

HUBUNGAN POLIMORFISME GEN $ER\beta$, *VARIABLE NUMBERS OF TANDEM REPEAT (VNTR)* INTRON 4 GEN CYP 19, DAN MIKRO-RNA LET-7 b TERKAIT KADAR ESTRADIOL (E2) TERHADAP FOLIKULOGENESIS PADA PASIEN ENDOMETRIOSIS

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INTISARI

Latar Belakang: Endometriosis merupakan penyakit tergantung hormon yang mempengaruhi sekitar 5 – 10% perempuan usia produktif yang ditandai dengan adanya jaringan menyerupai kelenjar dan stroma endometrium di luar kavum uteri. Terdapat 25 – 50% pasangan dengan infertilitas memiliki endometriosis. Endometriosis mempengaruhi kesuburan melalui berbagai mekanisme, termasuk gangguan folikulogenesis. Folikulogenesis memerlukan kerjasama yang sinergis antara hormon estrogen, *follicle stimulating hormon* (FSH) dan *luteinizing hormon* (LH). Adanya perubahan produksi estradiol yang diperantarai sitokrom P450 aromatase, dapat terjadi akibat polimorfisme gen CYP19 dan gen reseptor estrogen ($ER\beta$). mikroRNA let-7b juga diketahui memiliki hubungan dengan produksi aromatase dan memiliki efek pleiotropik terhadap endometriosis.

Tujuan: Menjelaskan keterlibatan polimorfisme gen CYP19, gen reseptor estrogen β ($ER\beta$), mikroRNA Let7-b pada folikulogenesis serta kualitas oosit dan pengaruhnya terhadap kadar estradiol (E2) pada pasien endometriosis

Metode Penelitian: Penelitian merupakan studi *case control*. Sampel penelitian merupakan pasien endometriosis dan non endometriosis dari klinik Infertilitas Permata Hati RSUP Dr. Sardjito. Pemeriksaan polimorfisme gen CYP 19 dan $ER\beta$ dilihat melalui hasil PCR, miRNA let-7b melalui hasil qRT-PCR, dan folikulogenesis dilihat melalui USG transvaginal.

Hasil: Dalam penelitian ini kadar estradiol (E2) pada kelompok endometriosis memiliki median yang lebih tinggi dibandingkan kelompok kontrol walaupun secara statistik tidak terdapat perbedaan bermakna. Genotipe polimorfisme (TTTA)_n gen CYP-19 antara kelompok endometriosis dengan kelompok kontrol tidak bermakna secara statistik ($p>0,05$). Ditemukan polimorfisme insersi/delesi TCT pada gen CYP 19 dan terdapat perbedaan signifikan ($p<0,05$) antara pasien endometriosis dan kontrol. Hasil analisis polimorfisme gen $ER\beta$ adalah berupa *single nucleotide polymorphism* (SNP) A/G, dimana antara kelompok endometriosis dengan kelompok kontrol tidak bermakna secara statistik ($p>0,05$). Tingkat ekspresi miRNA let-7b 3p dan 5p menunjukkan kecenderungan penurunan (*downregulated*) pada pasien dengan endometriosis dengan nilai *fold-change* 0,9265 dan 0,7684. Terdapat perbedaan signifikan rerata miRNA let-7b 5p antara kasus dan kontrol ($p<0,05$). Terdapat perbedaan signifikan jumlah folikel, diameter folikel di ovarium kanan maupun kiri pada hari ke-3, dan diameter ovarium kanan pada hari evaluasi ($p<0,05$) antara pasien endometriosis dan kontrol. Tidak ditemukan perbedaan yang signifikan antara folikulogenesis hari ke-3 dan folikulogenesis evaluasi dengan status endometriosis berdasarkan klasifikasi Enzian. Tidak ditemukan perbedaan signifikan pada polimorfisme CYP19 dan kadar miRNA let-7b terhadap kadar estradiol, namun terdapat perbedaan signifikan pada polimorfisme SNP *type* gen $ER\beta$ A/G terhadap kadar estradiol subjek penelitian ini ($p<0,05$)

Kesimpulan: Terdapat perbedaan signifikan antara polimorfisme Ins/Del intron 4 gen CYP 19, ekspresi mikroRNA Let-7b 5p, kuantitas folikulogenesis pada hari ke-3 antara pasien endometriosis dan kontrol. Terdapat perbedaan signifikan polimorfisme SNP *type* gen $ER\beta$ terhadap kadar estradiol.

Kata Kunci: CYP19, $ER\beta$, MikroRNA Let-7b, Endometriosis, Estradiol, Folikulogenesis

CORRELATION BETWEEN ER β GENE POLYMORPHISM, VARIABLE TANDEM REPEAT NUMBER (VNTR) INTRON 4 CYP 19 GENE, AND MICRO-RNA LET-7b RELATED TO ESTRADIOL (E2) LEVELS AND FOLLICULOGENESIS IN ENDOMETRIOSIS PATIENTS

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ABSTRACT

Background: Endometriosis is a hormone-dependent disease that affects approximately 5-10% of reproductive-aged women, characterized by the presence of tissue resembling the glands and stroma of the endometrium outside the uterine cavity. About 25-50% of couples dealing with infertility have endometriosis. Endometriosis impacts fertility through various mechanisms, including disruptions in folliculogenesis. Folliculogenesis requires synergistic cooperation between estrogen, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Changes in estradiol production mediated by cytochrome P450 aromatase can result from polymorphisms in the CYP19 gene and estrogen receptor (ER β) gene. The microRNA let-7b is also known to be associated with aromatase production and has pleiotropic effects on endometriosis.

Objective: To elucidate the involvement of CYP19 gene polymorphisms, estrogen receptor β (ER β) gene, microRNA let-7b in folliculogenesis, as well as oocyte quality and their influence on estradiol (E2) levels in endometriosis patients.

Methodology: The study is a case-control study. The research sample includes endometriosis and non-endometriosis patients from the Infertility Clinic at Permata Hati RSUP Dr. Sardjito. Polymorphism examination of the CYP19 and ER β genes is conducted through PCR, miRNA let-7b through qRT-PCR, and folliculogenesis is observed through transvaginal ultrasound.

Results: In this study, estradiol levels (E2) in the endometriosis group have a higher median than the control group, although there is no statistically significant difference. The polymorphism genotype (TTTA)_n of the CYP-19 gene between the endometriosis and control groups is not statistically significant ($p>0.05$). A TCT insertion/deletion polymorphism is found in the CYP19 gene, and there is a significant difference ($p<0.05$) between endometriosis patients and controls. The ER β gene polymorphism analysis reveals a single nucleotide polymorphism (SNP) A/G, where there is no statistically significant difference between the endometriosis and control groups ($p>0.05$). The expression levels of miRNA let-7b 3p and 5p show a downward trend in endometriosis patients with fold-change values of 0.9265 and 0.7684. There is a significant difference in the mean miRNA let-7b 5p between cases and controls ($p<0.05$). Significant differences are found in the number of follicles, follicle diameter in the right and left ovaries on day 3, and the right ovarian diameter on the evaluation day ($p<0.05$) between endometriosis patients and controls. No significant differences are found in folliculogenesis on day 3 and folliculogenesis evaluation based on the Enzian classification. No significant differences are found in CYP19 polymorphism and miRNA let-7b levels regarding estradiol, but there is a significant difference in ER β gene SNP type concerning the estradiol levels in this study ($p<0.05$).

Conclusion: There are significant differences in the Ins/Del intron 4 polymorphism of the CYP19 gene, expression of miRNA Let-7b 5p, and the quantity of folliculogenesis on day 3 between endometriosis patients and controls. There is a significant difference in the ER β gene SNP type polymorphism concerning estradiol levels.

Keywords: CYP19, ER β , MicroRNA Let-7b, Endometriosis, Estradiol, Folliculogenesis