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THE EPIDEMIOLOGY OF INFERTILITY

Report of a WHO Scientific Group

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Geneva, 30 June – 4 July 1975

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THE EPIDEMIOLOGY OF INFERTILITY

Report of a WHO Scientific Group

A WHO Scientific Group on the Epidemiology of Infertility met in Geneva from 30 June to 4 July 1975. The meeting was opened by Dr D. Tejada-de-Rivero, Assistant Director-General, on behalf of the Director-General.

1. INTRODUCTION

The WHO programme of research in human reproduction is concerned with problems that have clinical or public health importance such as infertility, disorders of pregnancy and lactation, and family planning. The Eighteenth World Health Assembly requested implementation of a programme of reference services and studies on the health aspects of infertility and the need for information and advice to couples on infertility was reiterated by the Twenty-first World Health Assembly in 1968. A WHO Scientific Group on the Biological Components of Human Reproduction [a] also identified the need for research into the incidence and causes of conditions that impair reproductive capacity. Infertility would appear to be particularly acute in certain countries in Africa south of the Sahara and the discussions of the Group focused mainly on the problem as related to these countries. Many of these countries are eager to set up services to prevent or cure the underlying causes, and formal requests for assistance have been received by WHO from several of them.

Involuntary infertility is a world-wide problem, but its frequency varies from area to area. It seems likely that up to 5% of all couples are infertile for complex reasons that are difficult to diagnose and for which present day treatment is therefore largely ineffective.

Superimposed on this "hard core", additional factors may raise the prevalence of infertility to 30% or even higher in some communities, particularly in certain countries in Africa south of the Sahara. If these additional factors could be defined, it is probable that much of the infertility would be preventable.

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[a] WHO Technical Report Series, No. 435, 1969.

In most cultures, failure to bear children may carry a sense of personal failure as well as a social stigma. Where infertility is widespread and has major social implications there is a significant demand for diagnostic and therapeutic services.

Preliminary investigations into the underlying causes have demonstrated gaps in the available information and point to the need for research. Major issues include the magnitude and geographical distribution of infertility, and the need to distinguish between the different conditions that are loosely grouped under the general term of infertility.

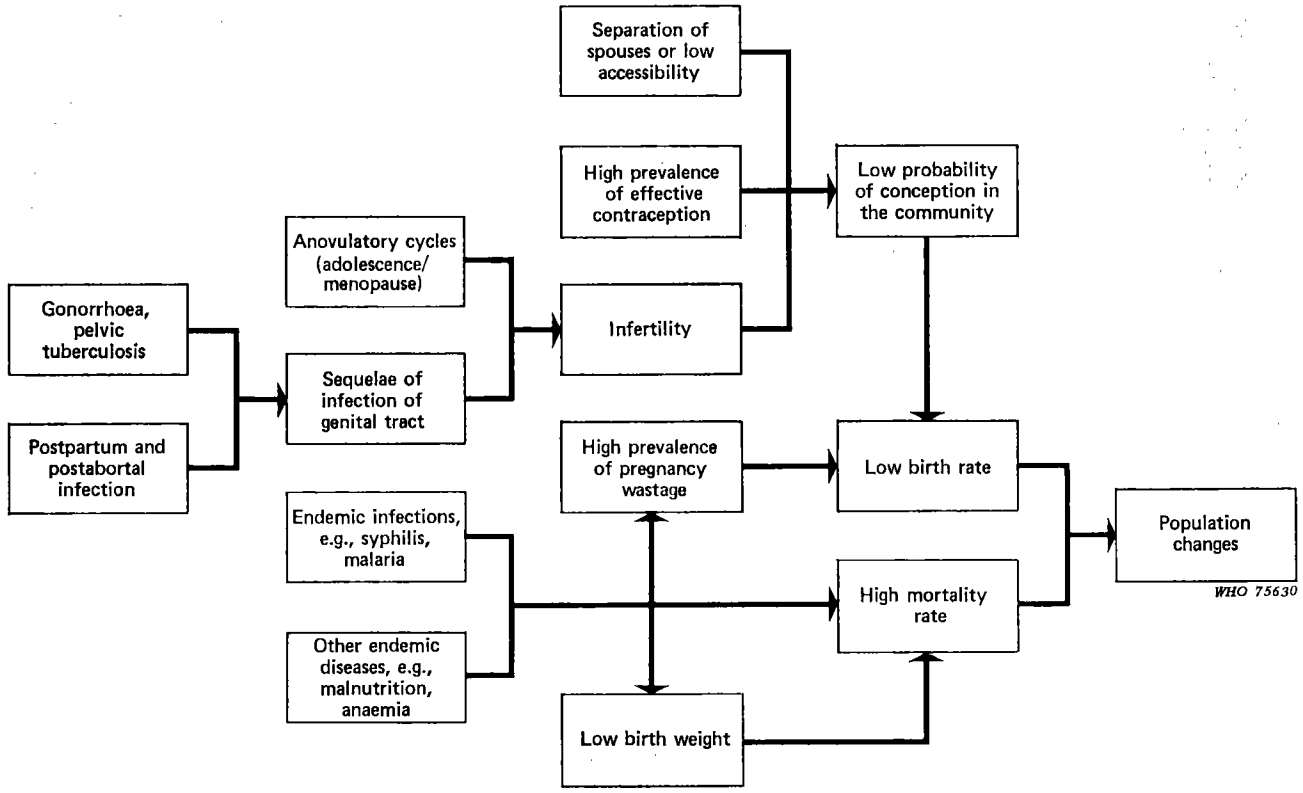
The term infertility is sometimes used by affected couples as though it were synonymous with childlessness; this is confusing. Demographically, the term infertility has also been mistakenly used to describe such situations as diminished fertility, low population growth rates, low population density, or even depopulation. Misunderstanding arises particularly when it is not certain whether the phenomenon refers to the individual couple or to the community as a whole. Throughout this report the term infertility is used in relation to couples. The indicator of the infertility of the couple is the woman, whether the infertility is due to failure of the woman to conceive or of the man to impregnate her. Infertility in the population as a whole is referred to in terms of prevalence rates.

In order to establish the underlying causes more clearly, it is necessary to differentiate between the inability to conceive, the inability to carry a conceptus to a live birth, and the failure of a live birth to survive. These three categories will be referred to as *infertility*, *pregnancy wastage*, and *child loss*, respectively. The relationship of these three categories, the factors affecting them, and their contribution to population changes are illustrated in Fig. 1 (the problem of population changes is beyond the terms of reference of this report).

Infertility can be considered in terms of primary infertility, when the woman has never conceived, and secondary infertility, when she has conceived at least once but not subsequently despite efforts to become pregnant. Infertility and pregnancy wastage are often perceptually linked as one problem by couples requesting services, and the associated or causative factors may be common to both. For these reasons, the Scientific Group considered both infertility and pregnancy wastage and concentrated upon the conditions thought to be responsible for high prevalence rates.

The first objective of the Scientific Group, once it had formulated operational definitions of infertility and pregnancy wastage, was to plan research on their prevalence in communities.

FIG. 1. CAUSES OF INFERTILITY, PREGNANCY WASTAGE, AND CHILD LOSS AND THEIR RELATIONSHIP TO BIRTH AND MORTALITY RATES AND POPULATION CHANGES



The second objective was to design research schemes, appropriate to field conditions, that will establish the relative importance of the various causes of infertility and pregnancy wastage. The results of such research should enable appropriate control measures to be introduced in the areas concerned.

2. MAGNITUDE OF THE PROBLEM OF INFERTILITY

Current estimates of the prevalence of infertility and pregnancy wastage are largely based upon demographic data derived from census surveys and a few epidemiological and clinical studies.

2.1 Demographic data

The primary purpose for which demographic information is obtained often affects the form, character, and completeness of the information. Census or household lists used for political or tax purposes generally do not provide a reliable basis for the calculation of infertility and the manner in which questions are asked and the definitions used to categorize individuals in census surveys affect the usefulness of the information in defining the problem of infertility.

Demographic data derived from census surveys often include information on the numbers of children per woman by age and marital status, but the different reasons for the absence of children are not indicated. These reasons might include voluntary childlessness, failure of the couple to conceive, failure of the woman to carry a pregnancy to term, or failure of an infant to survive. In some censuses the number of children per woman is recorded as the number currently living, in others as the number ever born (live and stillborn), and in others as the number of live births. The last designation has been the most frequently used. In a few census surveys the data have been recorded in terms of "ever pregnant". Information that would indicate secondary infertility (i.e., failure to conceive again since the last conception) is rarely collected.

Inaccuracy is a major problem with census data in many areas of Africa, and reliable information on age is particularly defective. Information on numbers of pregnancies is often incomplete because of failure to recall some events, especially abortions and stillbirths. Early neonatal deaths may not be distinguished from stillbirths, and when child deaths are thought to reflect poorly on a woman, or when discussion of

them is believed to bring bad luck to the survivors, she may be unwilling to mention them at all.

For all these reasons, existing demographic data can be used only as a very crude measure of infertility. However, despite these limitations, there is no doubt that an infertility problem exists in many areas of Africa. In parts of Gabon, Cameroon, Central African Republic, and Zaire the rates of childlessness among women aged 50 years or more have been reported to be as high as 20%–40%. Even higher rates have been noted among younger women. A similar situation has also been described in parts of East Africa, Sudan, and elsewhere in the continent. It would seem likely that infertility plays a role in these situations.

2.1.1 *Indirect indices of infertility*

The percentage of childlessness among all women of reproductive age in a community is a crude index of infertility. Even in societies where all women ultimately marry, the rate of childlessness is greatly influenced by the mean age of marriage, the mean age at menarche, the numbers of women in different age groups, and infant mortality.

Measurements of the prevalence rates of childlessness or of the mean number of children ever born among women who have completed their reproductive life would theoretically permit comparison of rates among different communities, but these statistics also have their limitations. Recall among older women is grossly incomplete with regard to abortions. Furthermore, an examination of these statistics among older women does not necessarily represent the situation as it currently exists. The sequence of events leading to childlessness in such women is likely to have taken place thirty or more years earlier. In addition, a high level of maternal mortality in an area reduces the number of fertile women at the end of their reproductive years, thus slightly increasing the magnitude of the problem as measured by the proportion of infertile women in the older groups.

To determine whether the problem still exists requires an analysis of data based on the reproductive histories of women currently in their most active reproductive years.

Data from large geographical units may show wide variation in the magnitude of the problem within a given country. Furthermore, it is not uncommon to find pockets of apparent infertility even within areas that are characterized by high levels of fertility.

In these circumstances, the ethnic or tribal group may be the best unit of study as the habitat, social conditions, and health problems are likely to be common to the whole unit.

A useful technique in establishing the etiology of infertility is to demonstrate that a change in the incidence or prevalence of some factors such as disease control measures involving the use of antimicrobial drugs is associated with a subsequent change in the prevalence of infertility in the same community.

Such an analysis requires a knowledge of the rates of infertility of the groups of older women when they were younger. This type of analysis is referred to as birth cohort analysis. It is the preferred technique for identifying changes of factors affecting a disease over a period of time.

2.2 Epidemiological and clinical studies defining the prevalence of infertility, pregnancy wastage, and child loss

Few published data exist from Africa on the relative importance of these different categories in contributing to the problem. Community-wide epidemiological or demographic studies dealing with infertility, pregnancy wastage, and child loss have been mainly concerned with communities experiencing depopulation. It is only in this type of study that the relative importance of the different categories of infertility, pregnancy wastage, and child loss has been examined.

The most complete epidemiological study on the prevalence of infertility, pregnancy wastage, and child loss is that by Scragg undertaken on the island of New Ireland in the Western Pacific.[a] This study of several villages combined a demographic survey and clinical diagnostic studies on defined groups of women. In the study (Table 1), the impor-

TABLE 1. INFERTILITY, PERINATAL DEATH, AND INFANT MORTALITY AS RELATED TO POPULATION CHANGE IN NEW IRELAND

Area	No. of women	Primary infertility	Secondary infertility	Still-births rate/1000 live births	Neonatal death rate/1000 live births	Total deaths under one year	% change over generation of 28 years
Lemankua	94	3.2	1.1	26	36	71	+154.0
Solas	133	4.5	4.5	16	131	319	+103.2
Tigak	196	21.9	22.7	67	80	125	— 24.8
Tabar	407	30.2	15.0	45	71	142	— 41.0

[a] SCRAGG, R. F. R. Depopulation in New Ireland : a study of demography and fertility. Administration of Papua and New Guinea, 1957.

tance of infertility is apparent. In the village of Tigak and Tabar, the combined primary and secondary infertility rates of 40% were clearly the main factor in depopulation. In Solas, although infant mortality was 31%, depopulation did not follow because the infertility prevalence rate was only 9%.

3. CAUSES OF INFERTILITY AND PREGNANCY WASTAGE

The epidemiological and clinical data on the etiology of infertility and pregnancy wastage in countries in Africa south of the Sahara are limited. Such studies as exist have either been incomplete in terms of the diagnostic procedures used, based on highly selected populations, or focused on testing the association of one single etiological agent or mechanism with infertility or pregnancy wastage.

Several studies have examined different possible causes of infertility in a series of women or couples who presented themselves with this complaint to a specific hospital or clinic for diagnosis and treatment. The populations in these studies represent highly selected groups who had access to, accepted, and used the particular health facility. There are further limitations to such exclusively clinical studies. For example, although it is possible to document carefully the presence of tubal occlusion in the individual patient, it is not usually possible to identify the underlying cause of the occlusion, such as gonorrhoea, or post-partum or postabortal infection.

The association between a specific condition and infertility or pregnancy wastage has been examined in several studies. These have generally focused on gonorrhoea and serological evidence of treponematoses. Only limited conclusions can be drawn from the results of such studies. If the condition is diagnosed in the individual couple, statistical and epidemiological techniques exist for defining the relative risk of an association with infertility or the attributable risk of that condition contributing to infertility or pregnancy wastage. If, however, the association is demonstrated merely by showing a correlation of the prevalence of the condition with the prevalence of infertility or pregnancy wastage in several communities, then the relative etiological importance of that condition in comparison with others cannot be directly determined from the study of individual couples.

Furthermore, the demonstration of an association, for example between serological evidence of syphilis and infertility, is not synonymous with causation. The positive serology is more likely to be an

indirect indicator of gonorrhoea, a known cause of infertility, and the occurrence of which parallels the occurrence of syphilis.

Table 2 lists some of the diseases that have been most frequently associated with infertility and/or pregnancy wastage and shows what is at present known or suspected about their relative importance. In the following sections, a more detailed discussion of the etiological and quantitative relationships is given that takes into account all the limitations of the existing data.

TABLE 2. POSSIBLE MAJOR CAUSES OF INFERTILITY OR PREGNANCY WASTAGE IN AFRICAN AREAS WHERE THERE IS A HIGH PREVALENCE OF CHILDLESSNESS

Disease	Cause/effect relationship		Degree of contribution	
	Infertility	Pregnancy wastage	Infertility	Pregnancy wastage
Gonorrhoea	well established, direct	none	potentially major	none
Syphilis	none	well established, direct	none	potentially major, usually minor
Genital tuberculosis	well established, direct	none	apparently minor	none
Postabortal or postpartum sepsis	well established, direct	none	potentially major	none
Obstetric difficulties	indirect (secondary infertility only)	direct and possibly indirect	potentially major (secondary infertility only)	potentially major
Other systemic and local infections (see text)	a few, weak correlation	several, established	minimal	apparently minor

3.1 Gonorrhoea and infertility

3.1.1 *Gonorrhoea, pelvic inflammatory disease, and tubal occlusion*

Pelvic inflammatory disease resulting from contagious spread of *Neisseria gonorrhoea* is the most common complication of primary genital tract infection. The infection in the woman starts as cervicitis, usually asymptomatic, and ascends by way of the uterine mucosa to produce endosalpingitis, followed by spread to the other layers of the fallopian tubes. Often salpingitis arises at the end of menstruation from a carrier state. Destruction of the tubal mucosa and subsequent scarring frequently leads to partial or complete tubal obstruction. The risks of occlusion appear greater the longer the infection

has continued and may also increase with repeated infection. Attempts to associate a gonococcal infection with tubal occlusion in individual cases are often difficult. The longer the duration of the salpingitis the smaller the possibility of identifying *N. gonorrhoea* in the individual.

3.1.2 *Gonorrhoea and its sequelae of infertility in the male*

In the male, gonorrhoea begins as urethritis and is usually symptomatic. However, an asymptomatic infection is not uncommon especially in areas with high prevalence of gonorrhoea and inadequate treatment. An ascending infection may involve the prostate gland and the seminal vesicles. The mechanism whereby the epididymis becomes involved is not well understood. It is generally thought to become affected as a result of retrograde passage of infected urine from the urethra along the lumen of the vas deferens. Both chronic seminal vesiculitis and chronic epididymitis may be associated with abnormal sperms, and the latter with occlusive azoospermia. The relative importance of the sequelae of gonorrhoea in man on the prevalence of infertility has not been well documented. However, very high prevalence rates of thickened epididymes (27.3%) have recently been reported from an area with low fertility and high prevalence of gonorrhoea.[a] In the era before effective chemotherapy, epididymitis was described as occurring in 17%–30% of the male cases of gonorrhoea.[b] But now, in areas with developed and widely available health services and with appropriate antibiotic treatment of gonorrhoea, this complication is rarely seen.

3.1.3 *The association between gonorrhoea and infertility in general*

In the absence of valid and reliable serological or other tests for gonorrhoea that are applicable several years after the original infection, the establishment of an association must depend on the simultaneous comparison of the prevalence rates of both infertility and gonorrhoea in several communities. Some supportive evidence can be obtained by cohort analysis of the prevalence of infertility or age-specific birth rates in communities where mass penicillin treatment for yaws or even gonorrhoea has taken place. An association of gonorrhoea and infertility has been inferred in several communities from a comparison, on a community basis, of such indices as prevalence rates of *N. gonorrhoea* in surveys, rates of reported gonorrhoea and urethritis, and urethral

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[a] ARYA, O.P. ET AL. *Bull. World Health Organ.*, **49** : 587–595 (1973).

[b] WHO Technical Report Series, No. 262, 1963.

stricture rates with such indicators of infertility as the percentage of childless women, general fertility rates, and total fertility. Arya et al. showed a high correlation of infertility and gonorrhoea prevalence in two communities, one with a high and the other a low level of infertility (Table 3).[a] A similar correlation was also demonstrated in respect of thickened epididymes.[b]

TABLE 3. FERTILITY AND THE PREVALENCE OF GONORRHOEA IN MEN AND WOMEN IN A RANDOM SAMPLE OF THE POPULATION FROM TWO DISTRICTS OF UGANDA

	Total population (1000s)	General fertility rate of people aged 16–45 years	Males		Females	
			No. examined	Isolation of *N. gonorrhoea*	No. examined	Isolation of *N. gonorrhoea*
Ankole district (high fertility)	859	241	166	7 (4.2%)	168	4 (2.4%)
Teso district (low fertility)	565	115	270	24 (8.9%)	295	54 (18.3%)

3.2 Non-venereal diseases and infertility

3.2.1 *Genital tuberculosis*

Tuberculosis of the reproductive organs is generally considered to be secondary to extragenital foci, usually the lungs, but it is not uncommon for the primary focus to be healed or undetectable. The fallopian tubes constitute the initial site of genital tuberculosis, and the gross appearance of these may be similar to that in other forms of chronic salpingitis. Endometrial involvement is secondary to tubal involvement, and is estimated to occur in 50% of the cases of tuberculous salpingitis.

Infertility, almost always primary, and amenorrhoea are the most common complaints of women with genital tuberculosis. The few clinical studies available from Africa suggest that it is probably a relatively unimportant etiological factor in infertility.

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[a] ARYA, O.P. ET AL. *Bull. World Health Organ.*, **49** : 587–595 (1973).

[b] ARYA, O.P. & TABER, S. R. Correlates of venereal disease and fertility in rural Uganda. Paper presented at the Spring Meeting of the Medical Society for the Study of Venereal Diseases, held in Malta, April 1975 (to be published).

3.2.2 *Postabortal or postpartum sepsis*

Tubal occlusion may be a consequence of a pyogenic non-gonococcal salpingitis. Many of the sequelae of abortion and obstetrical practices involve complicating infections, and some of these may result in salpingitis and tubal occlusion. Tubal occlusion associated with secondary infertility may therefore be a result of either gonococcal salpingitis occurring after the last puerperal or postabortal period, or of non-gonococcal postabortal or puerperal infection. As described among women in developed countries, the lumen and mucosa of the tubes are usually not involved initially in non-gonococcal cases but rather there is extensive interstitial infection with thickening and oedema. In theory, the lack of mucosal involvement should be associated with less risk of occlusion than in cases of gonorrhoeal salpingitis.

However, it is not certain that the same natural history of post-puerperal or postabortal infection is found among women in developing countries. These women suffer from a variety of endemic diseases and deficiencies that render them more susceptible to infections and their sequelae. Difficult and prolonged labour without skilled obstetrical assistance, as well as unskilled induced abortions, are likely to be followed by severe pelvic infections. The women are also less likely to receive early and intensive antibiotic treatment.

In all studies that have included an examination for tubal occlusion, this phenomenon has been shown to be the most important cause of infertility in Africa south of the Sahara and other areas where a high prevalence of infertility exists. Data are not available on the frequency of postpartum or postabortal salpingitis in Africa south of the Sahara and on the risk of subsequent infertility, but the rate of secondary infertility can be used as a crude indicator of the possible importance of these conditions, particularly if primary infertility is low. It must be kept in mind, however, that secondary infertility with tubal occlusion may also be due to a gonococcal infection acquired during or after the pregnancy.

3.2.3 *Other infections*

A number of other infectious diseases may be related to both male and female infertility. Mumps orchitis, like testicular trauma, can of course result in infertility but its importance in relation to the prevalence of infertility is thought not to be very great. Filariasis, schistosomiasis, and chlamydial infection may play a part in causing male (and possibly also female) infertility, but this has not yet been well defined.

There is no evidence that infection with *Mycobacterium leprae* contributes significantly to the problem of infertility among women, but there is evidence for a possible effect in men who have lepromatous leprosy.

There is no published material available on the possible association of either male or female infertility with leprosy in Africa south of the Sahara. However, since the sexual activity of leprosy patients has been limited by cultural and health care patterns, even in areas where the disease is highly prevalent, it is unlikely to be a major cause of infertility.

The role of *Trichomonas vaginalis* has been extensively discussed but is still uncertain. The organism is found very frequently in the genital tract and is transmitted as a venereal disease : any apparent effect might alternatively be attributable to gonorrhoea.

3.2.4 *Other conditions*

References to the role of thyroid disease in infertility have been frequent, but there have been no reports of any association of public health significance. Despite there being well defined pockets of endemic goitre in Africa, as well as other areas of the world, data are not available on infertility, pregnancy wastage, or childlessness in such areas.

The role of nutritional or dietary deficiencies in relation to hormonal changes has not been explored, except under circumstances of extreme deficiency such as during starvation or under experimental conditions. At present there is little direct evidence for an association between malnutrition and high levels of infertility.

Congenital abnormalities of the female genital tract, endocrine factors, and psychological factors causing infertility and pregnancy wastage are not discussed here since, although they represent some of the main causes of infertility, there is no evidence that they have any increased significance in Africa south of the Sahara.

3.3 Conditions affecting pregnancy wastage

3.3.1 *Syphilis*

Syphilis produces pregnancy wastage. The characteristic outcome of pregnancy in a woman infected with *Treponema pallidum* is either a spontaneous abortion not earlier than the second trimester of pregnancy, a macerated fetus, a live syphilitic infant, or a healthy infant who may have passively acquired maternal syphilitic antibodies and who may or may not manifest signs of syphilis at a later time. The more chronic the infection, the greater the chances of a healthy infant, and vice versa.

In areas where syphilis is suspected of being of major importance in pregnancy wastage, serological studies have often been confounded by cross-reactions to *T. pertinue* (yaws) and *T. carateum* (pinta) infections that are not generally considered to be associated with pregnancy wastage.

From the available data and our knowledge of the natural history of syphilis, there is no evidence to show that syphilis plays a role in the etiology of infertility. In some communities in which there is a high level of sexual activity among multiple partners, the recent introduction of syphilis may lower fertility rates because of increased levels of pregnancy wastage. If syphilis is common in a community, it is probable that gonorrhoea is also common. As previously noted, correlations of syphilis serology with infertility probably reflect a correlation with gonorrhoea.

3.3.2 *Obstetrical difficulties*

Obstetrical difficulties relate mainly to late fetal deaths, but also affect early neonatal deaths. They include prolonged or obstructed labour, eclampsia, precipitate delivery, major bleeding, and other delivery complications associated with a high risk to the fetus. Intrapartum deaths from asphyxia due to prolonged labour, and birth trauma due to mechanical difficulties are likely to be common where there is a high incidence of contracted pelvis. The relative importance of obstetrical difficulties is greater the less accessible are the health services. In many of the parts of Africa where antenatal care may be largely nonexistent and most deliveries take place at home without skilled supervision or assistance, its role is probably considerable.

Previous trauma to the genital tract, such as cervical lacerations or endometrial damage with subsequent intrauterine adhesions, can cause late or early spontaneous abortion. Such trauma may be more frequent in areas where unskilled induced abortions are frequent, but there is no evidence that they contribute significantly to pregnancy wastage in Africa south of the Sahara. The same applies to infibulation, which can sometimes result in extensive scarring of the vulva and potentially in obstruction of labour, but this has not been evaluated regarding its effect on pregnancy wastage.

3.3.3 *Non-venereal infections*

Toxoplasmosis, cytomegalic inclusion disease, listeriosis, brucellosis, rubella, and rickettsia are all very rare causes of pregnancy wastage in the non-tropical countries where they have been studied, and unless

local experience indicates a larger role in African communities south of the Sahara, they are probably unimportant. The role of *Mycoplasma* infections has not yet been defined.

Malaria *(Plasmodium falciparum)* contributes indirectly to fetal loss. In unprotected pregnancies, fetal growth may be impaired and premature labour precipitated, and severe degrees of haemolytic anaemia are common.

3.3.4 *Other causes*

Severe anaemia in pregnancy due to folate or iron deficiency or to malarial infections contributes to pregnancy wastage by impaired intrauterine growth, prematurity, and even late abortion or stillbirth.

The role of malnutrition is ill-defined. One way in which it may contribute to pregnancy wastage is by impairing the growth and development of future mothers when they themselves are children or adolescents, preventing them from reaching their genetically determined stature and resulting in a high incidence of contracted pelvis and thus pregnancy wastage due to mechanical difficulties in labour. Impairment of the future mother's health in childhood and adolescence by recurrent infections and malnutrition may also result in increased liability to produce babies of low birth weight.

Haemoglobinopathies can only make a small contribution to fetal wastage; S-homozygotes (haemoglobin-SS) very rarely survive to reproductive age in tropical African conditions, and haemoglobin-S/thalassaemia heterozygotes and SC-heterozygotes are rarer still in the countries where the problem appears to be most acute; the same holds true for rhesus-isoimmunization.

3.4 Sociocultural factors

Social and cultural factors are not considered as causes of infertility or pregnancy wastage but serve as intermediary variables permitting the spread of etiological factors or increasing their effects.

The first group of sociocultural factors are those concerned with risk of exposure to pregnancy. Seasonal or temporary migration of men, often to work far from their homes for a large part of the week or month, has the effect of reducing the duration of cohabitation. Marital instability and polygamy may also have similar effects. However, the effects of polygamy and possible marital instability, depending on the patterns of cohabitation, the frequency of intercourse, and the presence of certain

etiological causes, may have either no apparent association or a positive association with fertility.

The second group of sociocultural factors are those likely to increase the exposure to, or experience with, the causes of infertility and pregnancy wastage previously noted. Sexually transmitted diseases are clearly propagated more rapidly when the social structure leads to unstable conjugal unions or prostitution. The incidence of the sexually transmitted diseases is obviously increased with increased frequency of sexual activity and with multiple sexual partners. Such increases in sexual activity are often associated with seasonal or permanent migration of men to urban areas and their subsequent return to rural homes, military conscription, wars, and historically with colonization and the slave trade.

Risk of genital tract infection or injury may be affected by the local birth and postpartum practices, use of indigenous contraceptives or abortifacients, and less commonly by ritual operations on the genital tract such as infibulation or, rarely, female circumcision.

It must be recognized that the consequences of these different factors are not always in the same direction. For example, marital instability may favour spread of sexually transmitted diseases. However, a woman who has not had a child with her first spouse, might have one with a second spouse if the cause of the infertility was due to obstructive azoospermia in her first spouse. In this latter instance the change of partners would lower the level of infertility.

It is clear from the preceding review that some demographic data may be available to permit presumptive identification of affected communities, but that by themselves such data will not define the problem sufficiently to permit the formulation of public health policies.

4. RESEARCH APPROACHES

The infertility problem in communities where concern has been expressed must thus be analysed in terms of the relative contribution of primary and secondary infertility, pregnancy wastage, and child mortality.

The implications for public health action may be quite different depending upon the results of a preliminary classification of the problem. For example, in addition to the obvious health care implications of distinguishing child loss or pregnancy wastage from infertility, the differentiation between primary and secondary infertility may be useful in

indicating the major causes, particularly among the women. If only high levels of secondary infertility are found, then the sequelae of postpartum or postabortal infection would be the probable cause. If, however, high levels of both primary and secondary infertility are found, the sequelae of gonorrhoea are likely to play a major role as well.

4.1 Terminology

The terminology proposed in this report is intended simply for the purposes of the proposed research approaches presented in subsequent sections. The definitions are operationally defined for the collection of data in its simplest form with the maximum of reliability. These definitions are not intended to serve or resolve the differing needs and their traditional uses by clinicians, epidemiologists, and demographers.

The following operational definitions, as they relate to couples, are proposed :

(*a*) *Primary infertility :* the woman has never conceived despite cohabitation and exposure to pregnancy [a] for a period of 2 years.

(*b*) *Secondary infertility :* the woman has previously conceived but is subsequently unable to conceive despite cohabitation and exposure to pregnancy for a period of 2 years ; if the woman has breast fed a previous infant, then exposure to pregnancy should be calculated from the end of the period of lactational amenorrhoea.

(*c*) *Pregnancy wastage :* the woman is able to conceive but unable to produce a live birth. Loss of pregnancy during the first 28 weeks is referred to as early and intermediate fetal death, or abortion, and may be spontaneous or induced. Beyond 28 weeks of gestation and up to term, such losses are referred to as late fetal deaths, or stillbirths.

(*d*) *Child mortality :* all deaths of children born alive up to their fifth birthday. (Perinatal mortality, i.e., stillbirth plus all deaths of offspring within the first week after birth, may be recorded separately. In some cultures, however, the early neonatal deaths may be perceived as stillbirths and hence be difficult to elicit.)

(*e*) " *Unproven infertility* " or " *unproven fertility* " refers to problems sometimes perceived by individuals or couples as infertility or

[a] The Scientific Group, after reviewing the subject, concluded that " exposure to pregnancy " is difficult to define and standardize except in the context of specific local conditions.

included as infertility in demographic surveys, whereas, in fact, the woman is virtually not at risk of conception. The problem may be biological, such as among lactating women who are anovulatory, or couples practising contraception; or circumstantial, when there is the absence of cohabitation or coitus (e.g., women whose consort is temporarily away).

4.2 Problem definition

The Scientific Group did not address itself to the 5% "hard core" of infertility already mentioned, but to those situations in which the prevalence of infertility is markedly higher than this.

If it is possible to obtain (from a census or a representative survey) a reliable estimate of the proportion of women aged 50 years or more who have never had a child, a serious public health problem should be considered to exist when this proportion is more than 15%, in the absence of known voluntary infertility. However, it should be noted that such an estimate will only apply to the older generation of women, and that among the younger generation the situation could be different.

If the results of a survey show that 15% of the women from 20 to 29 years of age, for example, were categorized as infertile this would indicate that a serious problem exists. These age limits may be varied but age must be taken into account, since the proportion of couples who are naturally infertile increases with age, particularly rapidly after age 35. At the same time, fertility is generally not well established in the first 2–4 years after puberty.

Levels of pregnancy wastage, derived from interviews rather than from prospective studies, are in the range of 15–20% of pregnancies even in countries with well developed health services; most of these represent spontaneous abortions during the first trimester. Rates for stillbirths are about 1–2% of births. A pregnancy wastage rate (no. of abortions and stillbirths in 1 year $\times 100$/total no. of pregnancies in 1 year) of 30% would constitute a situation for public health concern.

4.2.1 *Preliminary assessment of the problem*

Before any resources are committed to studies of infertility, all available sources of information that may provide clues on the distribution, magnitude, and types of infertility should be carefully reviewed. These include demographic data (e.g., for studies of birth rates, total fertility, age-specific fertility, percentage of women who have never

given birth to a live child); vital statistics for studies of mortality (infant and child); clinical records (e.g., for studies of major causes of infertility, minimal estimates of pregnancy wastage including estimates of selected causes such as stillbirths); disease reports (e.g., for studies of rates of gonorrhoea, syphilis, and other diseases that may be associated with infertility or pregnancy wastage).

In addition to these sources of information, a social-anthropological profile of the community obtained from knowledgeable sources will often be useful in assessing the nature of the problem and indirectly the nature of any inquiry that may be required. Useful clues may be provided by patterns of migration, any characteristics of the economy that result in the separation of partners, and knowledge of the marital and coital practices and of the use of indigenous abortion, etc.

If the existing data do not provide a definition of the nature and magnitude of the problem with sufficient precision to permit the planning and commitment of health service resources, it is necessary to consider carrying out a simple survey on a regional or population basis to answer the question whether a problem of infertility or pregnancy wastage exists.

4.3 Regional or population diagnosis

In view of the above limitations, true assessment of the existence of a problem of infertility and/or pregnancy wastage in a community (or a region consisting of several communities or villages) requires a survey of a representative sample of the population. In the first instance this could be conducted by means of a simple questionnaire which would permit the classification of subjects into the categories of primary and secondary infertility, pregnancy wastage, childlessness due to infant and child mortality, and unproven infertility. The questionnaire should include simple questions to obtain the following data on the most recent pregnancy:

(*a*) Identifying data—name, age, residence, ethnic group.

(*b*) Marital status—duration of current union; whether divorced/widowed/separated—duration.

(*c*) Current situation: pregnant; breastfeeding—duration; amenorrhoea—duration.

(*d*) Most recent pregnancy: date, outcome of pregnancy (abortion, stillbirth, or live birth); for live births whether child is alive or dead.

(*e*) Total number of live births, total number of children living now.

(*f*) Husband—name, age, whether he has other wives, and whether they have had children by him.

(*g*) Cohabitation status : whether husband is at home ; whether couple is having intercourse, and how frequently.

(*h*) Contraceptive practice : type and duration since last pregnancy.

Although the questions would appear to be relatively simple, a community survey of this kind requires special resources and should probably not be undertaken unless there is fairly strong suspicion of elevated levels of infertility or of pregnancy wastage. The form in which the questions are put to a woman needs to be assessed locally. A sample composed of 316 women, 20–29 years of age, would be sufficient to classify a community as having an unusually high level of infertility or pregnancy wastage (see Annex).

With the above noted information (*a* — *h*) each woman can be classified into only one of the five categories : infertility (primary or secondary), pregnancy wastage, child loss, unproven infertility, and fertile.

4.4 Further research on the etiology of infertility

Even if the rates of infertility or pregnancy wastage are considered to constitute a public health problem, a decision must be made regarding the need for further studies on specific causes and on the nature of those studies. The resources and time required for further studies must be balanced against the amount of information to be obtained and the importance of this information to the choice of an appropriate public health programme.

As already noted, the main causes for the elevated levels of infertility may be grouped as follows :

— sequelae of gonorrhoea in women or men ;

— sequelae of postpartum or postabortal infection ;

— genital tuberculosis ;

— other causes.

If primary infertility is uncommon and the problem is one of secondary infertility and if the sociocultural profile confirms the impression that the social conditions do not favour a high level of gonorrhoea, then from a public health policy standpoint this information might be sufficient. When, however, primary and secondary infertility are both

present at high levels, as has been noted, no distinction can be made between the roles of the sequelae of gonorrhoea in male or female and the sequelae of postpartum or postabortal infection, and additional studies would be required. For the purposes of developing highly specific control measures, for example against gonorrhoea, additional studies would also be necessary if it was required to distinguish between the contributions of the male and the female to infertility.

Several alternatives for additional studies are available and are shown in Fig. 2. A decision as to which studies should be undertaken again involves consideration of the relative cost in terms of time and resources as compared with the expected returns.

The choice between alternative research approaches to establish the major causes of infertility can be made only when steps 1, 2, and 3 shown in Fig. 2, and discussed in previous sections (4.2.1 and 4.3), have been completed.

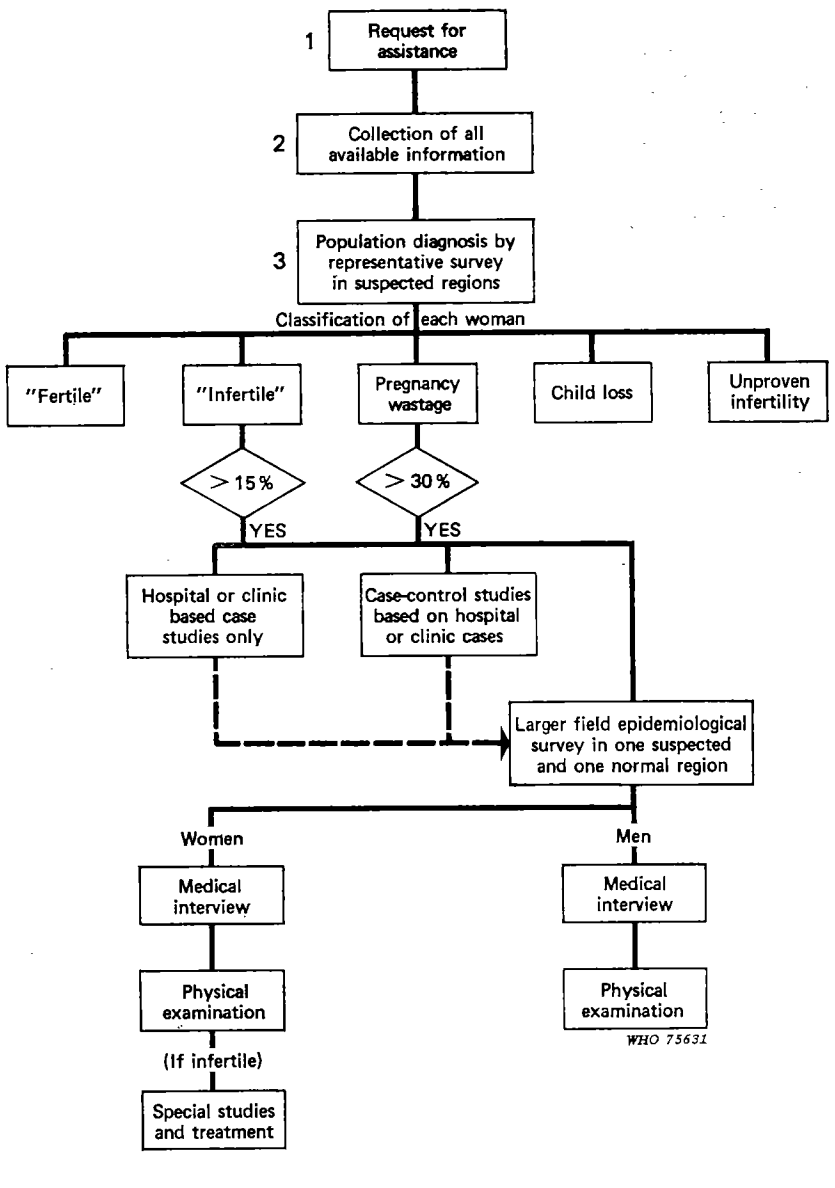
4.4.1 *Hospital or clinic based studies of affected couples*

The simplest studies would be diagnostic studies of affected couples, either those seen in a clinic or, preferably, those identified in the course of a previous community survey. The patients seen in a clinic are highly self-selected and may not represent the pattern of infertility as it is found in the community. Individual couple diagnosis will enable the investigator to determine the relative contributions of male and female infertility in the population from which the couples are drawn. By inference, most of the excess male infertility would be due to sequelae of gonorrhoea. In the case of the woman, it should be possible to determine the overall contribution of the sequelae of infection, i.e., tubal occlusion, and of genital tuberculosis.

4.4.2 *Case-control studies : health-facility or field based*

In order to establish the importance of the sequelae of postpartum or postabortion infections or of other possible causes of infertility, it is necessary to study both infertile couples and a comparable control group of fertile couples. In this way it is possible to compare the frequency of presumptive signs, symptoms, and laboratory findings in cases and controls to determine their degree of association with infertility. This approach is necessary since some findings may not always be present in infertile couples and may at times be present in fertile couples. Furthermore, to determine the relative importance of the different factors or causes in accounting for the high level of infertility

FIG. 2. THE SEQUENCE OF AND ALTERNATIVE APPROACHES TO RESEARCH ON THE MAGNITUDE, DISTRIBUTION, AND CAUSES OF INFERTILITY AND PREGNANCY WASTAGE



it is necessary to compare samples of infertile and fertile couples drawn from an area with a low level of infertility.

Case-control studies can be based either on hospital or clinic populations, or on cases and controls drawn from field studies representing the specific communities. As noted above, hospital or clinic based studies have the disadvantage of selectivity. The major problem in hospital or clinic based case-control studies is the identification of suitable controls. Women attending other clinics or hospital services unrelated to infertility or possible etiological agents are most appropriate. Other gynaecology patients are therefore usually not suitable. Careful attention must be paid in such hospital based studies to the matching of cases and controls in respect to age, tribal group, social class, etc. Erroneous conclusions may be drawn if this is not done. A case-control study based on a representative sample drawn from field studies has the disadvantages of higher costs and complicated logistics, but does have the advantage of being representative of the defined community.

4.4.3 *Community correlations*

Determining the contribution to infertility of the sequelae of gonorrhoea presents a special problem. The episode(s) of gonorrhoea that led to infertility is likely to have occurred some time before the diagnosis of infertility is made by which time it is usually not possible to culture the organism. In the absence of a reliable serological test, the specific diagnosis of gonorrhoea as the underlying cause cannot be made in individual cases. At the population level, however, it is possible to establish the degree of association between gonorrhoea and infertility by correlating the prevalence of gonorrhoea in several communities that differ with respect to the prevalence of infertility.

Since gonorrhoea is likely to be one of the major causes of infertility in many populations, epidemiological studies on the etiology of infertility should be designed to take these special requirements into account, by including a representative population made up of discrete communities such as several villages with a high (e.g., $\geqslant$15%) and several with a low (e.g., $\leqslant$8%) prevalence of infertility. Studies on the prevalence of gonorrhoea are easily encompassed within the design of field epidemiological studies for other associations, although a larger number of communities would be needed.

4.5 Data collection and analysis

The history of symptoms indicative of certain clinical entities such as postpartum or postabortal infection, and even pelvic inflammatory disease, that occurred at least two years earlier is likely to be incomplete and unreliable. However, such a history must be obtained with the hope, but not a high expectation, of a meaningful differentiation of cases of tubal occlusion resulting from gonorrhoea, from those resulting from postpartum or postabortal infection.

With all its imperfections, a standardized history should be obtained from all couples whether the approach be one of case studies or case-control studies. Information on the following items should be included.

4.5.1 *Data to be collected on all women*

4.5.1.1 *History*

(*a*) Identification data for locating and placing individuals and couples: name, age, marital status, residence, ethnic group, some socioeconomic data.

(*b*) Pregnancy history: dates, outcome (if less than full-term or dead at term, appearance of fetus); if live birth, whether still alive.

(*c*) Procedures, if any, associated with the last delivery, and whether at home or institution, e.g., instrumentation.

(*d*) Febrile illness, if any, during the last postpartum period.

(*e*) Procedures and illness associated with any abortions.

(*f*) Other gynaecological procedures and surgery, e.g., clitorectomy, pelvic surgery.

(*g*) Any other episodes of pelvic infection—pelvic pain, discharge, fever, treatment, etc.

(*h*) History of amenorrhoea.

(*i*) Cohabitation status. If possible, occurrence and frequency of intercourse.

(*j*) Contraceptive history: method(s) used and duration.

(*k*) Current lactation status.

(*l*) Pregnancies among other wives of consort (previous marriages, polygamous unions).

4.5.1.2 *Physical examination*

(*a*) Height, weight, skinfold thickness.

(*b*) Mucocutaneous lesions
(*c*) Lymphadenopathy
} if syphilis is being investigated

(*d*) Pelvic area :

(i) inguinal lymphadenopathy
(ii) mucocutaneous lesions
} if syphilis is being investigated

(iii) vaginal discharge

(iv) cervical discharge, scars, ulceration

(v) bimanual pelvic examination for tenderness, masses, mobility.

4.5.1.3 *Laboratory studies*

(*a*) Cervical smear and culture for *Neisseria gonorrhoea*. One of the two transport media—Stuart's medium or Transgrow medium— can be used for the transport and isolation of the gonococcus. With Stuart's medium, only charcoal swabs should be used to obtain material from the cervix. To achieve a high success rate, the culture specimens should reach the laboratory within 24 hours after collection. After this some loss may be expected. Other possibilities include plating the material on to selective culture media and keeping the culture plates in an atmosphere of carbon dioxide in candle-extinction jars, and the use of portable incubators.

(*b*) While *Trichomonas vaginalis* is unlikely to be an important cause of infertility this possibility is not yet completely resolved. As insufficient evidence is available, and as the organism can be easily demonstrated by simple tests, vaginal discharge should be examined for trichomonads. (In this way its role in the causation of infertility may be clarified.) However, as the use of a microscope (to examine the wet preparation) is unlikely to be possible under field conditions, an appropriate culture medium (such as Feinberg-Whittington's medium) will be needed.

(*c*) Serological tests for syphilis. In several areas of Africa where infertility surveys might be carried out, treponematoses other than venereal syphilis are likely to make the interpretation of serological tests very difficult. In such circumstances these tests are unlikely to yield information of much use to the study. Nevertheless, when reliable

information can be obtained (e.g., when other treponematoses are absent or not a major problem), these tests should be carried out. Although syphilis is rarely if ever a cause of infertility, a high prevalence of serological positivity would serve as an additional indicator of other sexually transmitted diseases.

However, syphilis can cause pregnancy wastage, and if the latter is considered to be a problem then serological tests for syphilis must be carried out. These tests should preferably include at least one specific test such as the fluorescent treponemal antibody absorption (FTA-ABS) test or the *Treponema pallidum* haemagglutination (TPHA) test.

A large number of the couples examined in field studies will have no problem of infertility but may have other health problems. Provision should be made by those responsible for the field study for the referral and treatment of these individuals. Not only is it imperative ethically to ensure that their problems are not ignored, but such action should help to foster good public relations with the given community. Infertile women will require additional specialized examination.

4.5.2 *Data to be collected on men*

All consorts in the entire sample should be examined.

4.5.2.1 *History*

(*a*) Identification data for locating and placing the individual: name, name of partner, age, marital status, residence, ethnic group, some socioeconomic data.

(*b*) History of children by other spouses, duration of current union.

(*c*) Past history of urethral discharge.

(*d*) Past history of genital sores (if syphilis is being investigated).

(*e*) Present history of urethral discharge.

(*f*) Difficulty in micturition.

4.5.2.2 *Clinical examination*

(*a*) Urethral discharge

(*b*) Epididymes

(*c*) Genital sores

(*d*) Lymphadenopathy } (if syphilis is being investigated see section 4.5.1.3.)

(*e*) Mucocutaneous lesions }

4.5.2.3 *Laboratory tests*

(*a*) Urethral smear and culture for *Neisseria gonorrhoea* (whether urethral discharge is apparent or not). (For culture techniques, see section 4.5.1.3.)

(*b*) Serological tests for syphilis. (If syphilis is being investigated, see section 4.5.1.3.)

4.5.3 *Special studies on couples diagnosed as infertile*

(*a*) *Female partner*

If bimanual examination has revealed tubo-ovarian masses, fixed tender uterine retroversion, etc., suggestive of chronic salpingitis, the cause of the infertility may be presumed to be tubal occlusion.

If there are no such physical signs, however, a tubal patency test should be performed, using carbon dioxide insufflation. (As this is contraindicated by the presence of active tubal inflammation, it should not be performed if there is adnexal tenderness.) If the gas fails to pass (i.e., negative test), tubal blockage is likely (but needs confirmation by hysterosalpingography, which is inappropriate under field survey conditions).

If a tuberculous origin for this tubal occlusion is suspected in a nullipara, especially if there is amenorrhoea, an endometrial biopsy may be obtained by aspiration currettage under clinic conditions. This has to be performed, however, in the premenstrual phase of the cycle, which may mean the recall of the patient. A negative result, again, does not exclude tuberculous salpingitis.

(*b*) *Male partner*

As part of the general survey the history and clinical examination will have already been completed among the male partners of an infertile union.

Ideally, the semen of the male partner should be accurately examined after collection either by masturbation, by coitus interruptus, or by condom, free of spermicidal agents. However, these methods may not be acceptable even among infertile couples.

Alternatively, semen collected from the posterior vaginal fornix within 4 hours of coitus may be examined. As this will only detect azoospermia it will only identify male partners who are completely infertile (as opposed to subfertile).

These postcoital tests should be performed on *all* infertile couples to identify the extent of male infertility, not just on those in whom no

obvious female factor has been found, as male and female factors may frequently coexist.

4.5.4 *Analysis of data*

The classification scheme for the analysis of data is based upon the current marital union, cohabitation referring only to the current spouse. It is recognized that there is increased conjugal mobility associated with infertility, and that some barren unions may be dissolved before the two years used in these operational definitions. Furthermore, since the analysis will focus on infertility, the classification of infertility will be as noted in Section 4.1, and infertile couples will be compared to *all others*, who for purposes of analysis are presumed to be fertile, since in these studies a precise definition and identification of fertile couples is not possible.

The analyses will compare symptoms, signs, and laboratory findings in different groups, to include :

(i) all infertile couples compared with all other couples,

(ii) all infertile couples compared with all other couples in the high infertility areas,

(iii) all infertile couples compared with all other couples in the low infertility areas.

The signs and laboratory findings of gonorrhoea will be compared between high infertility areas and low infertility areas.

The comparisons of all infertile couples with all other couples should give a measure of the degree of association of a given factor with infertility, whether primary or secondary or *in toto*. The separate comparisons in fertile and infertile couples in the high infertility area and in the low infertility area aim at demonstrating possible differences in the relative contribution of the various etiological factors to infertility, in these two types of area. This may permit identification of the factors that are the basis of the increased rate of infertility in the " high " areas. The comparison of the prevalence rate of clinical signs and laboratory findings of gonorrhoea in the high as compared with the low infertility areas will give a measure of the degree of correlation between the venereal diseases and infertility in these communities.

The data should be analysed to test the sensitivity and specificity of the classification scheme proposed in Section 4.3. Population diagnosis can be tested in areas where more detailed epidemiological studies are undertaken in the field. The classification based on the last pregnancy

can be cross-tabulated with a classification derived from the total pregnancy history.

4.6 Epidemiological investigation of pregnancy wastage

While it is difficult to assess the cause of infertility in an individual couple under field conditions, the retrospective diagnosis of the cause of an abortion or a stillbirth may be impossible. Even when it might have been due to a systemic disease, say toxoplasmosis, serological evidence that the individual has had such an infection in the past does not constitute proof that it was responsible for the abortion. In fact, high rates of pregnancy wastage are usually due to even less readily identifiable factors than infections.

Where high pregnancy wastage is found to be an important factor in childlessness in a community, a different approach is necessary. Specific community profiles of various possible factors should be drawn up and communities with high and low pregnancy wastage should be examined for these factors. Examples of such profiles are : dietary profiles indicating an association with specific nutritional factors or metabolic disorders, endemic disease profiles (syphilis, malaria, etc.)—close association with animals being suggestive of zoonoses such as brucellosis. Absence or defective use of maternity services will be associated with a raised stillbirth component of pregnancy wastage.

Community attitudes to induced abortion should also be studied. Where this is favoured, high fetal wastage may contain an otherwise concealed element of induced abortion.

However, where neighbouring communities with high and low rates of pregnancy wastage are not available for comparison, this method of attributing etiology by inference is not suitable. In these circumstances, different wastage levels within groups rather than between groups may have to be examined.

4.6.1 *Laboratory studies*

Most of the infectious diseases mentioned above that may have caused pregnancy wastage are likely to have been past events. Therefore, the chances of isolating the corresponding organisms from vaginal and cervical cultures are minimal. In the absence of any other diagnostic test, it would be necessary to carry out only serological tests for the following diseases : syphilis, toxoplasmosis, cytomegalic inclusion disease, listeriosis, rickettsia, rubella, and brucellosis. It should, however, be noted

that positivity of the serological test indicates only an association and not the cause and further investigation may therefore be indicated.

4.6.2 *Data analysis*

The rates for pregnancy wastage may be generally high or there may be areas of high and low incidence. If areas of high and low incidence are found then the analysis should take the form of a comparison of the frequency of various findings in the two areas as a whole and between those classified as having pregnancy wastage and those classified as not having pregnancy wastage as noted under the infertility analysis (Section 4.5.4). Women will be classified as having had pregnancy wastage (1) in the last pregnancy, or (2) in the last three consecutive pregnancies, in order to determine the importance of repeated pregnancy wastage. In the analysis of associations with pregnancy wastage, infertile women should be excluded.

If the rates of pregnancy wastage are elevated in all areas studied in a country, then the findings should be analysed by comparing the history and the physical and laboratory findings of women whose last pregnancy ended in wastage and of women whose last pregnancy ended in a live birth. If repeated pregnancy wastage appears to be a problem, then a similar analysis to identify associated factors could be undertaken.

4.7 Epidemiological investigation in populations with suspected problems of both infertility and pregnancy wastage

It is very probable that a mixture of increased infertility (i.e., $\geqslant$15% of couples) and of increased pregnancy wastage (i.e., $\geqslant$30% of pregnancies) may be found in all areas. Under these circumstances the design of an epidemiological study in terms of sample size, history, physical examination, and laboratory measurements should combine the elements required for a study of each condition separately.

In other situations the overall levels of infertility or pregnancy wastage may not meet the criteria of significance, although the initial survey indicates that a significant problem exists in the subgroups. For example, the rates of infertility or of pregnancy wastage in a young age group may be much higher than expected. In this situation, the general design developed will still apply but the overall sample size should be enlarged to increase the number of subjects in the affected subgroup. Alternatively, the study could be restricted to the affected subgroup, but this would also require a larger sample size than that of the original survey.

5. CONCLUSIONS AND RECOMMENDATIONS

From this review of the causes of infertility, it would seem that tubal occlusion in women and obstructive azoospermia in men appear to be mainly responsible for infertility in countries in Africa south of the Sahara. Although infertile women seek treatment in large numbers and thus place a heavy burden on the curative health services, the prospects for restoring fertility to the individual couple are unfortunately very poor.

This emphasizes the importance of preventing the causative infections within affected communities. Similarly, pregnancy wastage due to both abortions and stillbirths must be controlled by appropriate maternity care activities.

However, preventive measures can only be effective if they are specifically oriented to causative factors whose local importance has been identified by field studies. Hence the need for properly planned epidemiological research. As has been emphasized in this report, research should be directed at those potential causes that are treatable or preventable within the context of health priorities and resourses.

The following recommendations were made by the Scientific Group :

1. In view of the difficulties of undertaking large-scale field investigations, preliminary studies should be undertaken to define the magnitude of the problem before studies into the etiology are launched (see Section 4.3).

2. The implementation of population censuses and of the World Fertility Survey should be used by governments to obtain more precise information on the question of infertility. Additional questions should be considered in such surveys to obtain information on issues such as exposure to the risk of pregnancy, outcome of previous pregnancies, breastfeeding, and amenorrhoea.

3. In the implementation of research on infertility it is essential to involve scientists from different disciplines such as obstetrics and gynaecology, epidemiology, demography, and anthropology.

4. The fact that some of the sexually transmitted diseases probably play a major role means that diagnostic and therapeutic services for these diseases with ultimately have to be extended, improved, and integrated into the rest of the health services system.

5. There is a general need for improvement in the quality of information within health services, but this problem is of particular importance

to health activities related to infertility since case reporting and contact treatment is one means of venereal disease control. Records must be simplified if they are to be useful in statistical evaluation as well as for control efforts.

6. In view of the problems of research design, logistics, and resources, the Scientific Group suggests that WHO should assist research and provide a means by which such research on infertility can be coordinated and compared among different countries.

7. In order to assess the problem of infertility WHO should assist in the improvement of simple diagnostic services applicable to field conditions. Undue efforts should not be directed at the " hard-core " of infertility conditions, as in areas of high infertility prevalence these must be classed as esoteric.

Annex

CALCULATION OF SAMPLE SIZE

The *sample size* necessary for the population diagnosis studies should be based upon minimal estimates of infertility in relatively comparable areas where low and high prevalence is thought to exist. To judge from data from the Cameroons, 316 couples in both a high and a low prevalence area would have to be interviewed in order to demonstrate a true difference between 7% and 15% in infertility, that is to demonstrate that a problem of infertility actually exists. Such a sample size would be insufficient to show significant differences in any of the possible causes accounting for the differences between the high and low prevalence areas. This sample size would be more than adequate to show that a problem of pregnancy wastage exists in a community (i.e., a difference between 15% and 30%).

The formula used to calculate the sample sizes is described in Snedecor and Cochran.[a] It gives the size, N, of each of two independent samples under the conditions (1) that the probability, A, of falsely declaring a significant difference $= 0.05$, and (2) that the probability, B, of falsely declaring a non-significant difference $= 0.10$. The probability, $1-B$, is called the power of the test. The formula is

$$N = (z_A + z_B)^2 (p_1 q_1 + p_2 q_2) / (p_2 - p_1)^2$$

in which z_A is the standard normal deviate corresponding to $A = 0.05$ for a one-sided test or $A = 0.025$ for a two-sided test. Z_B is the standard normal deviate corresponding to $B = 0.10$. A few common values of $(z_A + z_B)^2$ are given below ($A = 0.05$; power $(1-B)$):

	0.80	*0.90*
Two-sided test	7.9	10.5
One-sided test	6.2	8.6

Also, in the formula, p_1 is the proportion of individuals in population 1 who possess the attribute of interest and p_2 is the corresponding proportion in population 2.

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[a] Snedecor, G. W. & Cochran, W. G. Statistical methods, 6th ed., Iowa, Iowa State University Press, 1967, pp. 111–114 and 221–222.

Therefore based on the above rates of childlessness

$$N = 10.5\,(0.15 \times 0.85 + 0.07 \times 0.93) \,/\, (0.15 - 0.07)^2$$
$$= 319.27$$

The sample size for the field epidemiological studies would depend on the " normal " prevalence rate compared with the expected increased prevalence rate of the specific cause that is least common, yet still of public health importance. For the purposes of discussion we might consider occlusive azoospermia as this critical variable. In some clinical studies in Africa it has been found in at least 8–10% of infertile couples.

If this level of azoospermia is applied in an area of high infertility (15%) the rate of azoospermia would be expected to be 1.5% ; estimates of the prevalence rate of azoospermia in an area of normal infertility are no more than 0.5%. Therefore, a total sample size of 2074 couples would be sufficient to show that such a difference was statistically significant.

A population of this size would identify approximately 300 infertile couples in the area of high infertility and 140 in the normal area.

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