menstruation. Thereafter, withdrawal of P_4 stimulates endometrial expression of matrix metalloproteinase (MMP) enzymes in the upper endometrial zones (Rudolph-Owen et al. 1998; Slayden and Brenner 2006). The MMPs are capable of degrading the extracellular matrix and are the primary effectors resulting in dissociation of functionalis zone tissues.

The vervet also menstruates at the end of each cycle, but menstruation in this species is very light requiring vaginal swabbing for detection (Carroll et al. 2007). Much of our understanding of the anatomical events of menstruation was described by Markee (Markee 1940, 1948, 1950) who visualized menstruation in macaque with endometrial autografts placed in the anterior chamber of the eye. In several studies we transplanted the endometrium to subcutaneous and intra-abdominal ectopic sites of macaques. Sequential treatment with artificial cycle capsules releasing E_2 and P_4 in animals bearing these "autografts" results in histological changes and menstruation within the grafts similar to the endometrium in situ (Brenner et al. 1996).

We have extended the use of artificial cycles to specifically study menstruation (Rudolph-Owen et al. 1998; Slayden and Brenner 2006). Withdrawal of P_4 at the end of the cycle (with or without withdrawal of E_2) results in expression of endometrial matrix metalloproteinases that act to breakdown the endometrium during menstruation.

The timing of menstruation and the abundance of menstrual spotting and breakthrough bleeding can be assessed in monkeys trained to present for sampling by vaginal swab (Slayden et al. 2007). Monkeys can also be trained to accept vaginal tampons for the collection of menstrual flow (Shaw, Jr. et al. 1972), and the tampons analyzed for menstrual blood. This technique has been used to assess therapies on menstrual blood loss (Brenner and Slayden 2012).

4 Steroid Receptor Antagonists

Steroid hormones induce their effects on tissues via interactions with steroid-specific receptors including estrogen receptors (ESR), progesterone receptors (PGR), and androgen receptors (AR). Studies on hormonal regulation of steroid receptor levels have been accomplished in artificially cycled NHPs using classical binding studies (West et al. 1987), immunohistochemistry (Slayden and Brenner 2004), and molecular methodologies (Keator et al. 2012). Immunohistochemical studies strongly support older work that quantified ESR and PGR by binding assays. Localization of these receptors is tightly correlated with morphological changes during the cycle (Slayden and Brenner 2004). Expression of these receptors, therefore, both indicates responsiveness to hormone stimulation and provides a sensitive marker for hormone action. Treatment of the E_2-primed endometrium with P_4, reduces ESR-1, PGR, AR, and membrane-associated progesterone receptors (Keator et al. 2012).

Many studies have treated NHPs with various steroid receptor antagonists including both estrogen receptor agonists (ERA) (Ethun et al. 2012) and progesterone receptor antagonists (PRA) (Chwalisz et al. 2006). Treatments have included