was better at Site A than at Site B (37/45 and 18/31, respectively). Of the 31 women at Site B who intended to use short-acting methods six had opted for implants instead (data not shown). Of the 44 women with an unmet need for sterilisation 16 out of 20 at Site B opted for implants and 17 out of 24 at Site A opted for injectables. Of the 22 women with an unmet need for LARCs at site A, 15 opted for injectables (data not shown).

Among the 267 women who answered the supplementary questionnaire at the end of follow-up and who were not pregnant, 25 (9%) reported a desire for more children in the future. All of these 25 women were applying measures not to conceive: two abstained from having sex and the remainder used a modern method of contraception. Of the 242 women not desiring children in the future three (1.2%) were not using any contraceptive method, 27 (11%) were...
abstaining and the others (88%) were using a modern method.

DISCUSSION

Our aim was to estimate the unmet need for LARCs and sterilisation among HIV-positive women, and to determine the impact of improved access to LARCs on postpartum uptake. Our data confirm that the unmet need for implants and sterilisation among HIV-positive women in Rwanda is substantial, but much less so for IUDs. Guaranteed access to implants (free-of-charge) and IUDs (for a small fee) increased the uptake of the former, but not notably that of the latter. Our findings are consistent with previous research showing that information about and access to implants increase use among both HIV-positive and HIV-negative women.

Uptake of implants by women who intended to use them was not 100% despite guaranteed access, and demand for and uptake of IUDs continued to be low. This suggests that access is not the only barrier to use, especially for IUDs. Negative perceptions and unfavourable rumours seem to play an important role in the low uptake of IUDs in many sub-Saharan countries. Furthermore, most women came to the clinic without their partner. It is therefore possible that initial intentions changed after discussion with the partner at home. Other studies have indeed shown that partner involvement is crucial in decisions pertaining to FP.

Another interesting finding in this study is that the demand for implants increased when the access increased. Women attending Site B may have become aware of the free provision of implants from previously enrolled participants. Word-of-mouth

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Total N=354</th>
<th>Site A N=179</th>
<th>Site B N=175</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Maternal age at enrolment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>80 (23)</td>
<td>42 (23)</td>
<td>38 (22)</td>
<td>0.21</td>
</tr>
<tr>
<td>25–29</td>
<td>125 (35)</td>
<td>62 (35)</td>
<td>63 (36)</td>
<td></td>
</tr>
<tr>
<td>30–34</td>
<td>91 (26)</td>
<td>52 (29)</td>
<td>39 (22)</td>
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</tr>
<tr>
<td>35+</td>
<td>58 (16)</td>
<td>23 (13)</td>
<td>35 (20)</td>
<td></td>
</tr>
<tr>
<td>WHO clinical HIV stage 3 &amp; 4</td>
<td>28 (8)</td>
<td>19 (9)</td>
<td>12 (7)</td>
<td>0.47</td>
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<tr>
<td>Living with partner</td>
<td>287 (81)</td>
<td>147 (82)</td>
<td>140 (80)</td>
<td>0.61</td>
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<tr>
<td>Formula feeding</td>
<td>225 (64)</td>
<td>116 (65)</td>
<td>109 (62)</td>
<td>0.62</td>
</tr>
<tr>
<td>HIV status partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>negative</td>
<td>43 (12)</td>
<td>23 (13)</td>
<td>20 (11)</td>
<td>0.58</td>
</tr>
<tr>
<td>positive</td>
<td>202 (57)</td>
<td>97 (54)</td>
<td>105 (60)</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>108 (31)</td>
<td>58 (33)</td>
<td>50 (29)</td>
<td></td>
</tr>
<tr>
<td>Education more than primary</td>
<td>100 (28)</td>
<td>44 (25)</td>
<td>56 (32)</td>
<td>0.12</td>
</tr>
<tr>
<td>At least one living child at enrolment*</td>
<td>266 (75)</td>
<td>145 (81)</td>
<td>121 (69)</td>
<td>0.01</td>
</tr>
<tr>
<td>Informed partner about study</td>
<td>258 (73)</td>
<td>129 (72)</td>
<td>129 (74)</td>
<td>0.73</td>
</tr>
<tr>
<td>Unintended pregnancy†</td>
<td>129 (61)</td>
<td>75 (69)</td>
<td>54 (53)</td>
<td>0.02</td>
</tr>
<tr>
<td>Used a modern method before‡</td>
<td>110 (51)</td>
<td>54 (49)</td>
<td>56 (53)</td>
<td>0.89</td>
</tr>
<tr>
<td>Intention to use contraception‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19 (9)</td>
<td>7 (6)</td>
<td>12 (11)</td>
<td>0.03</td>
</tr>
<tr>
<td>Short-acting</td>
<td>84 (38)</td>
<td>52 (47)</td>
<td>32 (30)</td>
<td></td>
</tr>
<tr>
<td>Long-acting and permanent</td>
<td>116 (53)</td>
<td>52 (47)</td>
<td>62 (59)</td>
<td></td>
</tr>
</tbody>
</table>

*At Site A, women were referred to public FP services for all contraceptive methods. Site B had guaranteed access to implants and IUDs.
†N=219 for these variables (111 at Site B and 108 at Site A) because this information was gathered only for women enrolled after February 2006.
recommendations from satisfied users may have
created demand, and has been described elsewhere16.
Our study had some limitations. First, our
results may not be generalised to the whole of
Rwanda because they were obtained within a
specific study setting with high quality of care and
intensive follow-up. Indeed, the overall uptake of
modern methods of contraception (84%) in our
setting was significantly higher than that in a routine
PMTCT setting in Rwanda (45%) and only three
out of 242 women without desire for future
children were not using contraception5. Further,
no data on continuation of contraceptive use
were collected beyond nine months postpartum.
However, studies from other countries indicate
that continuation rate for hormonal implants are
high17–20.
In conclusion, many HIV-positive women in
Rwanda are interested in using a LARC and
sterilisation in the postpartum period, underlining
the importance of access to these methods. We
showed that a substantial number of HIV-positive
women in one urban setting used implants when
access was guaranteed. In countries with high HIV
prevalence and low contraceptive prevalence, the
provision of a mix of contraceptives including
hormonal implants to HIV-positive women can
prevent many unintended pregnancies and HIV-
positive births.

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Declaraton of interest: The authors report no conflicts
of interest. The authors alone are responsible for the
content and the writing of the paper.

<table>
<thead>
<tr>
<th>Table 2 Uptake of contraceptive methods in the postpartum period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Modern contraceptives</td>
</tr>
<tr>
<td>Short-acting methods</td>
</tr>
<tr>
<td>Condom</td>
</tr>
<tr>
<td>Pill</td>
</tr>
<tr>
<td>Injectable</td>
</tr>
<tr>
<td>Long-acting methods</td>
</tr>
<tr>
<td>IUD</td>
</tr>
<tr>
<td>Implant</td>
</tr>
<tr>
<td>Tubal occlusion</td>
</tr>
</tbody>
</table>

| *At Site A, women were referred to public FP services for all contraceptive methods. Site B had guaranteed access to implants and IUDs. |

<table>
<thead>
<tr>
<th>Table 3 Contraceptive uptake in postpartum period and intention to use as reported during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of women who initiated use vs. the number of women who intended to use that particular method</strong></td>
</tr>
<tr>
<td><strong>Number of women who intended to use</strong></td>
</tr>
<tr>
<td>(N = 205)</td>
</tr>
<tr>
<td>None (n = 19)</td>
</tr>
<tr>
<td>Short-acting (n = 76)</td>
</tr>
<tr>
<td>Long-acting (n = 62)</td>
</tr>
<tr>
<td>Tubal occlusion (n = 48)</td>
</tr>
</tbody>
</table>

| *At Site A, women were referred to public FP services for all contraceptive methods. Site B had guaranteed access to implants and IUDs. |

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REFERENCES


