Decidualization, essential for embryo implantation, is the differentiation and proliferation of endometrial stromal cells into decidual cells during the mid-late secretory phase of the menstrual cycle. Although several molecules and pathways resulting in decidualization have been identified, the sequences of these pathways and direct relationships in the process remain unknown. The importance of prostaglandins (PGs) in initiation and maintenance of decidualization and implantation has been previously identified. Cyclooxygenase (COX), the rate limiting enzyme in PG synthesis exists in two isoforms, COX-1 and COX-2. These enzymes catalyze the conversion of arachidonic acid into a variety of PGs. Previous studies have demonstrated that COX-2 expression increases during the window of implantation, and most observations point to endometrial epithelial cells as the main source of PGs. We have determined that both COX-1 and COX-2 and PGs, PGE2 and PGF2 alpha are upregulated during in vitro decidualization suggesting the decidual cell itself is another source of PGs, which could effectively mediate downstream events. The aim of the present study was to further characterize the PG pathway in stromal cells.

Immortalized human endometrial stromal cells (T-HESCs) were cultured for 8 days in Dulbecco's Modified Eagles Medium - 0.5% charcoal stripped fetal bovine serum with 1 microM medroxyprogesterone acetate (MPA), 10 nM estradiol (E2) and .25mM cyclic AMP (cAMP) with and without 0.1 microM Indomethacin, a non-selective COX inhibitor. Markers of decidualization, prolactin (Prl), insulin growth factor binding protein 1 (IGFBP-1) and bone morphogenic protein 2 (BMP-2), and COX-1 were measured using qPCR (quantitative or real-time PCR). COX-2 was measured by RT-PCR (reverse-transcription-PCR). PGE2 and PGF2 alpha levels in the culture media were measured by enzyme immunoassay (EIA).

In order to determine that endometrial stromal cell decidualization was attained with E2, MPA and cAMP, real-time PCR was used to measure known markers of decidualization. Prl, IGFBP-1 and BMP-2 levels were significantly increased in treated cells compared with controls (untreated) by 12,000-, 5,000- and 6-fold respectively. COX-1 mRNA had an 8-fold induction and COX-2 mRNA levels qualitatively increased following in vitro decidualization. PGE2 and PGF2 alpha are products of COX enzyme activity, levels were determined in culture media from decidualized (treated) and undecidualized (untreated) cells. EIA quantitation confirmed that PGE2 and PGF2 alpha levels are increased in treated cells. Following in vitro decidualization, markers of decidualization were not effected by Indomethacin and the inhibition of PGE2 and PGF2 alpha.

These results indicate that PGE2 and PGF2 alpha are produced by decidualized endometrial stromal cells. The exact role of PGs in the decidualization process remains unknown but further studies may
elicit their primary purpose and subsequent downstream effects. Continual discovery of biomarkers of endometrial function may become the basis for diagnosing causes of infertility.