Primary infertility after genital mutilation in girlhood in Sudan: a case-control study

Lars Almroth, Susan Elmusharaf, Nagla El Hadi, Abdelrahim Obeid, Mohamed A A El Sheikh, Saad M Elfadil, Staffan Bergström

Summary

Background In theory, infections that arise after female genital mutilation (FGM) in childhood might ascend to the internal genitalia, causing inflammation and scarring and subsequent tubal-factor infertility. Our aim was to investigate this possible association between FGM and primary infertility.

Methods We did a hospital-based case-control study in Khartoum, Sudan, to which we enrolled women (n=99) with primary infertility not caused by hormonal or iatrogenic factors (previous abdominal surgery), or the result of male-factor infertility. These women underwent diagnostic laparoscopy. Our controls were primigravidae women (n=180) recruited from antenatal care. We used exact conditional logistic regression, stratifying for age and controlling for socioeconomic status, level of education, gonorrhoea, and chlamydia, to compare these groups with respect to FGM.

Findings Of the 99 infertile women examined, 48 had adnexal pathology indicative of previous inflammation. After controlling for covariates, these women had a significantly higher risk than controls of having undergone the most extensive form of FGM, involving the labia majora (odds ratio 4.69, 95% CI 1.49–19.7). Among women with primary infertility, both those with tubal pathology and those with normal laparoscopy findings were at a higher risk than controls of extensive FGM, both with borderline significance (p=0.054 and p=0.055, respectively). The anatomical extent of FGM, rather than whether or not the vulva had been sutured or closed, was associated with primary infertility.

Interpretation Our findings indicate a positive association between the anatomical extent of FGM and primary infertility. Laparoscopic postinflammatory adnexal changes are not the only explanation for this association, since cases without such pathology were also affected. The association between FGM and primary infertility is highly relevant for preventive work against this ancient practice.

Introduction

Female genital mutilation (FGM) is practised in more than 30 countries, mainly in a belt reaching from east to west Africa north of the equator. WHO estimates1 that more than 132 million women and girls in Africa have undergone FGM, and that about 2 million procedures are done every year.1 The most extensive forms of FGM are predominantly practised in northeast Africa, but are also seen in some areas in western Africa. About 90% of women in northern Sudan have undergone FGM, in general the most severe form.8 In this country the practice of FGM might be changing, however, with a tendency towards less severe forms and possibly abandonment of the tradition by some.1,4 Primary and secondary infertility are, respectively, thought to affect 3–5% and 16% of women in Sudan.1,4

A WHO classification recognises four degrees of FGM (panel). This classification could, however, give the false impression of anatomically distinct forms. In reality, the practice varies widely, not only regionally, but also locally between different practicians. Another difficulty with the WHO classification is that it defines as type III all forms of FGM that involve stitching of the vaginal opening, irrespective of whether the labia minora or majora are affected, and regardless of the extent of suturing. Thus, the anatomical extent of the operation cannot be ascertained.

The damage to the genital tissue provoked by FGM, with its inherent microbial contamination, creates a risk of vaginal infections. In the low oestrogenic environment of the prepubertal girl, the thin atrophic epithelium of the vagina might be susceptible to bacterial invasion. Furthermore, such infections often thrive because of the lack of vaginal acidity before puberty.4 In the absence of a protective environment, the infection might ascend to the uterus and the fallopian tubes, with risk of ensuing tubal damage and impaired fertility. Clinical experience in Sudan11 and Somalia12 lends support to this notion. Additionally, pelvic inflammatory disease, a risk factor for infertility, has been shown11 to be three times more common in women who have undergone infibulation than in those who have undergone only other harming procedures on clitoris or labia, or both.

Panel: WHO classification of FGM

| Type I: Excision of the prepucce and part or all of clitoris |
| Type II: Excision of the prepucce and clitoris together with partial or total excision of the labia minora |
| Type III: Infibulation. Excision of part or all of the external genitalia and stitching of the two cut sides together to varying degrees |
| Type IV: Pricking, piercing, incision, stretching, scraping, or other harming procedures on clitoris or labia, or both |


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a clitoridectomy. However, the selection and diagnostic criteria used in the study are not reported, and no statistical analysis of the data was done.

Complications of FGM have not been adequately researched. Few studies have been appropriately designed to measure the health effects of the practice, which is often cited as a cause of infertility in the absence of adequate proof. Our aim, therefore, was to test the hypothesis that FGM during childhood causes ascending infections that present as primary infertility in young women. On the basis that more extensive operations would have higher risks for infection, we further postulate that forms of FGM that involve the labia majora are more likely to result in primary infertility than milder forms, and that forms of FGM that involve stitching of the vaginal opening are particularly likely to lead to primary infertility.

**Methods**

**Participants**
To investigate the possible relation between FGM and primary infertility, we did a hospital-based case-control study in Sudan. Between March, 2003, and June, 2004, we recruited consecutive women with primary infertility and primigravidae controls from the outpatient clinics of Khartoum Teaching Hospital and Soba Teaching Hospital, Khartoum.

We included women in the group with primary infertility if they: were seeking medical care for primary infertility; were aged 35 years or younger; had regular sexual intercourse during the past 2 years; had regular menstrual cycles for the past year; had never been pregnant; had never used an intrauterine device or hormonal contraceptives; had no history of abdominal surgery; and whose husband’s semen analysis was within physiological limits with respect to count, morphology, and motility. To be included as controls, women had to be expecting their first baby, having fallen pregnant within 2 years of having regular sexual intercourse.

The study was approved by the ethics committees at the Faculty of Medicine, University of Khartoum, Sudan, and at the Karolinska Institutet, Sweden. Participating women received all investigations, medical procedures, and drugs free of charge. We maintain that to ask for written consent from respondents who are poorly educated, and in some cases illiterate, is ethically questionable; the women would not know what they were signing and might have concerns about whether the document could be used against them in any situation. We therefore decided to obtain oral consent (recorded by the attending doctor [NEH and AO among others] from respondents, having first told them in colloquial Arabic what was written on the standardised informed consent form.

**Procedure**
Cases and controls were recruited and examined in the same clinical settings by the same specially trained doctors (NEH and AO among others).

We obtained personal details—age, level of education, profession, tribe, religion, years of marriage, age at which the FGM operation was done if applicable, and any symptoms subjectively associated with this operation—by interview-administered questionnaire. We did a genital examination for every woman, noting the extent of FGM. We made a particular effort to avoid observer bias with respect to the extent of vulval damage in the two groups, by giving detailed instructions to the gynaecologist as to how to visualise and how to describe the extent of anatomical excision observed.

We did various laboratory investigations—serologies for *Chlamydia trachomatis* (IgG enzyme immunoassay species-specific method, Ani Labsystems, Oy, Helsinki, Finland) and *Neisseria gonorrhoeae* (gonococcal antibody test, Statens Seruminstitut, Copenhagen, Denmark), haemoglobin, blood group analysis, and urinalysis for *Schistosoma haematobium* ova—and recorded the weight and height of participants.

We inspected the internal genital organs of women with primary infertility with diagnostic laparoscopy done at Soba Teaching Hospital. We tested for tubal

<table>
<thead>
<tr>
<th>Cases*</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=99)</td>
<td>Tubal pathology (n=48)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27·2 (3·9)</td>
</tr>
<tr>
<td>Socioeconomic status (number, %)‡</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>60 (61%)</td>
</tr>
<tr>
<td>Medium</td>
<td>35 (35%)</td>
</tr>
<tr>
<td>High</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Years in school</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9·9 (4·9)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>12 (0–18)</td>
</tr>
</tbody>
</table>

*One case with inconclusive laparoscopy. ‡Information missing for some respondents, which means proportions do not sum up to 100.

Table 1: Social characteristics of patients
patency by perturbation with methylene blue through the cervix while inspecting the fallopian tubes.

We combined criteria to define socioeconomic status as low (household income <30 000 Sudanese Dinars [about US$115] per month, no house, poor level of education, unskilled labourer), moderate (household income 30 000–150 000 Sudanese Dinars [$115–575] per month, might rent house, skilled labourer, teacher, or salaried employee or clerk), or high (household income >150 000 Sudanese Dinars [$575] per month, owns house with water and electricity, husband most often has university degree or is businessman).

**Statistical analysis**

In November, 2003, we noted that there was a different age distribution in cases and controls. Since age might be an independent factor affecting the risk of undergoing FGM or the severity of the operation, we decided to match cases and controls for age within 2 years. We used exact conditional logistic regression, stratifying for age group (=22, 23–24, 25–26, 27–28, 29–30, 31–32, and ≥33 years), to reduce to a minimum the potential confounding effect of age in the comparison of cases and controls.

An exact method guarantees that the result will not exceed its nominal significance level, and the confidence interval will always equal or exceed its nominal coverage level. In the univariate stratified logistic model, we compared cases and controls by extent of FGM (form involving labia majora versus other forms of FGM or no FGM). To control for possible confounders, we also fitted a multivariate model to the data. To avoid data dredging, a candidate model was defined before the analysis. In addition to extent of FGM, we used three variables in the multivariate stratified model: years in school (treated as a continuous covariate), socioeconomic status (low versus medium and high), and seropositivity for at least one of N gonorrhoeae and C trachomatis versus negative for both. To investigate possible interactions, we included the corresponding product terms in the modelling process. The two models were fitted with LogXact-5 for Windows. We based the univariate model on 278 observations and the multivariate model on 210 observations. We calculated exact odds ratios (ORs) with 95% CI.

To compare cases with tubal pathology and cases with normal laparoscopy findings with respect to time interval between the FGM operation and time of observation, we used the Mann-Whitney U test. We judged a p value of less than 0.05 significant.

**Results**

99 women with primary infertility underwent laparoscopy, of whom 48 had adnexal pathology suggestive of previous inflammation. One laparoscopy was inconclusive (large fibroid made inspection impossible) and the rest did not show any pathological features. 30 of the 48 abnormal laparoscopies showed bilateral tubal blockage, the rest showed unilateral block or adhesions. We recruited 180 controls, 91 before matching and 89 after. All participants were married. Table 1 shows the age distribution, socioeconomic status, and level of education (years in school) of the women. There were only six Christians: three cases—one bilateral tubal block (no FGM), one inconclusive laparoscopy (no FGM), and one normal laparoscopy (FGM involving labia majora)—and three controls (two without FGM and one with FGM, involving labia majora). The remaining cases and controls were Muslims.

Table 2 shows the anatomical extent of the FGM operations, whereas in table 3 the operations are classified according to the WHO criteria. The major difference between these classifications is that all types of suturing of the two sides, whether of labia minora or majora, are classified as type III, according to WHO. Table 2 therefore shows the effect of the anatomical extent of FGM and table 3 the effect of suturing. The clitoris was damaged in all cases and controls with any form of FGM. In all forms that involved the labia minora the clitoris was also cut, and in all forms that involved the labia majora, the labia minora and the clitoris were partly or totally removed. No woman

<table>
<thead>
<tr>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adnexal pathology</td>
<td>Normal laparoscopy</td>
<td></td>
</tr>
<tr>
<td>No FGM</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>FGM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clitoris</td>
<td>1 (2%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Labia minora</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Labia majora</td>
<td>46 (96%)</td>
<td>46 (90%)</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>51</td>
</tr>
</tbody>
</table>

Rows describe maximum extent of operation. For example, a patient classified labia minora has undergone FGM, involving clitoris and labia minora, but not extending to labia majora. Data are number (%). *One case with inconclusive laparoscopy.

Table 2: Anatomical extent of FGM among respondents

<table>
<thead>
<tr>
<th>In fertile cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No FGM</td>
<td>2 (2%)</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>FGM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>5 (5%)</td>
<td>14 (8%)</td>
</tr>
<tr>
<td>Type II</td>
<td>1* (1%)</td>
<td>8 (5%)</td>
</tr>
<tr>
<td>Type III</td>
<td>91 (92%)</td>
<td>152 (85%)</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
<td>179</td>
</tr>
</tbody>
</table>

Data are number (%). *A case where labia minora as well as majora were o.t., but there was no stitching together.

Table 3: Types of FGM classified according to WHO criteria
had any sign of being deinfibulated (the bridging scar of type III having been cut).

The median age for the FGM operation was 7 years (range for cases 3–15; for controls 2–13) in both groups. Cases with tubal pathology had a longer interval between the FGM operation and our observation (median 21.5 years, range 12–32)—ie, longer exposure to the possible effects of FGM—than cases with normal laparoscopic findings (19 years, 7–25; p=0.015).

Immediate complications were reported by few, and there was no difference between cases and controls. Three cases and seven controls reported having had fever after the operation and two cases and six controls admitted that they had to seek medical care because of immediate complications.

Repeated subjective symptoms of urinary tract infection (more than three episodes) were significantly more common in cases (41% [41 of 99], OR 2.00, 95% CI 1.15–3.48, p=0.012), and in the subgroup of cases with normal laparoscopy findings (46% [23 of 50]; OR 2.41, 95% CI 1.19–4.88, p=0.011), than in controls (26% [47 of 180]). The difference between the subgroup with tubal factor infertility (38% [18 of 48]) and controls was not significant (p=0.16). None of the specific forms of FGM is related to repeated urinary tract infection.

Only two women had a body-mass index of less than 19 (both had tubal factor infertility) and nine cases had a body-mass index of more than 30 (five of whom had tubal damage).

None of the cases or controls had ova of S haematobium in their urine. Two of 79 cases (3%) and three of 137 controls (2%) for whom serology results were available were positive for N gonorrhoeae (p=0.87) and 11 of 81 cases (14%) and five of 139 controls (3–6%) were positive for C trachomatis (OR 4.2; 95% CI 1.3–16, p=0.013).

When we fitted the multivariate model, none of the tested product terms was significant, and there were no indications of relevant interactions. We decided not to use any product terms in the final model. When the univariate and multivariate model are compared with respect to the estimated ORs for extent of FGM, the results are similar. The three extra variables used in the multivariate model are not significant. From a clinical point of view, however, it seems relevant to keep them in the final model.

Women with primary infertility had a significantly higher risk of having undergone the most extensive form of FGM, involving labia majora, than controls, in both the univariate and the multivariate model (table 4). The two subgroups of cases (adnexal pathology and normal laparoscopy) both show significant associations in the univariate model and borderline significant associations in the multivariate model (table 4). Because of the missing data (mainly serological) 68 observations are missing from the model (table 4). The two subgroups of cases (adnexal pathology and normal laparoscopy) both show significant associations in the univariate model and borderline significant associations in the multivariate model (table 4).

There were too few cases (n=2) and controls (n=5) without FGM to allow any analysis of them versus those with FGM.

**Discussion**

Our findings indicate an association between severe forms of FGM, involving the labia majora, and primary infertility in Sudan. The OR is high, which indicates that this result is not only statistically significant, but also clinically significant and relevant for campaigns against the practice.
For those who practise FGM, the tradition has many positive values. It is often undertaken, for example, in the belief that the procedure will increase future chances of marriage, since FGM is thought to prove virginity and dignity, but also fertility. Furthermore, in many areas there is a symbolic association between FGM and fertility, and a widespread belief exists that the practice enhances fertility by making the young girl less masculine (clitoridectomy). Alleged complications have been used in campaigns against the practice for many years with little or no effect, perhaps because they do not challenge these positive traditional values, which an association with infertility might do. Women’s concerns about impairment of fertility are substantial in Sudan and in other countries where FGM is traditionally practised. Motherhood is the principal source of support, status, and security.

We are aware that there is no ideal group of controls available to recruit from the same population as the cases. Bearing in mind the need for genital examination, the control group recruited for this study would, however, seem to be the least biased that is also practically and ethically justifiable. Illiteracy levels for women are high in Sudan, but our population had a median of 12 years of schooling. On the other hand there is no difference in this regard, or with respect to socioeconomic status, between cases and controls. Therefore, we consider the results to be generalisable, concerning the effect of FGM, even if the study population is not representative of Sudanese women as a whole.

Matching might have introduced a selection bias, and controls recruited before matching perhaps should not have been grouped together with those recruited after. The effect of matching was, however, deliberately so, higher age among controls, but apart from this fact, matching had no significant effects. Characteristics of cases and controls differ very little, especially considering the general situation for Sudanese women. By stratifying for age when calculating the ORs, the age differences between cases and controls were taken into account and compensated for.

We did not enrol women whose husbands were infertile, and excluded women with most hormonal causes of infertility and possible iatrogenic pelvic inflammatory disease after surgery. The distribution of body-mass index among cases shows that extremes in weight with associated hormonal changes do not contribute significantly to infertility in our sample.

Theoretically, the type of provider of the FGM operation is a potential confounder, since less skilled providers might cut more extensively and are possibly less skilled in avoiding complications. In Khartoum, Sudan, FGM is almost exclusively done by midwives (two thirds) and traditional birth attendants (one third), and rarely by doctors (LA, unpublished data). Both these groups practise various forms of FGM and have knowledge of and access to modern antiseptic techniques and local anaesthetics. Thus, we believe that type of provider is unlikely to have affected our results.

We should perhaps have done endometrial curettage to enable proper diagnosis of genital schistosomiasis and tuberculosis. However, these diseases often cause irregular bleeding and would thus have been excluded from our study. Even though urinary and genital schistosomiasis frequently coincide, urinalysis is not sufficient to exclude genital schistosomiasis, since diagnosis based on a single urine sample misses about one third of cases. However, in the absence of clinical findings to indicate the disease (schistosoma ova in the urine, significant haematuria, typical symptoms, or laparoscopic findings) we conclude that genital schistosomiasis is unlikely to contribute to infertility in the present study. Genital tuberculosis is fairly rare, and often arises secondary to a primary focus elsewhere. The disease accounts for less than 2% of all tuberculosis, and usually presents with infertility, pelvic pain, or menstrual irregularities. The fallopian tube is the organ most often affected. We did not control for tuberculosis, but none of the cases had clinical or laparoscopic signs of the disease, so its contribution to infertility would probably be small. Only two cases and three controls had serological markers for N gonorrhoeae, which implies that its contribution to primary infertility in Sudan is low. C trachomatis, however, seems to contribute to primary infertility in the study population, but the prevalence is low even among cases.

By excluding the known risk factors for primary infertility mentioned above, and showing that the contribution of sexually transmitted infections to the problem is low, we conclude that the association noted between FGM and primary infertility is valid and is relevant in clinical practice in Khartoum. Since FGM is common in Sudan, it probably contributes more to primary infertility than sexually transmitted diseases do.

We made some unexpected observations about the association between FGM and infertility. First, the anatomical extent of FGM rather than suturing or closure per se (WHO type III) seems to be associated with primary infertility. Second, the group of infertile patients with normal laparoscopic findings had similar borderline significance between FGM and primary infertility to the group with adnexal pathology. Thus, the macroscopic changes that can be seen by laparoscopy are not the only factors contributing to infertility. For conception and nidation to take place, the structure and function of the reproductive tract—the cervix, endometrium, fallopian tubes, and fimbriae—need to be healthy. FGM might provoke changes in this organ system, for instance by altering the local environment and bacterial colonisation in the vulva or vagina or by causing low-grade chronic inflammation. The findings of several studies show an association between FGM and urinary and genital tract infections. In our study, more infertile women reported recurrent urinary tract
infections than controls, which could indicate disturbances in the local environment.

The age at FGM operation did not differ in the two groups, but cases with adnexal pathology had had FGM for a significantly longer time than cases with normal laparoscopy findings. This observation gives rise to the hypothesis that the macroscopic findings of tubal pathology could represent a later stage of the same process of FGM-induced inflammatory changes invisibly present in infertile cases with normal laparoscopic findings. Alternatively, the FGM operation might start another process, parallel to the inflammation leading to adnexal pathology, causing infertility at an earlier stage.

The fact that there is an association between the severe forms of FGM and primary infertility by comparison with milder forms cannot be used as an argument to medicalise the practice by having doctors perform less extensive operations. On the contrary, any alteration of the normal anatomy of the girl’s vulva could lead to structural and physiological changes, which in turn have negative effects on her reproductive health.

Observations from the World Fertility Survey\textsuperscript{30} in Sudan 1978/79 show a significant association between the most severe form of FGM and the incidence of infertility 5 years before the study. There have been two attempts to estimate the effects of FGM on fertility in the 1989–90 demographic health survey in Sudan. The first, by Balk,\textsuperscript{31} does not consider infertile women alone, but includes them in the group of low fertility, defined as having borne two or fewer children. There were no significant effects of FGM on fertility in that study. In the second study based on the demographic health survey, Larsen\textsuperscript{32} noted that women with infibulation and intermediate forms (both of which in Sudanese colloquial terms correspond to forms that involve the labia majora) of FMG had a significantly higher prevalence of primary infertility than women without FGM (OR 2.76).

To our knowledge, there has been only one attempt to do a clinical case-control study on the subject. A study in Egypt, 1988–89,\textsuperscript{33} compared 100 infertile cases (a mixed group of both primary and secondary infertility) and 90 fertile controls recruited from a hospital in Alexandria. The study design has methodological limitations, which have been explored elsewhere.\textsuperscript{34} There was a tendency that women having undergone excision (type II) had a higher risk of tubal factor infertility than those having undergone clitoridectomy (type I), but the results were not significant (OR 1.9, 95% CI 0.8–4.2).

To conclude, there is plausible theoretical support for the hypothesis that FGM can cause primary infertility. Our findings show a strong positive association between the anatomical extent of FGM and primary infertility. The association is not only statistically highly significant, but also highly relevant for preventive work against this ancient practice.

Contributors

I. Almroth conceived the study, coordinated its planning and implementation, did most of the data analysis, and wrote the manuscript. S Elmhuma joined to plan the study, coordinated data collection, and took an active part in data analysis and interpretation of the results. N El Hadi participated in planning and data collection as well as analysis and interpretation of results. A Obeid participated in the planning and data collection of the study, did most of the laparoscopies, and participated in analysis and interpretation of results. M A A El Sheikh participated in the planning and continuous supervision of the study, did some of the laparoscopies, and participated in analysis and interpretation of results. S M Elfadir participated in the planning and continuous supervision of the study and participated in analysis and interpretation of results. A Obeid participated in the planning and continuous supervision of the study, and supervised the analysis of the data and writing of the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

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