Hubungan Kadar Kisspeptin, Neurokinin B dan Dinorfin terhadap Rasio LH/FSH serta Polimorfisme dan Metilasi DNA Gen KISS1 pada Pasien Sindrom Ovarium Polikistik Nir-obese = Relationship of Kisspeptin, Neurokinin B and Dynorfin Levels to the LH/FSH Ratio and Polymorphism and DNA Methylation of the KISS1 Gene in Lean Polycystic Ovary Syndrome Patients

Gita Pratama, author

Abstrak

Sindrom ovarium polikistik (SOPK) adalah kelainan endokrin yang paling banyak ditemukan dan memengaruhi 5–20% perempuan pada usia reproduksi. Kadar LH dan rasio LH dengan FSH lebih tinggi pada pasien SOPK nir-obese dibandingkan obese. Sekresi LH dan FSH dipengaruhi oleh pulsatilitas GnRH neuron GnRH di hipotalamus. Kisspeptin diduga sebagai regulator utama sekresi GnRH, sedangkan neurokinin B (NKB) dan dinorfin mengatur sekresi kisspeptin neuron KNDy. Namun, patofisiologi gangguan neuroendokrin pada pasien SOPK nir-obese belum dipahami sehingga diperlukan penelitian untuk mengetahui hubungan kadar kisspeptin, NKB dan dinorfin dengan rasio LH/FSH serta hubungannya dengan polimorfisme dan metilasi DNA gen KISS1. Penelitian ini menggunakan desain potong lintang di Klinik Yasmin, RSUPN dr. Cipto Mangunkusumo Kencana dan klaster Human Reproduction, Infertility and Family Planning IMERI UI pada bulan September 2021 sampai Januari 2023 dengan subjek penelitian 120 pasien SOPK nir-obese. Dilakukan pengukuran parameter komposisi tubuh, skor Ferriman-Gallwey dan pemeriksaan kadar FSH, LH, rasio LH/FSH, kisspeptin, NKB, dinorfin, leptin, adiponektin, AMH, glukosa darah puasa, insulin puasa, HOMA-IR, testosteron, dan SHBG. Dilakukan analisis polimorfisme rs4889 dan rs5780218 gen KISS1 danmetilasi DNA gen KISS1. Analisis bivariat dan analisis jalur dilakukan untuk mengetahui hubungan antarvariabel. Terdapat hubungan negatif antara dinorfin dengan kisspeptin, sedangkan kadar NKB tidak berhubungan dengan kisspeptin. Tidak ada hubungan kadar kisspeptin dengan rasio LH/FSH; namun, dinorfin berhubungan positif dengan rasio LH/FSH pada pada analisis bivariat maupun analisis jalur. Kadar AMH berhubungan dengan rasio LH/FSH baik pada kedua analisis. Pada analisis jalur, terdapat hubungan positif antara HOMA-IR dengan FAI dan antara FAI dengan AMH. Pada analisis polimorfisme gen KISS1tidak terdapat hubungan antara frekuensi genotipe maupun frekuensi alel rs4889 dan rs5780218 gen KISS1 SOPK nir-obese dengan kadar kisspeptin dan rasio LH/FSH. Tidak terdapat perbedaan bermakna antara metilasi DNA dengan kadar kisspeptin dan rasio LH/FSH. Terdapat hubungan antara peningkatan dinorfin dengan penurunan kadar kisspeptin. Hubungan dinorfin dengan rasio LH/FSH kemungkinan disebabkan oleh rendahnya kadar progesteron. Peningkatan AMH berhubungan dengan peningkatan rasio LH/FSH pada pasien SOPK nir-obese. AMH merupakan variabel perantara HOMA-IR dan FAI terhadap rasio LH/FSH. Tidak ada hubungan polimorfisme rs4889 dan rs5780218 gen KISS1 serta metilasi DNA gen KISS1 dengan kisspeptin dan rasio LH/FSH pada pasien SOPK nir-obese. Perlu penelitian lebih lanjut untuk mengetahui potensi terapi terhadap dinorfin dan AMH dalam tatalaksana pasien SOPK nir-obese.

.....Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting 5–20% of reproductive age women. LH levels and LH/FSH ratios are higher in lean PCOS patients than in obese

patients. LH and FSH secretion are influenced by GnRH pulsatility of GnRH neurons in the hypothalamus. Kisspeptin is thought to be the main regulator of GnRH secretion, whereas neurokinin B (NKB) and dynorphin regulate kisspeptin secretion in KNDy neurons. However, the pathophysiology of neuroendocrine disorders in lean PCOS patients is not well established. This study aims to determine the relationship between kisspeptin, NKB and dynorphin levels with the LH/FSH ratio and the relationship between polymorphism and DNA methylation of the KISS1 gene. This study used a cross-sectional design at the Yasmin Clinic, RSUPN dr. Cipto Mangunkusumo Kencana and the IMERI UI Human Reproduction, Infertility and Family Planning cluster from September 2021 to January 2023 with 120 lean PCOS patients as subjects. Body composition parameters, Ferriman-Gallwey score, FSH, LH, LH/FSH ratio, kisspeptin, NKB, dynorphin, leptin, adiponectin, AMH, fasting blood glucose, fasting insulin, HOMA-IR, testosterone, and SHBG were measured. Analysis of KISS1 gene polymorphisms of rs4889 and rs5780218 and DNA methylation were performed. Bivariate analysis and path analysis were performed to determine the relationship between variables. There was a negative relationship between dynorphin and kisspeptin, while NKB levels was not related to kisspeptin. There was no relationship between kisspeptin levels and the LH/FSH ratio; however, dynorphin was positively related to the LH/FSH ratio in both bivariate and pathway analysis. AMH levels was positively correlated with the LH/FSH ratio in both analyses. In path analysis, there is a positive relationship between HOMA-IR and FAI as well as between FAI and AMH. In the analysis of the KISS1 gene polymorphism, there was no significant difference between the genotype and allele frequencies of rs4889 and rs5780218 of the lean KISS1 gene with kisspeptin levels and the LH/FSH ratio. There was no significant difference between DNA methylation with kisspeptin levels and LH/FSH ratio. There is a relationship between the increased dynorphin and decreased kisspeptin levels. The association of dynorphins with the LH/FSH ratio may be due to low levels of progesterone. Increased AMH is associated with increased LH/FSH ratio in lean PCOS patients. AMH is an intermediary variable between HOMA-IR and FAI with the LH/FSH ratio. There is no relationship between the rs4889 and rs5780218 KISS1 gene polymorphisms and KISS1 gene DNA methylation with kisspeptin and the LH/FSH ratio in lean PCOS patients. Further research is required to determine the therapeutic potential of dynorphin and AMH in the management of lean PCOS patients.