The Matrix Metalloproteinase-1 Gene Polymorphisms as Risk Factor of Pelvic Organ Prolapse in Balinese Woman

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ABSTRACT

Pelvic organ prolapse (POP) is a gynecological problem that can worsen the psychosocial, economic, and sexual function of women and often relapses after surgery. POP is associated with weakness of the pelvic floor supporting structures. Pelvic organ prolapse is associated with a reduced quality of life for millions of women worldwide. The purpose of this study was to determine the role of the MMP-1 rs 1799750 gene polymorphisms as a risk factor for pelvic organ prolapse in Balinese women. This observational case-control study involves 30 patients with pelvic organ prolapse as the case group and 30 patients without pelvic organ prolapse as the control group. The study was conducted at the Integrated Biomedical Laboratory, Faculty of Medicine, Udayana University. Three milliliters of venous blood samples were taken from each patient and DNA examination was performed to determine MMP-1 gene polymorphisms. Risk assessment of the MMP-1 gene polymorphism for pelvic organ prolapse was done by controlling for various confounding variables, including age, parity, heavy work, body mass index, menopausal status, and history of hysterectomy, through multivariate logistic regression conditional test. Result from this study is the MMP-1 gene polymorphism increased the risk of pelvic organ prolapse 4.33 times compared to non-prolapsed in Balinese women (OR 4.33, 95%CI 1.20 - 15.61, p = 0.020). After controlling for various confounding variables, MMP-1 gene polymorphism still increased the risk of pelvic organ prolapse up to 5.52 times (AOR 5.52, 95%CI 1.352-22.50, p = 0.02). Conclusion from this study is MMP-1 gene polymorphism significantly increases the risk of pelvic organ prolapse in Balinese women.

Keywords: Matrix metalloproteinase-1, pelvic organ prolapse, polymorphism.

I. INTRODUCTION

Pelvic Organ Prolapse (POP) is still a health problem experienced by women. Decreased quality of life is the significant impact of POP suffered by women. The incidence of POP increases with the increase in the life expectancy of women. This is not life-threatening but can worsen the women's psychosocial, economic, and sexual functioning. Disorders caused such as urinary disorders, defecation, and sexual and psychosocial can occur over a long period.

The costs for handling POP and the rate of recurrence of prolapse are still relatively high even though surgery has been carried out. Several hospitals have recorded and found that the incidence of POP ranges from 43-76% of all gynecological cases [1]. Surgery is performed in about 11% of these cases [2]. Approximately 30% of patients who undergo surgery experience recurrence and require reoperation in the future [3]. There are approximately 300,000 POP surgeries in the United States annually [4]. A study conducted in Turkey in 2014 found that more than 50% of the study sample were diagnosed with a POP grade two or more. According to the 2014 National Health and Nutrition Examination Survey (NHNES), about 3% of women in the United States complain of protrusion in their genitals. Based on the patient's age, the incidence of POP in women over 50...
years is about 2.7 - 3.3 per 1000 women [5]. Another study using the diagnostic standard pelvic organ prolapse quantification (POP-Q), an international standard, reported that the prevalence of POP was 23.5% to 49.4% [6]. In the United States, approximately 300,000 surgeries are performed to manage POP yearly. In 1997, 225,964 women were operated on for POP [7]. This shows that surgery to manage POP is commonplace and routine compared to other gynecological surgeries.

Iceberg phenomenon is the proper term to describe the prevalence of this POP. Events recorded by researchers and clinicians are patients who come to the hospital or clinic because of severe complaints and require further treatment. In Indonesia, the prevalence of POP has not been widely studied and is still unicentric. In research conducted at Hasan Sadikin Hospital in Bandung in 2007, the number of POP cases found was 30. The 2009 Annual Report of Obstetrics and Gynecology Sanglah General Hospital in Denpasar reported the number of POP patient visits in as many as 82 cases and the number of POP surgical procedures performed in as many as 34 cases [8]. This number of visits increased in 2015 to 91, and 36 surgical procedures were performed. Based on the data above, it was found that the majority of POP sufferers who went to the Reconstructive Urogynaecology clinic at Sanglah Hospital were from the Balinese tribe, with 83 cases (91.20%) [8]. The handling of POP is finally focused on preventing the occurrence of POP and the severity of the disease. Understanding the risk factors for causing POP is needed in a selective and targeted prevention of POP [8], [9]. This prevention effort requires a deep understanding of the anatomy of the female pelvic floor, risk factors, and the pathophysiology of the occurrence of POP.

Pelvic organ prolapse (POP) is a decrease in one or more pelvic organs from their normal anatomical position into the vaginal canal due to anatomical deformities and the function of the supporting tissues of the pelvic organs. POP risk factors can be divided into extrinsic factors and intrinsic factors. Extrinsic factors can be pregnancy and childbirth, work history, and various disorders that increase intra-abdominal pressure repeatedly. While the intrinsic factors are related to genetic factors, the aging process, the process of changing the extracellular matrix of the pelvic support tissue, and menopausal conditions [8], [10]. Pelvic organ prolapse is a complex disease with unknown origins, although POP is often associated with physiological and traumatic events by many investigators [11]. The known pathogenesis of POP can provide an overview and plan for the prevention and treatment of this disorder. The pathogenesis of POP has been widely described, but little is known about the histomorphology of the pelvic floor supporting tissue. The role of fibroblasts and the extracellular matrix of the pelvic floor ligaments, such as the sacrouterine ligament, has been widely studied. The extracellular matrix has a structural function in the tissue, which is the site of the processes of proliferation, adhesion, migration, differentiation, and remodeling. The balance between synthesis, cross-linking, maturation, and degradation of extracellular components by matrix metalloproteinase (MMP) is essential for maintaining tissue integrity in the remodeling process. Research shows that in POP, there is an abnormal synthesis and degradation of the two components of the extracellular matrix, namely collagen and elastin fibers. There are several types of collagen fibers. Type I collagen increases the tensile strength, especially in parts of the body that function as load-bearing. Type III collagen is a homotrimer composed of three -1 (III) chains and is usually distributed among type I collagen. Type III collagen plays a role in increasing the stretchability of the tissue. The ratio of collagen type I: to collagen type III is an indicator of tensile strength. The higher the composition of type I collagen, the greater the mechanical strength of the connective tissue [12].

In POP patients, there is a decrease in the ratio of type I and type III collagen found in the sacrouterine ligament. It has also been reported that an increase in the expression of MMPs, especially MMP-1, MMP-2, and MMP-10, is associated with the occurrence of POP [13]. Collagen is degraded by this MMP, decreasing the pelvic floor supporting tissue's number, quality, and function [14]. The unsatisfactory conclusion on the journey of POP in recent years has led researchers to conduct research that is more directed at the genetic role of POP. A European study reported that the risk of POP is increased five times in women whose twin sister has prolapsed compared to the general population [15]. Another study reported an increased POP risk in a woman whose sibling had POP.

Meanwhile, few studies have been conducted in Bali regarding the genetic influence on POP. Polymorphisms of several genes in patients with POP have been investigated for their association with the incidence of POP. Polymorphism is a variation in the DNA sequence in each individual. Research on polymorphism shows different results. Single nucleotide polymorphisms (SNPs) are the most common type of DNA sequence variation in human genes. These SNPs occur in one of the DNA base pairs or nucleotides, which can be either transitional or transverse. These polymorphisms do not show significant clinical or biological signs [16]. Research in Russia on type I collagen gene polymorphism in the Col1A1 gene was reported not to be associated with the incidence of POP [17]. Research in Korea, Taiwan, and the Netherlands showed an association between collagen 3 alpha 1 gene polymorphisms on the incidence of POP [18]. In a Russian study, POP was also associated with protein polymorphisms involved in elastin syntheses, such as fibulin-5 and LOXL1 [10].

Research on the role of MMP on the incidence of POP has also been extensively studied. Matrix metalloproteinases (MMPs) are a family of catabolic enzymes capable of breaking down collagen and other components of the extracellular matrix. There are several types of MMP, including MMP-1, MMP-3, and MMP-9. MMP-1 functions to degrade type I collagen, while MMP-3 plays a role in the activation of other types of MMP. MMP activity is regulated by the Tissue Inhibitor of Metalloproteinase (TIMP), which can bind to MMP and inhibit its performance. Matrix metalloproteinase-1 (known as collagenase-1) plays a significant role in the degradation of type I collagen [19]. Polymorphisms that occur in the MMP-1 gene are thought to increase MMP-1 activity.

The increase in MMP-1 activity will cause excessive degradation of type I collagen. This degradation causes a decrease in the pelvic organs' mechanical strength, leading to

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the process of POP [13]. Research conducted in Italy showed an association between MMP-1 gene polymorphisms and the incidence of POP [13]. In this study, after adjusting for age, body mass index (BMI), smoking habits, and the number of deliveries, the genotype at risk were found at -1607 1G/2G (P=0.04). Research conducted by Russia shows the same thing [20]. There are research that found at-risk genotypes at rs 1799750 1G/1G (OR=2.1, 95% CI, 1.05-4.38, P=0.03).

Another study in Poland showed different results, namely that there was no relationship between the MMP-1 polymorphism and the incidence of POP [17]. These different results may be influenced by the ethnic factors of the research subjects, as stated by Maria Augusta in a review article in IUGA magazine [16]. Identifying genetic predispositions to the incidence of POP will be beneficial in efforts to prevent POP.

Research in Indonesia on gene polymorphisms on the incidence of POP conducted on Indonesian women, especially Balinese women, has been studied by Megaputra et al. This study investigated the relationship between polymorphisms of the estrogen receptor gene, the collagen III gene (COL3A1), and fibulin-5 as risk factors for the occurrence of POP in Balinese women. This study showed polymorphisms of the estrogen receptor gene rs2228480 and the COL3A1 gene rs1800255 as risk factors for POP in Balinese women. Meanwhile, the fibulin-5 gene polymorphism rs2018736 is not a risk factor for the occurrence of POP in Balinese women [8]. Research on Indonesian women in general and Balinese women in particular on the effect of gene polymorphisms on the incidence of POP, which is still relatively small, makes hopes for understanding the pathogenesis of POP genetically unsatisfactory [8]. An understanding of the pathogenesis of POP in the biomolecular field helps many clinicians to identify and identify women who are at risk of developing POP early. This has prompted research on gene polymorphisms associated with POP to be carried out so they can be recognized as risk factors.

Research that has been done on Balinese women can be used as the basis of this research, and this research was conducted to strengthen the alleged relationship of genetic factors to the pathogenesis of POP. Suppose the polymorphism in the MMP-1 gene can be explained in terms of genetic pathogenesis and the risk to the incidence of POP in Balinese women. In that case, it is hoped that the strategy to prevent the occurrence and severity of POP in Bali will improve and positively impact the health sector and society.

II. DISCUSSION

This study using a case-control design was conducted on 30 samples of POP patients as the case group and 30 samples of non-POP patients as the control group using the patient's venous blood. This research was conducted at the Integrated Biomedical Laboratory, Faculty of Medicine, Udayana University Bali, from August 2020 to February 2021. The research has received approval from the Research Ethics Commission Faculty of Medicine Udayana University / Sanglah General Hospital in Denpasar with Number 1379/UN14.2.2.VII.14/LT/2020 dated July 1, 2020. This research has received an implementation permit from the Integrated Biomedical Laboratory Unit, Faculty of Medicine, Udayana University, with Number 768/UN14.2.2.VII.6/LT/2020.

Previous researchers sampled polymorphisms of the estrogen receptor gene, the COL3A1 gene, and the fibulin-5 gene as risk factors for the occurrence of POP in Balinese women. The sample is appropriately stored in the Integrated Biomedical Laboratory, Faculty of Medicine, Udayana University in Denpasar, Bali.

Examination of polymorphisms in the MMP-1 gene included DNA isolation, PCR examination, and purification. This examination was carried out at the Integrated Biomedical Laboratory, Faculty of Medicine, Udayana University, Denpasar Bali. The examination results are then sent to the Jakarta Genetics Science Laboratory for the sequencing process.

Pelvic organ prolapse is a health problem experienced by women. This disease can reduce the quality of life but does not threaten the sufferer's life. Pelvic organ prolapse is a disorder caused by various factors (multifatorial). POP risk factors may include parity, vaginal delivery, aging process, increased body mass index (BMI), and a history of hysterectomy. Other risk factors that have the potential to increase the occurrence of POP include delivery by forceps extraction, giving birth to a baby weighing more than 4,500 grams, prolonged vaginal delivery, family history of POP, shape, and orientation of the pelvic bones, heavy lifting work, constipation, and connective tissue abnormalities. In this study, statistical analysis was carried out aimed at comparing the factors between the case group and the control group. The distribution of characteristics of the research subjects in the case group and control group is shown in Table I.

The mean age in the case and control groups, respectively, was 57.47 ± 3.98 years and 56.63 ± 3.43 years with a P value > 0.05, so there was no significant difference between the two groups. In this study, the mean age in the case group was 57.47 years, and there was no significant difference between the case group and the control group. This study found that the average age of POP sufferers was almost the same as in several previous studies.

The increase in life expectancy and the population of women aged over 65 years causes POP to be a potential health problem. The number of women experiencing POP will increase with age. A study by Swift et al. in 2005 found that the prevalence of POP is around 40% in every decade of life [21]. Research conducted by Horst et al. in 2017 showed that women aged >35 years had an increased risk of developing POP by six times compared to those under 35. For every ten years of age increase, there will be a 40% increase in POP risk. Women older than 55 have a 2.6 times greater risk of POP risk. Women older than 55 have a 2.6 times greater risk of developing POP [22]. The POP risk also increases 5.2 times in postmenopausal women over 50 [23].

POP risk increases with age and peaks at 60-69 years. The pathogenesis of POP associated with increasing age is influenced by the aging process in general and the aging of all fibroblasts in the pelvic tissue. Mechanisms leading to the aging of fibroblasts may include gene instability and mitochondrial dysfunction [24].

The median parity value of the two groups is the same, namely 4, with the interquartile range (IQR) being 1. Parity is grouped into 2, namely parity < 4 and parity 4, which are obtained in both groups of 14 samples (46.70%) and 16
samples (53.30). In this study, the median parity value in the case group was 4, where parity of 4 was obtained as much as 53.30% in the case and control groups. While parity <4 was 46.70 in the case and control groups. The analysis results showed no difference in the proportion of parity between the case group and the control group.

Another risk factor for POP is parity. This parity is a modifiable risk factor. Aytan et al. 2014 showed an increase in POP risk by 1.5 times with an average parity of more than 3 [25]. Women with parity >5 had a three times greater risk of POP [26]. Women with parity of four or more have a five times risk of developing POP compared to nulliparas [22]. Vaginal delivery has the potential to cause damage to the pudendal nerve, which plays a role in the occurrence of POP [26]. Other pelvic structures traumatized by childbirth are the levator ani muscle complex, pelvic nerves, pelvic fascial structures, and the anal sphincter.

The median BMI value in the case group was 22.5 with an IQR of 4.09, while in the control group, it was 23.1 with an IQR of 3.66 and a P value of 0.906. From these results, it was concluded that there was no significant difference between the two groups. Body mass index was categorized into 4: thin, normal, overweight, and obese. Most of the BMI in the case and control groups was in the normal category, which was 70% the same. Only 13.30% of the case group and 6.70% of the control group were included in the obesity BMI category, but they were not statistically different, with a P value > 0.05. In this study, BMI was classified into 4 categories, namely Obesity (BMI 27 kg/m2), overweight (BMI 25-26.9 kg/m2), normal (BMI 18.5 – 24.9 kg/m2) and underweight (BMI <18.5 kg/m2). In the case group, the median BMI was 22.5 Kg/m2, and in the control group, it was 23.1 Kg/m2. These results showed no significant differences in the characteristics of the case and control groups based on BMI.

The incidence of POP is significantly increased by having a high body mass index (BMI), while POP recurrence is not significantly increased [22]. In comparison to obese women, those who are severely and morbidly obese (BMI > 49.5 kg/m2) had the highest prevalence of POP [27]. Other research has demonstrated that when obesity levels rise, POP symptoms become more common. Due to several factors, including chronically high intra-abdominal pressure, pelvic muscle and nerve injury, and additional obesity-related comorbidities such diabetic neuropathy and herniated intervertebral discs, POP is more likely to be obese patients [28]. The pelvic floor's pudendal nerve and other supporting components will become overstretched due to increased intra-abdominal pressure.

The samples with heavy work in both groups were the same, as many as 20 (67.70%). In this study, it was classified into heavy work and light work. Heavy work increases intra-abdominal pressure, and light work does not increase intra-abdominal pressure. In the case group, it was found that 33.30% of women with light work and 67.70% with heavy work. Statistical analysis showed that there was no significant difference between the case group and the control group.

A history of strenuous physical activity played a role in increasing the risk of women with multiparity (>5) experiencing POP by two times higher than without a history of strenuous physical activity [26]. Women with a higher risk of developing POP are advised to avoid work such as lifting heavy objects. This will increase intra-abdominal pressure and spread pressure to the supporting structures of the pelvic floor so that it can cause pelvic floor organ dysfunction. Other studies have shown that when women do physical activity, there is a positive correlation between lifting weights and an increase in intra-abdominal pressure [29].

The sample who had experienced menopause in the case group was 26 (86.7%), while in the control group were 24 (80.00%) with a P value of 0.49, which was not statistically different. In this study, there were no significantly different results between the case and control groups. In the case group, it was found that 86.70% of women had experienced menopause, while in the control group, as much as 80%.

POP symptoms can be caused by hormonal changes when women go through menopause. A high percentage of postmenopausal women in both passive and strenuous activities (21.6% and 24.3%, respectively) experience POP symptoms [29]. Hormonal changes when women experience menopause can cause a decrease in systemic estrogen concentrations, and this hypoestrogenic condition in the pelvic organs plays a role in changes in the composition and strength of collagen [30]. Estrogen can increase muscle and connective tissue strength through increased expression of type I collagen, overall cross-linked collagen, and deformation of type III collagen. Estrogen decreases the degradation of collagen and elastin through decreased MMP activity [31].

Postmenopausal women experience more damage to the abutment organs, leading to protrusion of the pelvic organs through the hymen, compared to women who have not been menopausal [32]. Research conducted in Indonesia found that the risk of POP increases about 5.2 times in postmenopausal women over 50 years old [23].

The history of having had a hysterectomy in both groups found only 1 sample (3.30%) with a P value = 1.00. so they are not statistically different. In this study, most women in the case and control groups had never had a hysterectomy. Twenty-nine women (96.70%) from each group of cases and controls had never had a hysterectomy. Meanwhile, as many as one people (3.3%) from the case and control group had a hysterectomy. From the analysis in this group, it was found that there was no significant difference between women and the case and control groups.

A study conducted in Sweden showed five times increased risk of POP in women who underwent vaginal hysterectomy and 2.5 times in individuals who underwent abdominal hysterectomy compared to those who never had it [33]. A study conducted in 2017 found a 1.4 times increased risk of POP in women with a history of hysterectomy [34]. Different results were obtained by a study conducted in America which showed that hysterectomy during POP surgery provided a protective effect, namely reducing the risk of repeated POP surgery by 1.3%.
Results Sequecing examination of each sample in the case and control groups for the presence of MMP-1 gene polymorphisms showed that 26 (86.7%) experienced MMP-1 gene polymorphisms in the case group. In contrast, in the control group, only 18 (6.7%) experienced MMP-1 gene polymorphism. A Chi-square test was conducted to determine whether MMP-1 gene polymorphism is a risk factor for POP. The results of the analysis are shown in Table II.

Table II shows different proportions of the MMP-1 gene polymorphism, signed between the case and control groups. In the case group with MMP-1 gene polymorphism, the risk of experiencing POP was 4.3 times greater than the case group without polymorphism. (odds ratio [OR]=4.33; 95% CI 1.20-15.61; p=0.020).

Several confounding variables such as age, parity, heavy occupation, body mass index (BMI), menopausal status, and history of hysterectomy were also analyzed in this study. These confounding variables were analyzed using a multivariate conditional logistic regression test analysis. This analysis controls for confounding variables, and the results are presented in Table III. MMP-1 gene polymorphisms remained a risk factor for the occurrence of POP after confounding variables were controlled. The risk of the MMP-1 gene polymorphism to the incidence of POP was 5.3 times higher than those without MMP-1 gene polymorphism (adjusted OR=5.52; p=0.02; 95% CI=1.352-22.50).

In this study, the analysis showed a polymorphism of the MMP-1 rs 1799750 gene in Balinese women. This polymorphism increased the risk of POP by 4.3 times higher in women who experienced the MMP-1 gene polymorphism rs 1799750 compared to women who did not experience the polymorphism. These results were also consistent after controlling for all risk variables such as age, parity, BMI, occupation, menopausal status, and history of hysterectomy.

The distribution of the MMP-1 rs 1799750 gene polymorphisms in Table II shows that in the case group, there were 26 women (86.7%), and in the control group, there were 18 women (60%) who had MMP-1 rs 1799750 gene polymorphisms. In comparison, 4 (13.3%) women from the control group and 12 (40%) from the case group did not have MMP-1 rs 1799750 gene polymorphisms. This study detected a statistically significant sample was genotype 1G/1G.

Matrix metalloproteinases are proteolytic enzymes (endopeptidase) involved in the destruction and remodeling of connective tissue. The polymorphism in MMP-1 is the insertion of Guanine (G) at position 1607, resulting in increased proteolytic enzyme production [20]. Guanine insertion at position 1607 determines the presence of the allele of the gene, namely the 1G allele. The result of this
polymorphism will change the MMP-1 protein structure. Changes in the MMP-1 protein structure will change the affinity for the catalytic region of the MMP-1 enzyme, resulting in increased binding to the substrate and the activity of the MMP-1 enzyme. A single insertion of Guanine in the promoter region will increase the transcription and local expression of MMP-1. When MMP-1 levels increase, proteolytic activity on connective tissue will also increase. MMP-1 is a collagenses-1 synthesized by connective tissue fibroblasts and monocytes. MMP-1 is an enzyme responsible for the catabolism of type I collagen. Type I collagen is flexible with high tensile strength, so it plays an essential role in load-bearing. MMP-1 is one of the matrix metalloproteinases whose job is to degrade type I collagen, so the MMP-1 gene polymorphism rs 1799750 where increased MMP-1 levels will cause an increase in the degradation of type I collagen [13]. This imbalance will cause reduced flexibility to high tensile strength so that it can cause a POP. This increased expression of MMP-1 will cause excessive degradation of type I collagen and will decrease the flexibility and tensile strength of the pelvic floor supporting tissues [13].

A new finding from this study is that it is known that there is a role of genetic variation in the incidence of POP in Balinese women, namely the MMP-1 gene polymorphism rs 1799750. The results of this study are expected to provide developments for genetic screening in the future so that it can detect women at risk earlier. POP. Women with the MMP-1 gene polymorphism rs 1799750 are advised to avoid risk factors associated with POP such as obesity, multiparity, heavy work, hysterectomy, and things that can increase intra-abdominal pressure. This will be very helpful in reducing the risk of POP in women with the MMP-1 gene polymorphism rs 1799750. This genetic screening is still very rarely done in Indonesia due to the very high cost and rare health facilities to conduct this screening.

![Fig. 1. MMP-1 rs 1799750 gene polymorphism IG.](image)

### III. CONCLUSION

It was found that the MMP-1 gene polymorphism rs 1799750 increased the risk of POP in Balinese women by 4.3 times.

### CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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