A-124In-vitro study on the effect of ulipristal acetate on human embryo implantation using a trophoblastic spheroid and endometrial cell co-culture model

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Objectives: Ulipristal acetate (UPA), a selective progesterone receptor modulator, has been introduced for use in emergency contraception. The main mechanism of action is inhibiting or delaying ovulation. Whether UPA can have secondary action by inhibiting implantation is still uncertain. The present study examined the effect of UPA on human embryo implantation using an in-vitro human trophoblastic spheroid and endometrial cell co-culture model.

Method: We studied the effect of UPA on implantation using a trophoblastic spheroids-endometrial cell attachment assay. The JAr (human choriocarcinoma) and Ishikawa (human endometrial adenocarcinoma) cell lines were treated with graded concentrations of UPA (0, 0.04, 0.4 and 4μM) for 24 hours. We took the peak serum drug level after oral administration of UPA 30 mg, i.e. 0.4 μM, as the pharmacological concentration, and our experimental range covered ten-times below and above this. After treatment, the JAr cells were trypsinized and gently shaken at 106rpm overnight to form spheroids of 100-150mm size, which were used as the embryo surrogate. A confluent monolayer of the Ishikawa cells was used as the endometrium surrogate, onto which the spheroids were seeded and cultured for 1 hour at 37^{o}C under 5% CO_2. The co-culture was then shaked at 140rpm for 10 minutes to remove any unattached spheroids. The number of attached JAr spheroid was then counted under light microscope. Attachment rate was defined as the ratio of the number of attached spheroids to the total number seeded. The experiment was also repeated using cultured primary human endometrial cells (aspirated 7 days after the LH surge) as the endometrium surrogate, which was co-cultured with trophoblastic spheroids for 3 hours after treating the respective cells with 4μM UPA. The results were pooled from 19 and 7 independent repeats for the Ishikawa and primary endometrial cell experiments respectively.

Results: In the Ishikawa experiments, there was no significant difference in the trophoblastic spheroid attachment rate after treatment with UPA at 0 (93.0%), 0.04 (93.6%), 0.4 (93.4%) and 4 (91.4%) μM concentrations ($p > 0.05$). In the primary endometrial cell experiments, again no significant difference was observed in trophoblastic spheroid attachment rate between the treatment group (UPA 4μM, 42.1%) compared to the control (without UPA treatment, 48.3%, $p > 0.05$). Significant suppression of spheroid attachment rate ($p < 0.001$) was observed in the positive controls which were set up with methotrexate 5μM treatment.

Conclusions: UPA at pharmacological concentration used for emergency contraception may not have inhibitory effect on embryo implantation.