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Pharmacological actions of progestins to inhibit cervical ripening and prevent delivery depend upon their properties, the route of administration and the vehicle

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Measurements of cervical light-induced fluorescence (LIF) in pregnant, non-treated animals show (Figure 7) a continuously decreasing photon count throughout pregnancy, reaching lowest values at term, and reversal postpartum (pp). In accordance to the results obtained with the collascope, the surface area (SA) of the cervix in normal pregnancy is continuously increasing throughout gestation and progressively reversing in the pp period (Figure 9). Before any treatment, LIF and SA at day 13 show no significant differences between the treated groups and the control groups. LIF is significantly higher and increases in SA are lower in the s.c. P4 group compared with vehicle controls for any day of gestation (Figures 10 and 11) and delivery is completely blocked. There are no significant differences, neither of the LIF nor of the SA, between the vaginal P4 group and vehicle controls at any time in gestation (Figures 12 and 13) and vaginal P4 failed to inhibit delivery (Figure 21). LIF is significantly higher in the 17P treated group (until day 19 only) compared with vehicle controls (Figure 14) and increases in SA are lower, but again only until day 19 ($P < 0.05$) (Figure 15). This treatment does not delay delivery ($P < 0.05$) (Figure 20). After treatment with vaginal R5020 LIF is significantly higher (until day 19 only) compared with vehicle controls (Figure 16) and delivery is completely blocked (Figure 21). Injections of R5020 also completely block delivery (Figure 22). Oral P4 suspended in sesame oil or H_2O had no effect on the time of delivery. However, topical P4 in sesame oil (partially) and in fish oil (completely), but not in Replens® prolongs delivery ($P < 0.05$) (Figure 22). LIF is lower ($P < 0.05$) in the RU-486 treated group 24 and 72 hours after treatment compared with vehicle controls (Figure 17) and animals delivered preterm. RU-486 treatment increases the SA ($P < 0.05$) (Figure 18). P4 plasma levels decrease significantly in control animals from day 18 to day 21 of gestation (Figure 19). On day 21 of gestation P4 plasma levels are higher ($P < 0.05$) in s.c. P4 and topical P4 in fish oil, but not in vaginal P4 treated animals ($P > 0.05$) compared to control animals (Figure 19). This study demonstrates that LIF can be useful to assess quantitative changes in cervical ripening in vivo. In addition we introduce the optical evaluation of the cervix with measurements of the SA as a new and promising in vivo technique for the assessment of cervical changes that occur in pregnancy. This method contains a huge potential also in the context of other gynaecological conditions such as cervical dysplasias. These two innovative methods are not only helpful to observe the regular changes throughout pregnancy and pp, but also demonstrate preterm cervical changes and the success of pharmacotherapy and interventions. As shown in this study progestins have the ability to delay cervical ripening and delivery in term pregnant rats. Injections of P4 show (Figures 10 and 11) the longest effect on delaying cervical ripening in rats of all

compounds used. Cervical ripening is only attenuated until day 19 of gestation with R5020 and 17P in contrast to injection of P4 which also prevents further ripening on day 21 (Figures 10, 11, 14, 15 and 16). This indicates how properties of the progestins are significant factors affecting action. As only injected and topical but not vaginal or oral P4 delayed term delivery and forestalled the physiological P4 withdrawal, the importance of the route of administration is clearly demonstrated. The proposed concept of the "uterine first-pass effect" and focussed effects on the uterus after vaginal administration of P4 is not substantiated by this study. The choice of vehicle is a significant factor for the success of progestin treatment, as transdermal (topical) P4 in fish oil completely, in sesame oil only partially inhibits but in Replens®, a bioadhesive gel, not at all inhibits delivery (Figure 22). This indicates that Replens® does not release P4 as effectively as oil and this is also evaluated and confirmed for the vaginal route of administration. As the cervix manages to ripen at the end of pregnancy despite any treatment, inhibition of delivery, probably by non-genomic actions, by some progestin treatment (e.g. s.c. P4 and vaginal R5020) is not due to an unripe cervix, but must be due to the inhibition of uterine contractions. Parenteral and topical P4 treatment may be the preferred treatment to prevent preterm cervical ripening, the inhibition of uterine contractions and delivery as it does during term delivery. Action of progestins on the uterus and cervix to inhibit delivery depends upon many factors including the properties of the compound, route of administration, and the vehicle. These elements should be critically evaluated in clinical studies with progestins to inhibit preterm delivery. In addition, the use of progestins for other indications (such as menstrual cramps, uterine and other cancers, osteoporosis, contraception, amenorrhea and abnormal uterine bleeding, infertility, endometriosis, etc.) might be greatly improved by the methods described in this study.