

ENDOMETRIAL RECEPTIVITY ON ENDOMETRIAL POLYP WITH POLYMORPHISM PROGINS

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ABSTRACT

Introduction: Women with primary infertility eumenorea during infertility examination have endometrial polyps. Their effect on endometrial receptivity is assessed by pinopode expression at mid luteal phase. Progesterone receptor gene polymorfism (PROGINS) seems have a correlation with impairment of endometrial growth inducing polyp.

Method: Cross Sectional Study, Gynecology Jakarta Fertility Centre, from July 2015 - July 2017, primary infertility woman with endometrial polyp was recruited for this study.

Intervention(s): In this study the patients undergoes transvaginal ultrasound, saline infusion hysterosonography, hysteroscopy procedures and endometrial biopsy to evaluate the pinopode expression and cytology examination of the polyp, along with blood sample collection for determined the PROGINS polymorphism.

Result(s): 41 patients undergoes hysteroscopy procedure dan endometrial biopsy. Pinopode expression negatif in 23.8%, isolated 31%, scattered 38%, clustered 3%. no significant correlation on polymorphism PROGINS T1T1 homozygot (92,1%); T1T2 heterozygot (7.9%)was observed.

Conclusion: Pinopode expression is a reliable marker for endometrial receptivity and PROGINS polymorphism can be used to determine increased risk of endometrial polyp.

Keywords: Endometrial Polyp, Pinopode expression, PROGINS polymorphism.

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INTRODUCTION

Endometrial polyps defined as localized overgrowth of endometrium that contain both endometrial glands, blood vessel and stromal cell. Most of endometrial polyp are benign and have a variable presentation; they can occur as single or multiple lesions, can be sessile or pedunculated, and range in size from millimeters to centimeters. Usually endometrial polyps is asymptomatic, and the symptom is commonly present as abnormal uterine bleeding.[1-3]

Mostly polyp is identified during examination on woman with abnormal uterine bleeding, but some of them are also identified on eumenore woman during routine check up or infertility evaluation. Modalities of examination can be through transvaginal ultrasound, hysterosalpingography, saline infusion hysterosonography, or

hysteroscopy. Each type of examination have a different sensitivity dan spesifty in diagnosing endometrial polyp.4-6

The prevalence of endometrial polyp is 7.8-34.5% depending of the population studied, and 32% of women with unexplained infertility have endometrial polyps on hysteroscopy, but their effect on endometrial receptivity and fertility is uncertain. A number of studies found an alteration in endometrial receptivity.[5-8]

Pinopode as a marker of endometrial receptivity have a significant role on embryo implantation.[9] Progesteron receptor ia a potent antagonis of estrogen induced proliferation. Thus, progesteron receptor gene polymorphism (PROGINS) seems to have a correlation with impairment of endometrial growth.[10]

MATERIAL AND METHODS

Patients

Among the patients of the gynecological fertility clinic Jakarta, with primary infertility, eumenorea (mean age: 21 - 42 years) diagnosed by hysterosalpingography, transvaginal sonography, Saline Infusion Hysterosonography, if the polyp endometrial was diagnosed the patient undergoes operative hysteroscopy polypectomy, guided endometrial biopsy. The tissue sent to pathology department to evaluate the pinopode and morphology of the polyp. Blood sample was taken to investigate the polymorphism PROGINS.

After explaining the objectives of the study obtaining and signed form of informed consent, patients clinical data, diagnostic examination, hysteroscopy procedure and biopsy, pathology examination, and peripheral blood samples is taken. This study is approved by Research Ethics Committee the Faculty of Medicine Gadjah Mada University - dr Sardjito General Hospital. (Ref: KE/FK/740/EC/2015).

Methods

Endometrial sampling: Endometrial biopsy samples were obtained during hysteroscopy procedure at mid luteal phase (day 19-21) from the wall of the uterine cavity. Each sample is immediately fixed in a solution containing 0.5% paraformaldehyde, and 2.5% glutaraldehyde.[11]

Scanning electron microscopy: The specimens were washed twice in a buffer containing 0.15 mol/L of sodium cacodylate and 3 mmol/L of calcium chloride (pH, 7.4) and once in distilled water. Samples were dehydrated in ethanol with increasing concentrations of (70%, 95%, and 99.5%) and then in acetone. Followed by drying in a critical-point dryer using carbon dioxide. After that specimens were mounted and coated with platinum, and examined using a scanning electron microscope.[12]

DNA Extraction: Peripheral blood collected from each patient in EDTA-containing tube. Then sent to Gadjah Mada biochemical laboratory for Genomic DNA extraction from lymphocytes in the peripheral blood according to the manufacture instructions

(GE Life Science, USA), illustrated blood genomic Prep Mini Spin Kit.[13]

PCR: Molecular analysis of the PROGINS progesterone receptor gene polymorphism was performed according to the protocol with modifications. The primers used were 59-GGC AGA AAG CAA AAT AAA AAG A-39 (forward) and 59-AAA GTA TTT TCT TGC TAA ATG TC-39 (reverse). The PCR reaction was carried out in a final volume of 25 µl, containing 1X buffer, 2.5 mM MgCl₂, 0.1 mM of each dNTP, 50 nM of each primer, 1 U of Taq Polymerase (Invitrogen), and 200 ng of DNA. Amplification was performed with an initial denaturation step at 95 °C for 7 min, followed by 35 cycles of denaturation at 95 °C for 45 sec, annealing at 50 °C for 1 min, and extension at 72 °C for 1 min and a final extension step at 72 °C for 7 min. The amplification product was visualized in a 2% agarose gel under UV light.[13] The PCR product presented a single band of 149 bp in the homozygous individuals without the mutation, designated as T1T1. The presence of one 149-bp and one 455-bp band indicated heterozygous individuals, who have one allele without the mutation and one allele with the mutation; these individual were designated as T1T2. The presence of a single 455-bp band indicated individuals with the mutation in both alleles, and these individuals were designated as T2T2.[13]

Statistical analysis: Allele and genotype frequencies were compared using bivariat and multivariat analysis.

All p values were two-tailed. A p-value > 0.05 was considered statistically significant, with 95% confidence intervals (CI) were calculated.

RESULT

From May 2015 to April 2018 there was 42 patients enrolled and gave their approved and informed consent for this study. All of the patients performed transvaginal ultrasound, Saline Infusion Hysterosonography and operatif hysteroscopy. During hysteroscopy endometrial biopsy and operatif hysteroscopy for polypectomi was performed. One patient was excluded because necrosis of the tissue sample, so overall patients were 41.

Table I list the characteristic for patients enrolled in this study.

Table I. Population study characteristic (n=41)

Characteristic	mean±SD; median (Min-Maks)	n (%)
Age (year)	33.4±3.53; 33.5 (27 - 40)	-
25 – 34		29 (70.73)
>35		12 (29.27)
Duration of marriage (year)	4.9±2.78; 4.0 (2 - 12)	-
Body Mass Index	27.2±2.90; 27.2 (23.0 – 32.4)	
- Normal		13 (31.71)
- Overweight		17 (41.46)
- Obesity		11 (26.83)
Hystory of Diabetes	-	20 (48.8)
Educational		
- High school		10 (26.2)
- University		31 (73.8)
Job list		
- House wife	-	21 (50.0)
- Government employe	-	8 (19.0)
- Non government employe	-	7 (16.7)
- Private employe	-	4 (9.5)
- Professional	-	1 (4.8)

The mean age for this subyek and infertility patiens was 33.4 ±3.5 years (range 29 – 39). The mean infertility duration was 4.9 ± 2.78 years. The mean body mass index was 27.2 ± 2.9. The family hystory for diabetes mellitus was 47.6 %. The most education level in this group of study was university graduate 73.8 %.

By Saline infusion hysterosonography and hysteroscopy all of the subyek study was diagnosed had endometrial polyp, with transvaginal ultrasound only 3 (3.7%) endometrial polyp diagnosed, and with HSG only 1 patient (2.4 %) found to have endometrial polyp.

Table II. Endometrial polyp mode for diagnoses in this study group of patients (n=41) by Saline Infusion Hysterosonography, Hysteroscopy, transvaginal ultrasound and Hysterosalpingography (HSG)

Mode of diagnostic	Endometrial Polyp	
	Present n (%)	Absent n (%)
Saline Infusion Hysterosonography	41 (100%)	0 (0,0%)
Hysteroscopy	41 (100%)	0 (0,0%)
Transvaginal Ultrasound	3 (7.1)	38 (92.9)
Hysterosalpingography (HSG)	1 (2.4)	40 (97.6)

Hystopatologi examination reveal that most endometrial tissue reveal simplex non atipic hyperplasia (70.73 %).

Table III. The association between pinopodes expression score during implantation window with endometrial polyp (n=41)

Pinopodes expression score	Endometrial Present	Polyp
0 = negatiffor absent	8 (19.51)	
+ = isolated pinopods	13 (31.0)	
++ = small groupns of pinopods	17 (41.46)	
+++ = confluent pinopodes	3 (7.32)	

When examined by scanning electron microscope (SEM) for pinopodes evaluation and assigned score for pinopodes expression of the endometrial sample from the population study, pinopodes score +2 found for the most of the sample endometrial tissue from this study 41.46 % (17 subj). Pinopodes score +1 was the second 31 % (13 patients). Good

pinopodes score +3 was found only in 7.32 % (3 patients) and 19.5 % (8 patients) display no pinopodes. All of the endometrial sampling for this pinopodes evaluation taken in the window of implantation period and from endometrial sampling with endometrial polyp confirmed.

Table IV. Progesterone Receptor Gen Polymorphism (PROGINS) in our population study group of endometrial polyp patients (n=41)

PROGINS Polymorphism	n (%)
T1/T1	38 (92.6%)
T1/T2	3 (7.4%)

When Polymorphism Progesterone Receptor Gene (PROGINS) was studied by PCR for this population of patients the result found that 38 patients (92.6 %) are homozygote (T1/T1) and only 3 patients (7.4%) heterozygote (T1/T2), so our study population of patients with endometrial polyp have tendention to be homozygote and had no PROGINS polymorphism for their progesterone receptor gene.

Table V. The relationship between PROGINS Polymorphism and pinopodes expression score (n=41)

Pinopodes score	PROGINS polymorphism	
	T1/T1 (homozygote)	T1/T2 (heterozygote)
Negative	8 (20.5%)	2(66.7%)
+1	13 (30.8%)	1(33.3%)
+2	17 (41.0%)	0(0.0%)
+3	3(7.7%)	0(0.0%)

p=0,3; test χ^2

When we examination the PROGINS polymorphism in relation with pinopodes expression, our result revealed that in 3 patients with PROGINS heterozygote 2 (66.7 %) of them had no pinopodes or score 0 and 1 of them had pinopodes with score +1. And for no polymorphism group of PROGINS – T1/T1 the results found 8 (20.5 %) patients had no pinopodes, 13 (30.8 %) had pinopodes score +1, 17 (41.0 %) had pinopodes score +2 and only 3 (7.7 %) patients had good pinopodes score + 3. The results of statistical analyses shows there is significant association between PROGINS polymorphism with pinopodes expression score in endometrial polyp patients.

DISCUSSION

Endometrial polyp is a common gynaecologic problems which the precise incidence not known because many polyp have no symptoms, the prevalence reporter between 7.8% - 34.9% according to population study. The risk factors for endometrial polyp are age, hypertension, obesity, and tamoxifen.[14]

Barbosa et al, in their metaanalysis found that saline infusion hysterosonography to diagnose endometrial polyp and submucous myoma in reproduction age women with and without abnormal uterine bleeding had pool sensitivity 0.93 (95% CI, 0.89 – 0.96) and pool spesificity 0.81 (95 % CI; 0.76 – 0.86). Their meta analysis use hysteroscopy as gold standard examination.[15]

In our study as previous many study before the Saline Infusion Hysterosonography and Hysteroscopy better than other modalities of examination for finding endometrial polyp in infertility patients with normal menstrual cycle. All of 41 patients recorded that SIS results gave

concordance result by hysteroscopy finding. Transvaginal ultrasound alone failed to diagnose the presence of polyp in 39 of our patients. And HSG only finding only reveal one case of endometrial polyp.

Study comparing modalities to diagnosed endometrial pathology through transvaginal ultrasound with SIS found that SIS had sensitivity 92.9% and spesifisity 89.7% compare to transvaginal ultrasound 71.4% and 67.7%. There was concordance between SIS and hysteroscopy 91% compare to 69% with transvaginal ultrasound (p=0,02). The strength of SIS for diagnosis three main gynecology pathology of endometrium (endometrial hyperplasia, polyp and submucous myoma) are better than transvaginal ultrasound.16 Prospective study in 2005 of 1000 infertile woman schedule for IVF, found that endometrial polyp prevalence seem increase among infertile patients. They found the polyp prevalence 32% in eumenore infertile patients. Their high prevalence reveals causal association between the presence of polyp and infertility.[17]

Endometrial polyps patophysiology to infertility is unclear and the mechanism is poorly understood. It might because mechanical intervention on sperm transportation, through intrauterine inflammation, increased production of inhibitory factor, or pinopode growth on mid luteal phase during embryo implantation.18 But, the causal relationship between endometrial polyp and infertility had been confirmed in study of 213 eumenorea infertility patients treated by hysteroscopy polypectomi, 93 patients become pregnant in one years period after the operation, with relative risk of 2,1 (95% confidence interval 1.5-2.9).19

Retrospective study with 230 infertility women undergoing hysteroscopy polypectomy, found result that the location of the endometrial polyp play a pivotal role in fertility outcome and pregnancy rate. After surgery this study found pregnancy rate within 6 month is 57.4 % for polyps located at the uterotubal junction, 40.3 % for multiple polyps, 28.5 % for posterior wall polyps, 18.8 % for lateral wall polyps and 14.8 % for anterior uterine wall polyps. These results suggest that the mass of polyps may interfere with the reproductive processes such as sperm transport, embryo implantation or early pregnancy development.[20] Another retrospective study also found no difference pregnancy outcome after hysteroscopy polypectomy for 83 women with abnormal uterine bleeding, hysteroscopic polypectomy appeared to improve fertility and pregnancy rates irrespective of the size or number of the polyps. This pregnancy outcome increase because the symptom of abnormal bleeding is recovered after the operation.[21] Similar result also found in woman post hysteroscopy polypectomy for a small endometrial polip (less than 10 mm) in size, comparing with those who had bigger or multiple endometrial polyp. No difference between size of polyps and pregnancy outcomes goes against a mechanical effect, as a bigger effect would be expected in the presence of larger polyps. The molecular mechanism is the same, but the mechanical effect of this space occupying lesion from endometrial polyp is depend on location and size.[22]

In normal menstrual cycle, glycodelin, a glycoprotein that inhibit sperm-oocyte binding and NK cell activity levels are very low between 6 days before and 5 days after ovulation. Low glycodelin levels to facilitate fertilisation, and then, the levels increase significantly 6 days after ovulation to suppress NK cell activity, prepare for blastocyst implantation. It is possible that fertilisation and endometrial receptivity maybe altered, if glycodelin production is increase inside uterine cavity of patients with leiomyomas and polyps at mid menstrual cycle, defecting endometrial receptivity if uterine glycodelin levels decrease.[23]

Endometrial receptivity established molecular markers like *HOXA10* and *HOXA11* gene expression is altered when there is endometrial polyp present. It is also suggested that removal of endometrial polyps have positive impact increasing pregnancy rate through natural conceptions, or artificial reproductive technique like intra uterine insemination (IUI) or in vitro fertilization (IVF).[24]

Numerous publications conclude that there is positive correlation between polypectomy and

increase spontaneous pregnancy rates. Between 1975-1999, Varasteh a single surgeon undergoes hysteroscopy diagnostic procedure for infertile women with and without endometrial polyps and found a pregnancy rate of 78.3 % after polypectomy compared with 42.1 % in those with normal uterine cavity.[25]

Spiewankiewicz et al., reported a pregnancy rate of 76 % where 19 out of 25 infertile patients conceived within 12 months after polypectomy.[26] Shokeir et al., reported a 50 % pregnancy rate after polypectomy in such patients.[27] Both of this study conclude woman with unexplained infertility may benefit from hysteroscopy polypectomy procedure.

Randomized control study on 215 woman with unexplained primary infertility, with ultrasonographically diagnosed endometrial polyps undergoing IUI, to either hysteroscopic polypectomy in the study group or diagnostic hysteroscopy and polyp biopsy in the control group. Patients who underwent hysteroscopic polypectomy had a better possibility of becoming pregnant after polypectomy and increase the endometrium receptive to implantation with a relative risk of 2.1 (95 % confidence interval 1.5–2.9).[28]

In another study, 120 infertilty woman was diagnosed with endometrial polyps planned to have IUI, and not in IVF or FET schedule, they are randomly divided into 2 group. The first group will have hysteroscopy polypectomy, and the second group have no intervention before IUI. All subject were scheduled to have IUI until four cycles, suggesting that hysteroscopy polypectomy prior to IUI is an effective measure and improves pregnancy rates. The cumulative pregnancy rates were significantly higher in the study group (38.3% vs 18.3%; $p = 0.015$).[29]

Study among subgroups with polyps of different location, size and number were included, they underwent hysteroscopic evaluation which revealed endometrial polyps, and then assessed the pregnancy rates after procedure. Patients with any intrauterine pathology other than polyp and those undergoing frozen embryo transfer (ET) cycles were excluded. Patients were evaluated according to polyp location, size and number. Rates of β -hCG positivity and clinical pregnancy were compared. Clinical pregnancy rates after polypectomy seems to change after hysteroscopic treatment. Pregnancy rates 11.8% for fundal polyps, 22.2% for posterior uterine wall polyps, 27.3% for cornual zone polyp, 28.6% for anterior wall polyps, 30.8% for isthmus zone polyps, and 41.7% for multiple polyps ($p = 0.532$). These conclude that after hysteroscopy polypectomy at different locations in the uterine

cavity, there is no difference in the probability to conceive regarding size and number of this endometrial polyps [30].

Our study revealed there were significant relationship between reseptor progesterone gen polimorphism PROGINS and the presence of polyps that may alter pinopodes expression. But the weakness of this study is in all subject is still in polyp, and also all the patient not in hormone therapy to make hormonal condition similiar and also all the patients not in progesterone induction for influence maturing the endometrium.

On the other hand, there is another study repoting about pinopodes variation between cycle at natural cycle without stimulation report significant inconsistency, lack of association regarding reproductive outcomes and seems no difference after hysteroscopic polypectomy.[31]

From various study it seem that pinopodes evaluation was time consuming and subjective, leaving a problem which must be solve if this examination will be applied in daily clinical practice. Maybe with development of automated image capture software this problem is solving and more easy to do the examination and decrease subjectivity and increase presision on pinopodes expression counting.[32]

Before our study progesterone receptore polimorphism PROGINS was study in correlation with several topic, included endometriosis, mioma, idiopatic infertility, ovarian cancer and breast cancer. Progesterone hormone is a potent antagonist of estrogen-induced proliferation in the endometrium. Progesterone receptor gene is located at chromosome 11q22-23 and has two isoforms A and B to modulate action of progesterone hormone.[33]

The reverse action of progesteron isoform A and B, play a significant mechanism in endometrial growth during menstrual cycle. Isoform A, which is capable of inhibiting the activation of the estrogen receptors, and isoform B, which has the capacity to activate the estrogen receptors. Several polymorphisms have been described for this gene, among which one stands out: a polymorphism named PROGINS, which arises due to the insertion of an Alu element into intron G between exons 7 and 8 of isoform A of the PR gene, resulting in an increase of 306 bp in the gene product.[33]

Gimenes et al., 2010 found the frequencies of genotypes T1T1, T1T2 and T2T2 of the PROGINS polymorphism in the 179 patients with endometriosis associated infertility were 93.9%, 5.4% and 0.7%, ($p = 0.2101$). And the control group, 88.3% presented the normal homozygous genotype T1T1, 10.6% showed the heterozygous genotype T1T2, and 1.1% had the homozygous

mutated genotype. Considering the alleles, allele T1 was present in 96.6% of patients with endometriosis-associated infertility. This show progesteron receptor gene play a pivotal role in the pathogenesis of endometriosis. [34]

Wieser et al., studied 95 women with endometriosis and 107 women without endometriosis and concluded that the PROGINS polymorphism is associated with susceptibility to endometriosis.[35]

Lattuada et al., studied the PROGINS polymorphism in 131 women with endometriosis and a control group of 127 women and confirmed the relationship between this polymorphism and endometriosis.[36]

Govindan et al., studied 445 Indian women, divided into 3 group. 100 subject with endometriosis, 80 with leiomioma, 157 with breast cancer, and 108 healthy woman as control group. This study resulting that the PROGINS polymorphism can be considered a risk marker for breast cancer but not for endometriosis or leiomioma.[37]

Van Kaam et al., studied 72 women with endometriosis, 40 women with adenomyosis, 102 benign gynecology tumor and 93 healthy woman, concluded that the PROGINS polymorphism does not seem to modify the risk of endometriosis, but increase the risk of benign gynecology tumor.[38]

Pisarska et al.,found an increase in the prevalence of PROGINS mutations among 26 women with the diagnosis of unexplained infertility compared to 28 control women (42% vs. 14%).[39]

However, in the current study, the PROGINS polymorphism was not correlated with primary infertility eumenorea woman (14.0% vs. 11.7%). Results shows association between infertility and PROGINS polymorphism; but in this study the power calculation of the sample was low, so we need to confirm by larger number of sample subject.

The PROGINS polymorphism causing this progesterone receptors to lose its ability to inhibit the action of the estrogen receptors, because these polimorphism produces a decrease in the stability of the progesterone receptor gene. Hormone progesterone is having a significant influence on the regulation of enzyme extracellular matrix metallo proteinase, for stimulating the inhibiting factors of enzymes extracellular matrix metallo proteinase, it also acts on the expression of angiogenic factors and on endometrial cycle regulating factors. This polymorphism makes inadequate control of progesterone receptors, so the endometrium more vulnerable to the action of estrogen hormone, and may influence active cell proliferation, increase viability, and reducing

apoptosis in endometrial cell growth. Increased expression of isoform B (which is responsible for the activation of the estrogen receptors) when it includes the PROGINs polymorphism will contributing a higher oncogenic proliferation of this subject with polymorphism.[40]

All of the subjek of this study are patients with primary infertility, eumenore and also found to have endometrial polyp with no symptom, it means population of subject is homogen and proper to pinopodes expression and PROGINs polymorphism evaluation. Until now, as along with our literature study there is no study in PROGINs polimorphism in relation with patogenesis of endometrial polyp. And also study in PROGINs

polimorphism in relation with pinopodes not yet performed.

This study found that PROGINs polymorphism T1/T1 present in 92% of patient. Maybe this is a new report, that individu with PROGINs polymorphism T1/T1 is a risk factor and have a tendency to developed endometrial polyp although not yet proved by statistical analysis. Our study pointed that relationship between PROGINs polymorphism with pinopodes characteristic is significant with endometrial polyp patient. This finding maybe need to be confirm in subject without endometrial polyp because maybe there are another factors have contribution with endometrial polyp patogenesis which inhibit pinopodes developmental or decrease pinopodes expression.

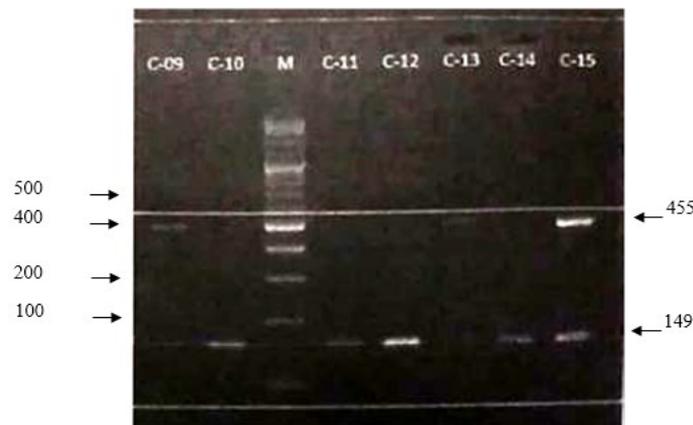


Figure 1.: Agarose 2% gel profile is shown and bands corresponding to the polymorphism PROGINs 149 base pair and 455 base pair are indicated

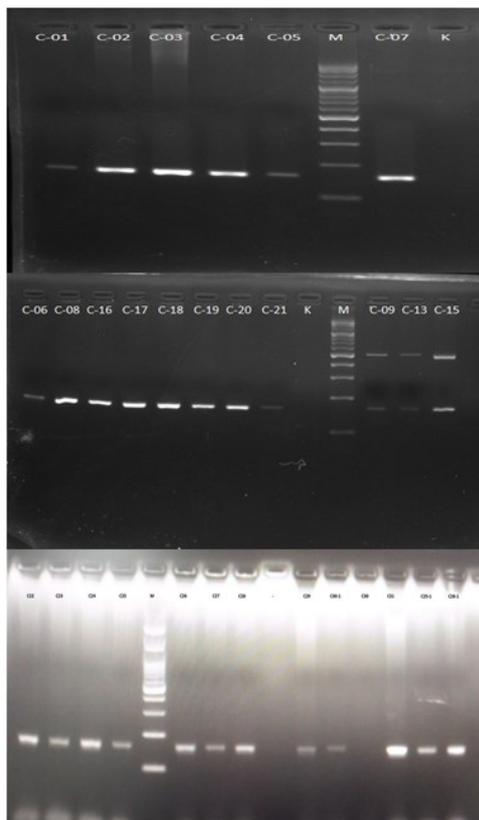


Figure 2.: Polymorphism PROGINs on primary infertility eumenorhea woman with endometrial polyp.

CONCLUSION

In this study it was found that transvaginal ultrasound and saline infusion hysterosonography may be routinely performed on all primary infertility women or secondary infertility to know for certain the anatomical anatomy of the uterus, especially the uterine cavity.

Hysteroscopic examination as a definite guide to uterine cavity pathology evaluation, and suggested to be performed in all cases of primary and secondary infertility, also prior to assisted reproduction techniques (intra uterine insemination or in vitro fertilization). Operative hysteroscopy is a *gold standard* handling cases of endometrial polyps. Followed by cytological examination of endometrial polyps to determine the prognosis of pregnancy success, and recurrence in cases of endometrial polyps.

There is a marked change in endometrial polyp cytology with atypical non-atypical simplex hyperplasia and atypical non-atypical complex hyperplasia. Pinopode as endometrial receptivity markers decrease significantly in cases of endometrial polyps. Inspection of the type and distribution of pinopode should be performed prior to embryo transfer in patients undergoing IVF with

freezing embryo, as a predictive factors for successful embryo implantation. In relation to the receptor progesterone polymorphism, the presence of alu insertion in PROGINs showed significant difference for endometrial polyps, it can be performed to determine etiologies and genetic based therapies in the future.

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