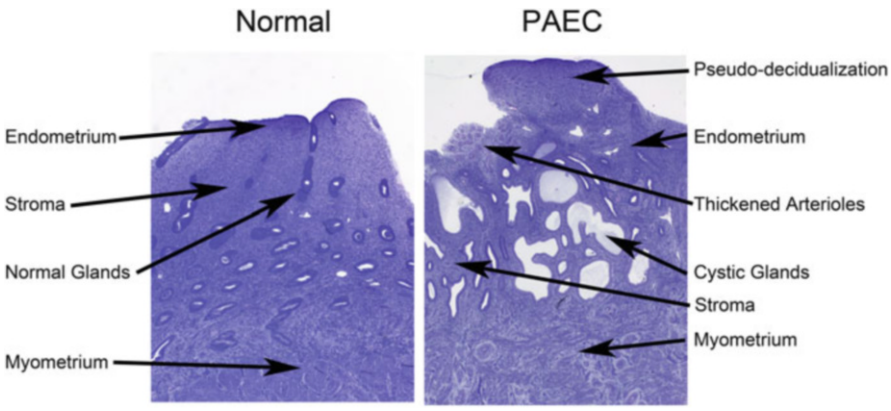

Fig. 1 Photomicrograph of H&E stained endometrium of rhesus macaques. Normal endometrium shows typical mid-cycle morphology with tubular glands. PAEC was caused by treatment with low-dose PRA. Note the cystic glands, hypertrophied spiral arteries, and pseudodecidualized stroma in the upper 1/3 of the endometrium

with low-dose PRAs often results in endometrial thickening. Resultant histology presents as cystic dilatation of endometrial glands, pseudo-decidualization, and thickening of the spiral arterioles. Collectively these changes have been termed "PGR modulator-associated endometrial change" (PAEC) (Williams et al. 2007). Our early studies in NHPs failed to detect PAECs and reported that PRA treatments resulted in endometrial thinning (Brenner et al. 2002; Chwalisz et al. 2000b). This outcome appears to be the result of the high (menstruation inducing) doses of PRA administered during these trials (Slayden et al. 1993; Slayden and Brenner 1994; Wolf et al. 1989). Recent experiments with low-dose PRAs in cycling NHPs demonstrate glandular cysts with significant secretion and spiral artery morphology similar to PAEC in women. Figure 1 shows a low-power image of rhesus macaque endometrium showing PAEC after treatment with low-dose PRA. While there is no evidence that PAEC in women leads to atypical hyperplasia or endometrial carcinoma, the striking change in endometrial appearance can be alarming and has delayed development of effective progesterone receptor modulator-based contraceptives.

Treatment with PRAs induced striking increases in endometrial ERα, PR, and AR. AR in particular was elevated in both the endometrial stroma and in the glandular epithelium of the functionalis zone. The mechanism through which PRA suppresses E_2 effects on cell proliferation has not been fully explained (Slayden et al. 1993, 1998, 2001a; Slayden and Brenner 1994). Hodgen's laboratory reported that RU 486 treatment resulted in excessively elevated ESR, and they suggested that elevated ESR could produce a super-estrogenized state (Neulen et al. 1990, 1996). Since super-physiological doses of E_2 are reported to be inhibitory to endometrial growth (Neulen et al. 1987), then overexpression of ESR could result in a similar antiproliferative action. However, as mentioned above, PRA