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Protocol

Rationale of a comparative analytical study on matrix metalloproteinases associated with genital prolapse in Congolese women from the town of Kananga in the Democratic Republic of Congo: research protocol

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ABSTRACT

Background: Genital prolapse is a pelvic static disorder associated with urinary, digestive and genital disorders which bother the patient. The fear of these discomforts has pushed many Western countries to adopt beneficial preventive measures for women at risk, notably the administration of estrogen-progestogens and the prevention of obstetric trauma. These two preventive factors play an inhibitory role on matrix metalloproteinases degrading the collagens which ensure ligament firmness. This link between matrix metalloproteinases and collagen is implicated by many researchers in the occurrence of genital prolapse. Objectives are to determine the epidemiological and clinical profile of genital prolapse, to identify the non-molecular factors associated with it, to determine the level of matrix metalloproteinases-1, -2 and -9 in non-prolapsed and prolapsed pelvic tissues, and to identify the types MMPs associated with genital prolapse in Congolese women from the town of Kananga in central Kasai in DR Congo.
Methods: We designed a protocol for a comparative analytical study focusing on the epidemiology and the level of matrix metalloproteinases in non-prolapsed and prolapsed pelvic tissues in the Bon-Berger and Saint Georges hospitals in the city of Kananga. Women over 40 years of age and of any parity suffering from genital prolapse and other benign gynecological pathologies requiring hysterectomy will be included in the study according to non-probabilistic convenience sampling.
Conclusions: This study will evaluate the level of matrix metalloproteinases-1, -2 and -9 in prolapsed tissues and identify the type of matrix metalloproteinases most associated with genital prolapse in our setting.

Keywords: Epidemiology, Matrix metalloproteinases, Genital prolapse, Kananga, DR Congo

INTRODUCTION

Genital prolapse is defined as a permanent or strained protrusion in the vaginal canal, at the vulvar orifice or outside it, of all or part of the vaginal walls more or less lined with the bladder, the rectum and adjacent peritoneal cul-de-sacs, as well as the vaginal fundus attached to the cervix.[1]

Genital prolapse is a reason for consultation and surgical interventions that is increasing in both gynecological and urological units.[2,3] Taking into account various factors, notably the increase in life expectancy, the number of patients suffering from genital prolapse will double in the coming decades.[4] Economically, the direct cost of treating genital prolapse is very high, exceeding $1 billion per year in the United States of America with nearly 200,000 surgical interventions.[5,6]

The prevalence of genital prolapse varies from 2.9 to 97.7% worldwide depending on the study methods used. It is estimated from 2.9 to 11.4% when the method used is a symptom questionnaire and from 31.8 to 97.7% when a clinical examination is carried out with the classification of pelvic organ prolapse (POPQ).[7-13] In Asia and Africa, the prevalence of genital prolapse is not known due to a lack of surveys and studies in the general population.[14,15]

Genital prolapse is a disease of the endopelvic ligaments and fascia characterized by the reduction of their collagen content and modification of the extracellular matrix (ECM).[16,17] Its cause is either hereditary or genetic (mutation of the genes COL1A1, COL1A2, COL3A1, COL5A1, FBN1, and NF1, giving rise to several hereditary syndromes associated with genital prolapse such as Ehlers-Danlos syndrome, Marfan syndrome, and neurofibromatosis) at the basis of a defect in the synthesis of collagen fibers, either acquired or modifiable linked to excessive destruction of collagen secondary to an imbalance between matrix metalloproteinases (MMP) and their tissue inhibitors (TIMP) in favor of matrix metalloproteinases , to situations of oxidative stress and those of massive fibroblastic cell apoptosis.[16-18]

The risk factors involved in the occurrence of genital prolapse are now known with their pathogenetic mechanism. They are divided into 2 groups, namely: modifiable risk factors (obesity, vaginal delivery, parity, smoking, fetal macrosomia, perineal tears, carrying heavy objects, low socio-economic level , anemia, malnutrition, situations of oxidative stress and massive fibroblastic cell apoptosis, decrease in collagen content and increase in matrix metallo-proteinases -1, -2 and -9 in the pelvic tissues of support, and non-modifiable risk factors (age, race including white race, menopause, chronic obstructive pulmonary disease, spinal curvature abnormalities such as thoracic kyphosis, loss of lumbar lordosis, history family of genital prolapse inferring the role of genetic factors, personal history of genital prolapse, previous pelvic surgeries, chronic constipation).[19-22]

Genital prolapse is a collagen disease characterized by loss of mechanical stability of the genitourinary tract secondary to loss of integrity of connective tissues supporting the bladder neck, urethra and pelvic organs.[23-26]

In recent years, several investigators have identified reduced collagen content and increased expression of MMPs in pelvic support structures in women with genital prolapse.[17,18,23,25] Increased degradation of collagen by MMPs underlies genital prolapse. The difficulty in quantifying collagen is inherent to its supermolecular structure. In fact, this very stable protein is virtually impossible to solubilize in most physiological buffers.[23,27,28]

The most frequently used biochemical assay to quantify collagen is hydroxyproline. However, this assay, which requires a significant amount of tissue, is an indirect measure of total collagen and is not specific for collagen.[23,28-30] To overcome these limitations, a group of authors studied collagen metabolism by measuring the easy-to-measure expression of MMPs.[23,31-33]

Combined or isolated increased expression of MMP-1, MMP-2 and MMP-9 is significantly associated with genital prolapse and its recurrence.[18,23,33-36] It has therefore been suggested that increased degradation of collagen by MMP-1, MMP-2 and MMP-9 leads to a decrease in mechanical resistance, predisposing women to PG.[32-35]

Estrogens and progesterone are important in regulating the activity of all MMPs involved in the occurrence of genital prolapse by blocking the transcription of their genes responsible for the decrease in their messenger ribonucleic acids (mRNA), and by activating the production of TIMPs in pelvic fibroblasts. Which inhibits the breakdown of pelvic collagen.[16,32,35,37] Thus, the prolonged absence of these hormones during menopause causes the excessive degradation of collagen, the source of excessive laxity of pelvic ligaments and genital prolapse. Hence the prescription of these hormones in hormonal replacement treatment in at-risk menopause.[16,34,35,38] Pelvic trauma, particularly that of vaginal childbirth, stimulates the activity of MMPs (via inflammatory cytokines: interleukin 1, tumor necrosis factor alpha, transforming growth factor beta-1) to destroy traumatized tissues, including connective tissues, the exaggeration of which is the basis of the weakness of the pelvic floor, a source of genital prolapse.[32,39-41]

Jackson et al in 1996, Phillips et al 2009 and Dviri et al in 2011 reported a significant association between reduced collagen content and increased tissue expression of MMPs-1 and -9 in samples of vaginal tissue, round ligaments and uterosacral ligaments collected from women with prolapse genital compared to controls while the case series of Usta et al in 2014, by Moalli et al in 2005, by Strinic et al in 2009 and Chen et al in 2002 identified significantly elevated expression of MMP-9 or MMP-1 but not MMP-2 in the group of women with genital prolapse.[18,23,27,31-33,42] In contrast, Liang et al in 2010 and Boris et al 2006 found higher expression of MMP-2 but not MMP-1 in the uterosacral and round ligaments of women with genital prolapse compared to the control group.[29,35] Two recently published literature reviews report that the combined action of these MMPs is capable of degrading all components of the ECM, with different specificities for each MMP.[16,43]

Rationale of the study

Genital prolapse and its multiple disorders have proven to be significant in our environment.[15,22] The benefits of estrogens or estrogen-progestins and the prevention of obstetric trauma during vaginal deliveries have been demonstrated in the prevention of genital prolapse, particularly for their action in the reduction and inactivation of MMPs. Identifying the expression of

MMPs associated with genital prolapse would improve the means of preventing genital prolapse in our environment. Thus, because no study in our field has focused on the association between the expression of MMPs and the occurrence of genital prolapse. The particularity linked to race, nutritional status and socio-economic level, generally low, leads us to think of the possibility of a particularly high expression of MMPs in Congolese women.

Objectives of the study

In order to contribute to improving the management of genital prolapse by adding estrogen-progestins and the prevention of obstetric trauma in our environment, our study aims to determine the epidemiological and clinical profile of genital prolapse, to identify the factors non-molecular molecules associated with genital prolapse, to determine the expression level of MMP-1, MMP-2 and MMP-9 in non-prolapsed and prolapsed pelvic tissues, and to identify the types of MMPs associated with genital prolapse in Congolese women from the town of Kananga in central Kasai in DR Congo.

METHODS

Study overview

This protocol was designed to test the hypothesis that the expression of MMP-1, MMP-2 and MMP-9 is elevated in prolapsed pelvic tissues and associated with this condition in Congolese women from the town of Kananga in central Kasai in DR Congo. Our study is a comparative analytical study of two groups, one of which is a study group made up of patients suffering from genital prolapse and the other a comparison group made up of patients suffering from other benign gynecological pathologies. Considering the frequency of genital prolapse of 1.16% in our environment, the minimum sample size is 47 cases in each study group, calculated according to the following formula.

$$n \geq \frac{\left(1+\frac{1}{c}\right)\left(Z_{\alpha}+Z_{1-\beta}\right)^{2} p(1-p)}{(p_0-p_1)^2}$$

Where n=number of cases in the study group, c=number of comparison cases per case studied, p_0=expected proportion of comparison cases exposed (0.0116), p_1=expected proportion of study cases exposed (0.195), p=proportion of subjects exposed in the two groups (study and comparison) (0.1035), Z_{α}=value of Z for the risk of the first kind (1.645), α=the risk of type I error (0.05), $Z_{1-\beta}$=value of Z corresponding to a surface equal to the power of the test (1 – β), the latter constitutes the probability of finding a significant difference (1.282), (1 – β)=the desired power of the test (0.9), OR=minimum OR that we set for the study to be of public health interest (20).

$$p_1 = \frac{p_0 \times OR}{1 + p_0(OR - 1)}; p = \frac{p_1 + cp_0}{1 + c}$$

The number of comparison group cases is equal to the product n×c.

A comparison case will be matched to a study case (c=1) and the matching criteria will be age and menopausal status.

We assumed a power of 0.9 and α=0.05. The odds ratio (OR) is estimated at 20 (based on studies based on the Visco and Yuan model, which found that tenascin gene expression was 20 times higher).[44]

After incorporating all the elements of the formula and considering the frequency of genital prolapse in our environment at 1.16%, our sample size will be greater than or equal to 47 women or cases in each study group (i.e. ≥47 cases studied and ≥47 comparison cases) which we will round to 50 cases in each group or 100 cases.[15] This study was designed and financed by our own funds.

Patient selection

Our sampling is of a non-probabilistic convenience type and constituted taking into account the following criteria.

Inclusion criteria

We will include the following patients will be included in our study: those suffering from genital prolapse having undergone a hysterectomy as part of reconstructive surgery in the gynecology and obstetrics departments of the hospitals mentioned above, those suffering from benign gynecological pathologies having undergone a total hysterectomy in the gynecology and obstetrics department of the hospitals mentioned above and the one having signed the informed consent form

Non-inclusion criteria

We will exclude the patient who has already been operated on for genital prolapse, the one who did not sign the informed consent form, the one receiving hormonal replacement treatment (in the case of complicated menopause), the one suffering from pathologies gynecological malignancies and those who have freely decided to end their participation in the study at any time.

Selection and enrollment procedure

The study will be carried out for 9 months (from 01 April to 31 December 2023) in the gynecology and obstetrics departments of the Bon-Berger hospital of Tshikaji and Saint Georges hospital of Katoka in the town of Kananga in central Kasai in DR Congo. One of us will recruit study patients from among women scheduled to undergo hysterectomy without distinction of age and parity. To these patients, the study and its purpose will be clearly explained to obtain their informed consent. After written and signed consent for each patient admitted to the study, information will be collected by interviewing the patients

and in medical records. Two tissue biopsies will be collected from each woman during the surgical procedure: one from the uterosacral ligament and one from the round ligament. The biopsies will be fixed in 10% formalin and stored until the time of immunohistochemical analysis.

Study variables

We will use anthropometric variables (patients' age, weight, height and body mass index), medical variables (occupation, history of chronic pulmonary diseases, spinal abnormalities, smoking, family history of genital prolapse and personal history of genital prolapse), gynecological and obstetrical variables (menopause, parity, vaginal deliveries and their number, fetal macrosomia, perineal tears, pelvic surgeries, diagnosis) and paraclinical variables : Types of tissues collected, expression level of MMP-1, that of MMP-2, and that of MMP-9.

Immunohistochemical analysis

Immunohistochemical staining

All tissue samples will be routinely fixed in 10% buffered formalin and processed into paraffin blocks by routine methods. Sections are cut at 5 µm thickness, mounted on coated slides and stained using the avidin-biotin-immunoperoxidase technique.[18,23,28,29,33-35] Each sample will be stained with hematoxylin and eosin and immunohistochemical stains using antibodies against MMP-1, MMP-2 and MMP-9.[18,23,28,29,33-35]

The staining procedure will be as follows: fixation in 10% formalin then in paraffin, cutting at 5 µm thickness, incubation of the sections in paraffin overnight at 60°C, their deparaffinization and hydration in descending alcohol series, blocking peroxidase activity by incubating slides in 3% hydrogen peroxide and absolute methanol for 10 min (non-specific binding will be blocked with normal horse serum for 15 minutes), antigen retrieval combined with a high temperature antigen unmasking technique (Dako target retrieval solution, Glostrup, Denmark; 100 °C, 15 min), the use of primary monoclonal antibodies against MMP (human MMP-1, activated MMP-2 and human MMP-9) diluted in Dako antibody diluent, further immunohistochemical staining will be continued using the Vectastain Elite ABC-Peroxidase kit (Vector Laboratories Inc.) according to manufacturer's instructions, careful washing of slides with phosphate-buffered saline (PBS) after each step of the procedure, use of diaminobenzidine peroxidase (DAB) substrate to allow visualization of the antibody reaction (series of Sigma FASTTM 3,3-diaminobenzidine tablets), counterstaining the sections with hematoxylin, dehydrating them and mounting them on the microscope for histological examination.[18,23,28,29,33-35]

The examination of these sections will be associated with their comparison with the positive control slide and that of the negative control.

Positive control

Positive control slides for MMP-1, MMP-2 and MMP-9 will be prepared from placental tissue. In positive control tissue, the monoclonal antibody will be stained similarly.[18,23,28,29,33-35]

Negative control

The negative control slide will be prepared from the same block of tissue as the sample. We used the standard procedure for immunohistochemical staining. As negative controls, we will perform the same procedure with omission of primary antibodies (replaced with phosphate-buffered saline).[18,23,28,29,33-35]

Immunohistochemical and morphological analysis

All slides will be evaluated by an experienced pathologist from whom information on the origin of the samples (from a case or control patient) will be hidden. The percentage of fibroblasts immunoreactive for MMP-1, MMP-2 and MMP-9 will be recorded. Additionally, the degree of extracellular stroma immunoreactivity will be graded from 1 to 4, as follows: grade 1=0-25% (focal immunoreactivity), grade 2=26-50% (focal immunoreactivity to moderate), grade 3=51–75% (moderate to diffuse immunoreactivity), grade 4=76–100% (diffuse immunoreactivity).[18,23,28,29,33-35]

Statistical analysis

Our data will be entered and analyzed with statistical package for social sciences (SPSS) 29 software. We will use the mean±standard deviation to present quantitative variables and the frequency or proportion for qualitative variables; the Anova test to carry out the intergroup comparison of means; the Chi^2 test to carry out the intergroup comparison of proportions; univariate logistic regression to evaluate the strength of association between the level of expression of MMPs and the occurrence of genital prolapse; multivariate logistic regression to identify MMPs and their expression level associated with the occurrence of genital prolapse. The statistical significance threshold for our results is set at the value of $p<0.05$.

Ethical considerations

This protocol was approved by the ethics committee of the School of Public Health of the University of Kinshasa. For all patients included in the study, a written informed consent form is obtained in advance and signed by the patient herself in advance. She will receive a copy of the consent form and the investigator will receive another. The data will be collected anonymously and kept confidential. To guarantee anonymity and confidentiality, this information will be completed on a coupon which will have the same number (or code) as the rest of the patient's research elements (documents and samples). After being

completed, this coupon will be immediately separated and kept under seal by the Principal Investigator alone and no further reference will be made to it.

Expected results of the study

In this study, we aim to determine the epidemiological and clinical profile of genital prolapse, to identify the non-molecular factors associated with genital prolapse, to determine the expression level of matrix metalloproteinases -1, -2 and -9 in prolapsed tissues (in women suffering from genital prolapse) and to identify the types of matrix metalloproteinases associated with genital prolapse in our environment.

DISCUSSION

The prevalence of genital prolapse is not known in the Democratic Republic of Congo due to a lack of surveys and studies in the general population.[14,15] To our knowledge, there are no data yet available to estimate its incidence. However, two hospital studies have been carried out on this subject in our country, including that of Ntabe et al in North Kivu and that of Tshimbundu et al in Kinshasa who had respectively found a frequency of 2.2% in 2016 and 1.15% in 2020.[14,15] In addition, there is abundant literature identifying the link between genital prolapse with several risk factors classified as molecular and non-molecular factors.[19-22] This allows the identification of women at risk specific to each environment. Our study aims to collect results related to these aspects.

Genital prolapse is a disease or disorder of the pelvic floor that can both worsen or regress, especially in the postpartum period.[11,45] It carries a high risk of recurrence after surgical treatment.[45,46] It is always associated with several disorders: urinary (stress urinary incontinence, and urgent urination), digestive (anal incontinence, constipation) and genital (dyspareunia, intravaginal mass) which bother the patient.[7,10,46] The fear of these discomforts has pushed many Western countries to adopt beneficial preventive measures for women at risk, notably the administration of estrogen-progestogens and the prevention of obstetric trauma.[16,32,34,35,38-41] These 2 preventive factors play an inhibitory role on matrix metalloproteinases degrading the collagens which ensure ligament firmness.[36-38] Thus, the inhibition of matrix metalloproteinases by these factors cited above implies the absence of collagen degradation in the pelvic ligaments, its presence in sufficient quantity to ensure ligament firmness and avoid genital prolapse. Uninhibited, matrix metalloproteinases degrade collagen, causing a reduction in its content in the ligaments, ligamentous hyperlaxity and the development of genital prolapse. This link between matrix metalloproteinases and collagen is implicated by many researchers in the occurrence of genital prolapse.[16,32,34,35,38-41] However, in the Democratic Republic of Congo, no study on the dosage of matrix metalloproteinases associated with genital prolapse and on the evaluation of their strength of association has been carried out, to our knowledge, in order to find an argument approving the use of estrogen-progestins and prevention of obstetric trauma as preventive measures in women at high risk of developing genital prolapse. All these aspects will be addressed in our study.

The strengths of the study are those of being the first study on the epidemiological and clinical profile of genital prolapse in the city of Kananga, on the matrix metalloproteinases associated with genital prolapse in Congolese women, to demonstrate the significant link between these metalloproteinases and the risk factors for genital prolapse in our environment, to measure both the 3 types of matrix metalloproteinases (MMP-1, -2 and -9) associated with genital prolapse in order to identify the type(s) specific to our environment and if its results are consistent, they will constitute a positive argument for the addition of estrogen-progestins and the prevention of obstetric trauma in the preventive management of genital prolapse in women at risk in our environment.

The weaknesses of the study are the absence of research into congenital collagen deficiency syndromes in our patients, the failure to take into account genetic factors associated with genital prolapse, the small sample of the study (due to financial constraints), the absence of the experimental use of estrogen-progestins on fibroblasts having presented a high expression of matrix metalloproteinases in culture with a view to confirming their effectiveness in reducing the level of expression of matrix metalloproteinases and the absence of a second immunohistochemical evaluation of the expression level of matrix metalloproteinases on fibroblasts after use of estrogen-progestins.

CONCLUSION

The study on matrix metalloproteinases associated with genital prolapse in Congolese women of town of Kananga will fill the lack of studies on this subject, providing positive arguments for the use of estrogen-progestins and the prevention of obstetric trauma in preventive treatment of genital prolapse in our town of Kananga in the Democratic Republic of Congo.

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