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Type B Progesterone Receptor Polymorphism Increases the Risk of Pelvic Organ Prolapse in Balinese Women

I Gede Mega Putra, I Wayan Megadhana, Putu Doster Mahayasa, Made Suyasa Jaya,
I Gusti Ngurah Harry Wijaya Surya, and Ngakan Ketut Darmawa

ABSTRACT

This study aims to determine the role of type B progesterone receptor gene polymorphisms as a risk factor for pelvic organ prolapse in Balinese women. This paired case-control study involves 29 patients with pelvic organ prolapse as the case group and 29 patients without pelvic organ prolapse as the control group. The study was conducted at Sanglah Hospital, Denpasar and the Integrated Biomedical Laboratory, Faculty of Medicine, Udayana University. Three milliliters of venous blood samples were taken from each patient and PCR examination was performed to determine the type b progesterone receptor gene polymorphisms. Risk assessment of the type b progesterone receptor gene polymorphism for pelvic organ prolapse was done by controlling for confounding variables, including age, parity, body mass index, occupation, menopausal status, and history of hysterectomy, through multiple logistic regression tests. The type b progesterone receptor gene polymorphism increased the risk of pelvic organ prolapse three times compared to non-prolapsed in Balinese women (OR 3.90, 95%CI 1.16-13.07, p = 0.023). After controlling for various confounding variables, type b progesterone receptor gene polymorphism still increased the risk of pelvic organ prolapse up to four times (AOR 4.54, 95%CI 1.16-17.68, p = 0.029). The type b progesterone receptor gene polymorphism significantly increases the risk of pelvic organ prolapse in Balinese women.

Keywords: Polymorphism, type B progesterone receptor, pelvic organ prolapse.

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I. G. M. Putra
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
I. W. Megadhana
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
P. D. Mahayasa
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
M. S. Jaya
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
I. G. N. H. W. Surya
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
N. K. Darmawan*
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
(e-mail: wawandarmawan291289@gmail.com)

****Corresponding Author***

I. Introduction

Prolapse organ hip (POP) is wrong. One problem is gynecology which is defined as dropping one or more aspects of the vagina and uterus, including the anterior vaginal wall, posterior vaginal wall, uterus (cervical), or apex from the vagina [1], [2]. The prevalence of POP worldwide varies, starting from 2.9% to about 75%, depending on the diagnostic criteria used. The prevalence of POP increases along with increased age hope life in females. Though the disease has several low mortalities, POP can cause disturbance quality of meaningful life [3].

Various factors play a role in POP events, consisting of intrinsic and extrinsic factors. Age is wrong; one factor intrinsic in the development of dysfunction base hip, where incident and prevalence POP reported increase along with enhancement age. Prevalence relative POP increases about 40% each additional decade life begins from 40 years. Age role in POP events is associated with various factors like existence change physiology from the component base pelvis and hormonal changes that occur during post-menopause [4], [5].

Progesterone is one hormone believed sexual have a role in pelvic organ prolapse (POP). Progesterone directly plays a role in incident POP through enhancement expression enzyme GGCT, which helps metabolism glutathione,

antioxidant important which is required for preventing stress oxidative induce damage cell by enhancement reactive oxygen species (ROS). This is supported by research that marker stress oxidative increase meaning in the sacrouterine ligament on a patient with POP and found enhancement fibroblast on group case consequence existence stress mechanic. Progesterone also increases the expression of Epithelial Cadherin (CDH1), which therefore prevents transition epithelial-mesenchymal (EMT) so which hinder happening degradation component composer base pelvis and allow the start process synthesis component matrix extracellular (ECM) [6]. Progesterone, together with estrogen, also plays a role in push activity proteolytic matrix metalloproteinase (MMP)-13. MMP-13 is collagenase which plays a role in degrading fibrillar collagen and initiating cascade degradation by activating other MMPs. Degradation causes strength muscle composer base pelvis to weaken and triggers the pelvic prolapse floor [7].

Progesterone needs to bond with the receptor to use produce an effect biologically. Receptors progesterone (PR) has been researched and found in the female genital structure, including the vagina, cervix, uterus, fallopian tubes, ligaments sacrouterine, muscle levator ani, and urethra, and cardinal ligaments pelvic floor [8]. Reference [9] shows that expression PR in ligament sacrouterine is significantly lower on group POP than control that is not experiencing POP. Percentage expression receptors Progesterone is also seen higher in women who have not experienced menopause than in women who have menopause. You are welcome to experience POP [9]. Decreased progesterone levels in circulation and tissue will lower the amount of receptors progesterone in a network. Adequate protection against POP will also be disturbed. Importance role of progesterone and PR in pathogenesis happening POP cause development study about both, wrong the only one is polymorphism progesterone receptors [8].

Polymorphism is a variation of sequence DNA that occurs in a population with a 1% or more frequency [10]. One study by [12] in China has evaluated polymorphism PR rs484389 (3'-untranslated region C/T) and PR rs500760 (exon 8 A/G) in POP. Mutation specific to sour nucleotide amino is known to push work bus on receptors progesterone type B (PR-B) so that damage regulation genetics on PR-B and change from PR-B Becomes receptors progesterone type A (PRE). The second type of PR has a structure and mechanism work which different. PRE, opposite from PR- B, will hinder activator transcription next and affect proliferation from working estrogen for activates processes that lead to protection occurrence of POPs [11], [12]. Results of study obtained that PR rs484389 CT genotype associated significantly with POP, where genotype this increase the risk of POP is 3.02 times compared to those who do not have genotype CT. Whereas for polymorphism PR rs500760 no found difference genotype, which was significant Among group control and case [12].

Studies about description polymorphism receptors progesterone in the POP patient have only been implemented in China, and research similar has not yet been done in Indonesia. This causes information about PR polymorphism in the case of POP to be very limited in Indonesia, precisely in Bali. because of that, the study aims to know the role type B progesterone receptor gene polymorphism as a factor risk happening pelvic organ prolapse in Balinese women.

II. Materials and Methods

Study this is a study case-control in pairs involving 58 Balinese women. A total of 29 Balinese women who were diagnosed with POP at Sanglah Hospital, Denpasar, were selected using consecutive sampling. Furthermore, 29 Balinese women were selected who did not experience POP To do matching on variable parity, index mass body and work with comparison Among case and control 1:1 to reduce selection bias or confounding bias. Criteria inclusion in research is Balinese women aged 30-70 years, diagnosed with POP (for group case) or patient other gynecology (for group control) who underwent check-in clinic Urogynecology Reconstruction and clinic gynecology, Obstetrics and Gynecology Clinics Sanglah Hospital Denpasar, and readily follow as well as in study after signing informed consent. Criteria exclusion in research is the presence of a diagnosis or comorbid in the form of malignancy and pregnant conditions. POP diagnostic criteria used in the study drop one or more pelvic organs (uterus, bladder, rectum) through the hole vagina at least 1 cm above the hymenal line. POP staging uses the system POP-Q where POP which includes in the study, is POP degree II or more.

History, examination physique general, and inspection of urogynecology performed on every subject research. History is conducted to get characteristics like identity, age, parity, complaints, and job history—inspection physique general for knowing existence disease attendant prolapse organ pelvis and forget index mass body. Inspect urogynecology to determine the degrees of clinical prolapse organ pelvis using the POP-Q standard. They were next, done taking as much venous blood as 3 ml. Sample venous blood is inserted into a tube containing EDTA and carried to Laboratory biomedical Integrated Faculty Medical University Udayana Denpasar Bali for DNA isolation and examination DNA sequencing through PCR test to determine the existence of PR-B polymorphism.

TABLE I: Characteristics Subject Study

Risk Factor	Group Case (n = 29)	Group Control (n = 29)	P-value
Age (mean ± SD)	58.45±10.35	56.10 ± 9.57	0.378 [a]
Parity (n, %)			
Multipara	28 (96.6)	28 (96.6)	1,000 [b]
Nullipara	1 (1.7)	1 (1.7)	
Work weight (n, %)			
Yes	15 (51.7)	15 (51.7)	1,000 [b]
Not	14 (48.2)	14 (48.2)	
BMI (n, %)			
Fat (BMI > 25 kg/m ^{2})	9 (31.0)	8 (27.6)	0.773 [b]
Normal (BMI 18.5-25 kg/m ^{2})	20 (69.0)	21 (72.4)	
Menopause Status (n, %)			
Menopause	24 (82.8)	21 (72.4)	0.345 [b]
Not menopausal	5 (17.2)	8 (27.6)	
History of Hysterectomy (n, %)			
Once	1 (3,4)	1 (3,4)	0.754 [b]
Not	28 (96.6)	28 (96.6)	

*P value<0.05 is considered significant
[a] T-independent test ; [b] Fisher-exact test ; [c] Chi-square test

All data obtained analysed use device soft Statistical Product and Service Solutions (SPSS) version 21.0 for Windows. All data collected conducted analysis descriptive. Test normality was conducted for knowing distribution data parity, index time body, and profession using Shapiro-Wilk. Test Chi-Square to know the ratio odds polymorphism gene receptors progesterone with pelvic organ prolapse. Study this already get agreement appropriateness ethics from Research Ethics Commission Faculty Medical University Udayana / RSUP Sanglah Denpasar dated 23 June 2020, number 1290/UN.14.2.2.VII.14/LT/2020. A study with design case-control was performed on 29 samples of pelvic organ prolapse (POP) as group cases and 29 non-POP patients as group control. Table I shows no difference in average age, parity, occupation weight, BMI, menopausal status, and history of meaningful hysterectomy in the second group ($p>0.05$)

III. Results and Discussion

Pathogenesis happening POP is influenced by various factor risk (multifactorial), both modifiable and not. Risk factors that cannot be modified are age. In contrast, what can be modified are parity factors, heavy work, obesity as indicated by the index body mass (BMI), menopausal status, and history of hysterectomy. Age distribution increased significantly in women who experienced symptoms of POP (POP symptomatic). A study by [13] shows that almost 50% of women with POP are aged 80 years, while 31% of them are aged 50-59 years, and the remaining 6% are aged 20-29 years. There is a positive relationship between increasing age of women and the number of patients seeking POP treatment. The number of women aged 30-39 years with POP who visit health services is as much as 1.7/1,000. This number increases in women aged 60-69 years to 13.2/1,000. The highest number of groups seeking consultation medical for POP reported for age 70-79 as significant as 18.6/1,000 [14]. Older age is a primary risk factor for POP. A woman who experiences POP at a younger age is more likely to experience recurrence POP after surgery than older women because of connective tissue weakness. Although however, the relationship between age as a risk factor for POP is still controversial. Research by [15] shows that women aged >35 years are associated with an increased risk of POP by six times compared to those under 35 years of age. Every increase in age by ten years, there will be an increased risk of POP by 40%. Research by [16] shows the mean age group of women with POP is 53.96 ± 10.91 years, while in the control group without POP, it was 49.60 ± 8.82 years. There is a significant difference between the over 50 years old proportion of a woman with POP compared with the control. A systematic review by [17] showed different results on age as a risk factor for recurrence POP. Many studies show age in the lower 60 years to be a significant risk factor for POP recurrence; other studies have shown no significant difference between ages more than 70 years or less than 70 years with POP.

Parity is a modifiable primary POP risk factor. Multiparity can be the most decisive predisposing factor for POP. Women with one child had a four times higher risk. Women with two children had an 8.4 times higher chance of developing POP requiring hospitalization compared to nulliparous women [18]. Research by [16] on 228 women showed the mean parity in the group of women with POP was 5.2 ± 2, while in the control group it was 3.97 ± 2.3. Women with parity >5 have almost three times higher risk of experiencing POP than women with parity more than 5. Despite being a primary risk factor for POP, parity did not show a significant relationship with POP risk recurrence [17]. The role of parity in increasing the risk of POP is related to the traumatic impact of vaginal delivery. Vaginal delivery can cause damage to the pudendal nerve, which plays a role in the pathophysiology of POP. 16 Other pelvic structures that are traumatized by childbirth are the levator ani muscle complex, pelvic nerves, pelvic fascial structures, and the anal sphincter [5] parity with labour vaginal have risk experience complaint related POP as big as 5.5 times compared with labour per abdominal [19].

The heavy profession is a main factor in a study classified becomes where is the complex work activity mainly can cause an increase in pressure intra-abdominal, like a farmer, a trader in market or laborer builder, and there is no heavy profession that can make no increase intra-abdominal pressure, such as office workers or housewife. Research by [16] showed that the history of strenuous physical activity in the group of women with POP was significantly different from that of women without POP. A history of strenuous physical activity contributes to an increased risk of multiparity (>5) women experiencing POP two times higher than without a history of strenuous physical activity. Another study involved women in Tanzania and Nepal who worked as sand and stone carriers. The results showed that women carrying heavyweights in Tanzania (median 20 kg) and Nepal (median 57.5 kg) had higher mean lower abdominal symptom scores related to POP than those who lifted light weights. A self-administered questionnaire measured the assessment of lower abdominal symptoms [20]. However, different results were obtained from [19] research. Physically inactive or physically active women who lift weights of 15 kg experience more POP-related complaints than women who lift heavier weights. These different results may be caused by lifting weights as an exercise program of choice and not being carried out routinely. The daily life of the study population may be less exposed to strenuous activities than in previous studies. Women with the risk of experiencing POP are recommended to avoid heavy professions, like lifting objects heavy. This is related to increased intraabdominal pressure and transmission of pressure to supporting structures pelvic organs when lifting weights, thereby contributing to pelvic dysfunction floor. Physiological research shows that when women do activity physique, there is a correlation positive Between lift burden with an enhancement of intra-abdominal pressure [19].

Index mass body (BMI) is the highest risk factor significant for primary POP but not significant for recurrence POP [17]. On a cross-sectional study, 964 women showed a positive correlation between BMI and compartment prolapse posterior (rectocele) based on physical examination or ultrasonography, but not with compartment anterior and central [21]. Different results from several studies show no relationship significant among obesity and POP [15], [19]. Study in 3,934 women by classifying BMI into less/normal BMI, overweight, and obesity, no find a connection which

significant among group POP and non-POP [19]. Difference results could be influenced by the absence of standardized POP assessments and population differences between research [22]. In theory, POP is more common in obese patients for various reasons, including chronically elevated intra-abdominal pressure, damage to the muscle hip, damaged nerve, and the existence of comorbid related obesity other like Diabetic neuropathy intervertebral disc herniation [23]. Obesity directly affects POP symptoms. Pressure increases intra-abdominal chronic, damage nerve, and comorbid on woman obesity contribute to dysfunction base pelvis. Enhancement pressure intra- the abdomen causes overstretching of the pelvic structures, including the nerves pudendal [23], [24]. However, in this study, it was not found that there was an influence of BMI factors on increasing incident POP.

Postmenopausal women experience more organ damage buffer, which causes protrusion organ pelvis past hymen, compared with a woman which not yet menopause [25]. Change hormones when menopause causes a drop in concentration. Systemic estrogens and hypoestrogenic conditions in the pelvic organs play a role in changes in the composition and strength of collagen [14]. Symptoms of POP vaginal like enhancement sensitivity could be caused by changes in hormones at menopause. There is a high percentage of postmenopausal women with inactive and strenuous activity women (21.6% and, respectively) 24.3%) who experience symptoms of POP, possibility consequence awareness existence sensation bump on the vagina [19].

Hysterectomy is associated with an increased risk of recurrent POP surgery. A prospective study in Sweden shows that there is an increased risk of POP is five times in individuals undergoing vaginal hysterectomy and as big as 2.5 times in individuals with a history of total hysterectomy abdominal compared which no once run it [26]. Results Similar findings were also found by [27]. The latter conducted a cohort study on the woman who not yet once do operation repaired POP. The result showed that vaginal hysterectomy had three times higher risk of requiring surgical repair of POP than total abdominal hysterectomy [27]. Incident POP also relate to the indication that medically performed a hysterectomy. The incidence of POP surgery was found to be twice as high in women undergoing hysterectomy with indications of prolapsed disease compared to other indications [26]. Different results were obtained by studies in America which showed that hysterectomy during POP surgery has a protective effect, namely: lower risk operation POP repeated future as much 1-3%. Hysterectomy is associated with a reduced risk of repeat surgery from POP anterior, apical, and posterior compared with those without a history of hysterectomy [2].

As many as 13 (44.8%) POP groups experienced PRB polymorphism. In contrast, only 5 (17.2%) group POP experience polymorphism PR - B. Table II shows differences in the proportion of polymorphisms gene PR-B between case and control groups. Patients with PR-B polymorphism have a 3.9 times more risk of experiencing POP tall than patients with no polymorphism PR (OR=3,900; 95% CI 1.163-13,078; p=0.023).

TABLE II: POLYMORPHISM GENE PR - B AS FACTOR POP RISK

PR-B. polymorphism	Group		OR	CI95%	P-value
	Case n(%)	Control n(%)			
Positive	13 (44.8)	5 (17.2)	3,90	1.163 – 13.078	0.023 [a]
Negative	16 (55.2)	24 (82.8)			

Score p<0.05 is considered significant; [a] Test Chi Square

TABLE III: RELATIONSHIP RECEPTOR GENE POLYMORPHISM PROGESTERONE TYPE B AND POP AFTER CONTROLLED WITH VARIABLE CONTROL

Variable	*Adjusted* OR	CI 95%	P-Value
Polymorphism PR	4,544	1.168-17,680	0.029 [a]
Age	0.985	0.895-1.085	0.863 [a]
Parity	1,921	0.047-78,691	0.730 [a]
Load Heavy Work	1,736	0.496-6.069	0.388 [a]
BMI	1.251	0.345-4.531	0.733 [a]
Status Menopause	1,480	0.192-11.407	0.707 [a]
History Hysterectomy	1.091	0.055-21,470	0.954 [a]

Score p<0.05 considered significant; [a] Test Regression Logistics multiple

Several confounding variables, such as age, parity, heavy work, index body mass (BMI), menopausal status, and history of hysterectomy, which are known to play a role in incident POP also analyzed in this study. Analysis multivariate use test conditional regression logistics conducted for control variable confounder and result could be seen on Table III. Type B PR gene polymorphism remains a risk factor for POP after the variable confounder is controlled. Polymorphism gene PR Type B give risk The occurrence of POP is 4.544 times higher than those who do not have POP polymorphism gene PR (adjusted RO = 4.544; p=0.029; CI95% = 1,168-17,680).

Previous studies have shown that the PR gene polymorphism rs484389, a risk factor for POP, is the CT heterozygous genotype. In this study, these genotypes were analysed and discussed as factors risk POP. Sample detected have to genotype heterozygous CT on gene PR categorized as having a PR polymorphism [12]. Results of statistical analysis in this study showed that women with PR - B gene polymorphisms had a 3.9 times risk of experiencing POP compared with which no who have polymorphism gene PR - B. These results are also consistent after controlling for the variables confounder other.

In China, one previous study by [12] assessed polymorphism PR rs484389 (3'- untranslated region C/T) on POP with a case-control research design. This study found that the PR rs484389 CT genotype was significantly associated with POP, whereas this genotype increased POP risk by 3.02 times compared to those who did not have the CT genotype [12]. Specific mutations in the nucleotides of these amino acids are known to suppress the action of BUS on PR-B, thereby impairing genetic regulation of PR-B, where there is a change from PR-B to PR-A. As it is known, the second type of PR has a structure whole and mechanism work which different. In contrast to PR-B, PR-A will inhibit transcriptional activator next, and proliferative effect of estrogens [11]. Progesterone plays a role in the occurrence of POP through increased expression of enzyme GGCT.

Enzyme GGCT follows and metabolism glutathione, which is expressed in the nucleus and cytoplasm from cell epithelium in system reproduction. Glutathione is an important antioxidant required to prevent oxidative stress-inducing cellular damage by increasing reactive oxygen species (ROS). This is supported by research that marker stress oxidative increase means in ligament sacrouterine on a patient with POP and found enhancement fibroblast on group case consequence existence stress mechanic. ROS is also known for directly inducing the occurrence of an EMT [6]. Progesterone and estrogen play a role in push matrix metalloproteinase (MMP)-13 proteolytic activity [2], [29]. MMP-13 is a collagenase that plays a role in degrading fibrillar collagen and initiates a degradation cascade by activating MMP other [7], [29]. Collagen is initially degraded to fragments by MMP-13 and MMP-1 and -8 before being dissolved by MMP-2 and -9. Enhancement expression MMP indicates accelerated remodeling and collagen degradation. MMP is inhibited by TIMP and decreased TIMP expression was associated with increased MMP expression [7] This degradation causes the strength of the muscles that make up the pelvic floor to become weak and lead to pelvic floor prolapse [7], [29].

This study indicates that the PR-B gene polymorphism is a factor risk happening POP in Balinese women, with the hope existence developments in genetic screening in the future so that it can be known for women who have the risk of POP. Women with polymorphism POP could is recommended to avoid or minimize the risk factors for POP that can be modified, such as multiparity, vaginal delivery, obesity, heavy-load work or disease-causing chronically elevated intra-abdominal pressure, and hysterectomy surgery. This will help reduce the chances of this happening POP on a woman with polymorphism PR -B. Screening genetics is already many conducted in-country Up; however, in Indonesia and other developed countries, an inspection of genetics for knowing polymorphism gene PR -B is still hard to reach and expensive.

IV. Conclusion

Polymorphism PR-B gene is a factor risk significant happening POP on Balinese woman. Inspection screening existence polymorphism gene PR -B on Balinese women could be possible in the future uses for detection existence POP risk. Study role PR-B gene polymorphism against POP needed events that bigger scale on other women ethnic groups others in Indonesia will be needed in the future.

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