Gene expression profiling of hyaluronic acid synthetase 2 (HAS2), prostaglandin-endoperoxide synthase 2 (PTGS2) and gremlin 1 (GREM1) in cumulus cells among women with diminished ovarian reserved (DOR)

Mohd Faizal Ahmad[1], Marjanu Hikmah Elias[2], Norazilah Mat Jin[3], Muhammad Azrai Abu[1], Saiful Effendi Syafruddin[4], Ani Amelia Zainuddin[1], Nao Suzuki[5], Abdul Kadir Abdul Karim[1]

[1]Advanced Reproductive Centre (ARC) HCTM UKM, Department of Obstetrics & Gynecology, Faculty of Medicine, National University of Malaysia, Kuala Lumpur, Malaysia, [2]Faculty of Medicine & Health Sciences, Universiti Sains Islam Malaysia, Nilai, Negeri Sembilan, Malaysia, [3]Department of Obstetrics & Gynecology, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Selangor Branch, Sungai Buloh Selangor, Malaysia, [4]Medical Molecular Biology Institute, National University of Malaysia, Kuala Lumpur, Malaysia, [5]Department of Obstetrics & Gynecology, St Marianna School of Medicine, Kanagawa, Kawasaki, Japan

ABSTRACT

Introduction: The management of women with diminished ovarian reserve (DOR) in the field of in-vitro fertilization (IVF) is challenging. Elevated cycle cancellation due to poor ovarian response to stimulation with failure of fertilization is often observed. Thus, molecular insight of cumulus cell (CCs) gene expression reflecting oocyte quality should be elucidated to enhance the understanding and propose an improved management strategy. **Materials and Methods:** The prospective cohort study was conducted in a university hospital setting, considering non-invasive CC gene expression for GREM1, HAS2 and PTGS2. Quantitative polymerase chain reaction with normalization was performed using housekeeping genes, specifically RRS18 and GAPDH. **Results:** A total of 40 women were recruited: 20 for normal ovarian reserve and 20 for the DOR group. The women with DOR are older than those with NOR (37.5 ± 5.021 vs. 32.5 ± 3.873) and with anti-Mullerian hormone levels of 4.64 (2.13-6.59) compared with that of NOR at 22.09 (15.94-26.75). The majority of women in both groups had unexplained infertility (NOR; 35%, DOR; 45%). Age was found to be significantly associated with the level of ovarian reserve ($p<0.05$). All the genes amplified with single melting curves were observed. The expression of all genes was consistently downregulated in women with DOR compared with that with NOR. The expression levels of GREM1 and HAS2 were significantly downregulated ($p=0.0061$) compared with that of PTGS2 ($p=0.4286$). **Conclusion:** Overall, our finding was consistent with the current evidence, indicating lower expression of GREM1, HAS2 and PTGS2 genes in CCs among women with DOR. Thus, a new strategy, namely, adjuvant supplementation, specific media formulation, or new stimulant regime can be developed to achieve improved IVF outcomes among women with DOR in the future.