

MAINTENANCE OF EARLY PREGNANCY IN RUMINANTS

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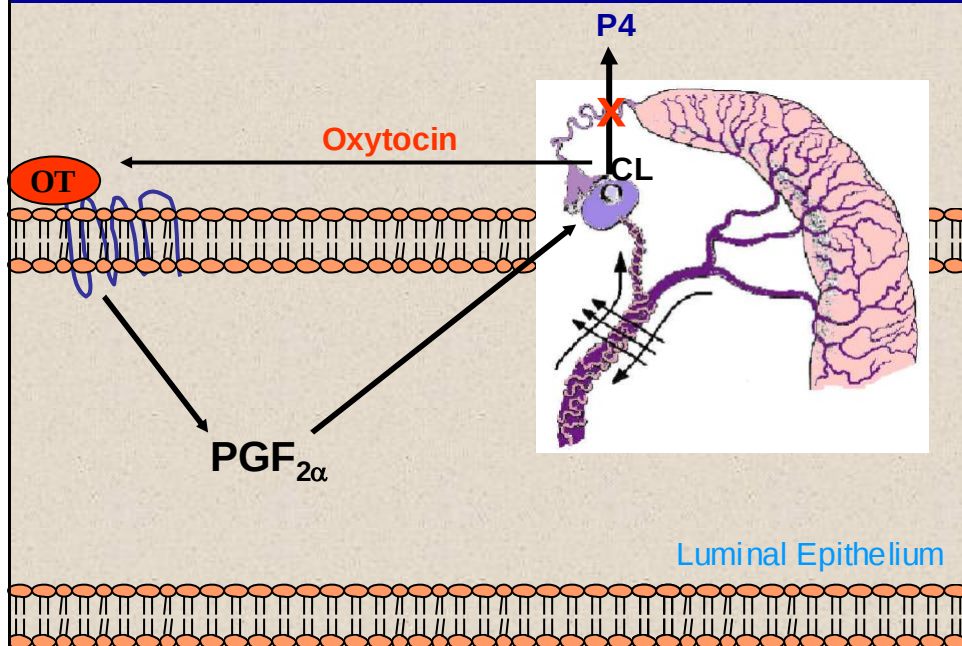
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INTRODUCTION

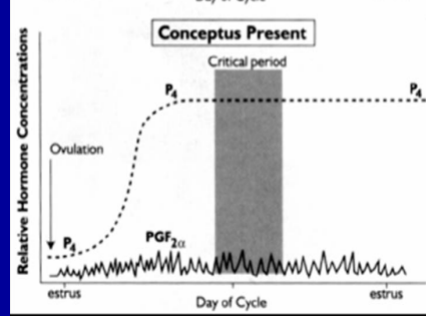
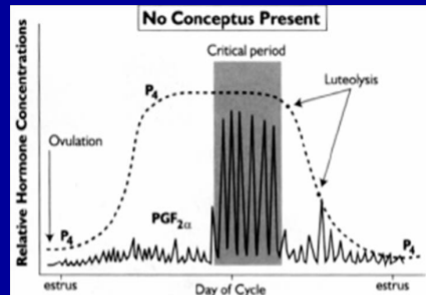
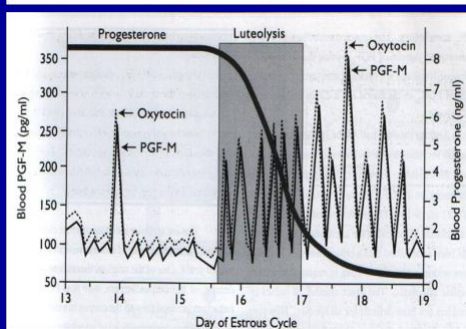
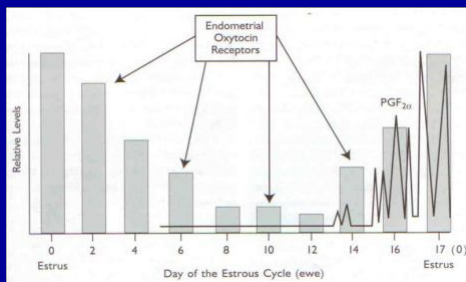
- Genetic pressure for milk production has decreased reproductive efficiency (Price et al., 1999).
- Conception rate: 65 % to 44 % 1975 to 1995, UK
66 % to 40 %, 1951 to 1999, USA
- A major factor contributing to low fertility in cattle is early embryonic mortality (Mann et al., 1999).
- Up to 40 % of total embryonic losses occur between Days 8 and 17 of pregnancy (Thatcher et al., 1994, 1995).

→ failures in maintenance of CL ?

LUTEOLYSIS

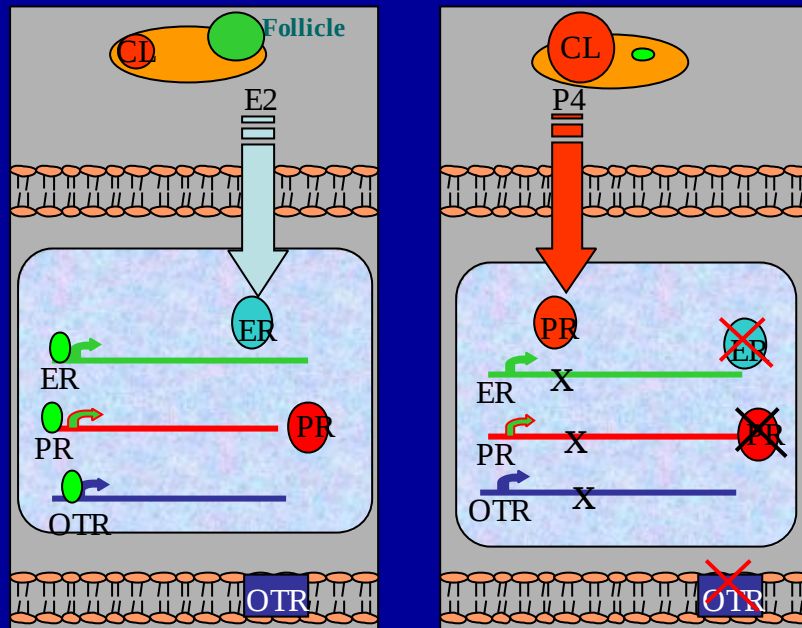


Hormonal Profile of Luteolysis

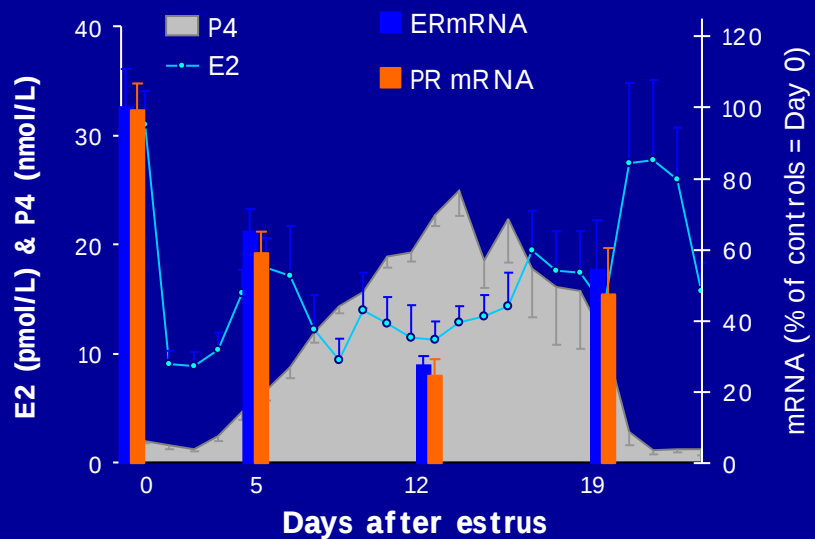


Senger PL. Pathways to Pregnancy and Parturition

Ovary-endometrium interaction during the luteolysis

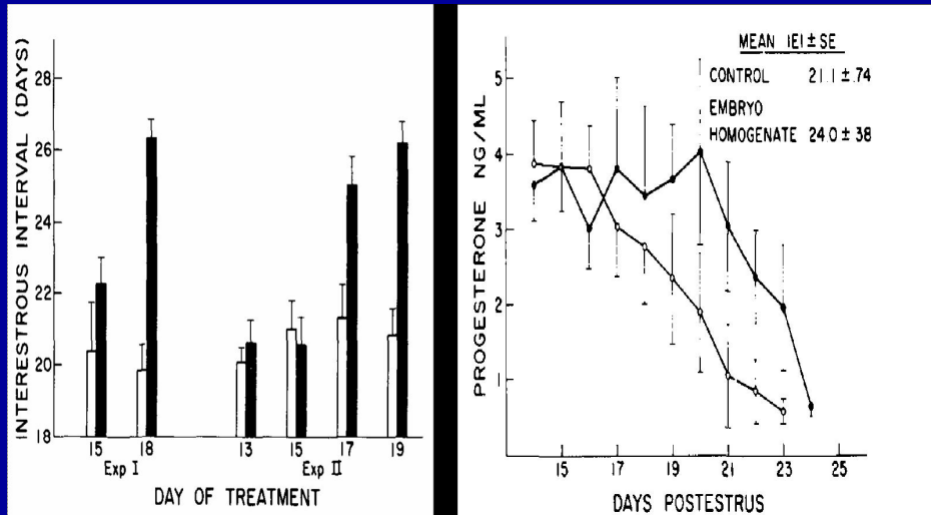


Endometrial mRNA expression of ER α and PR



Courtesy of Dr. Ana Meikle, University of Uruguay

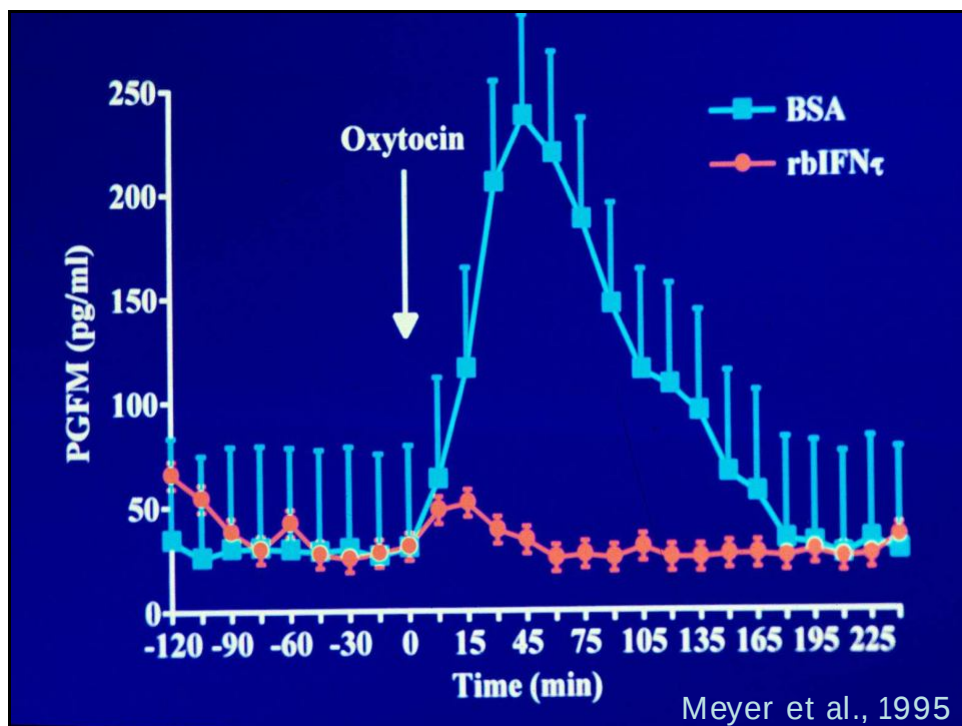
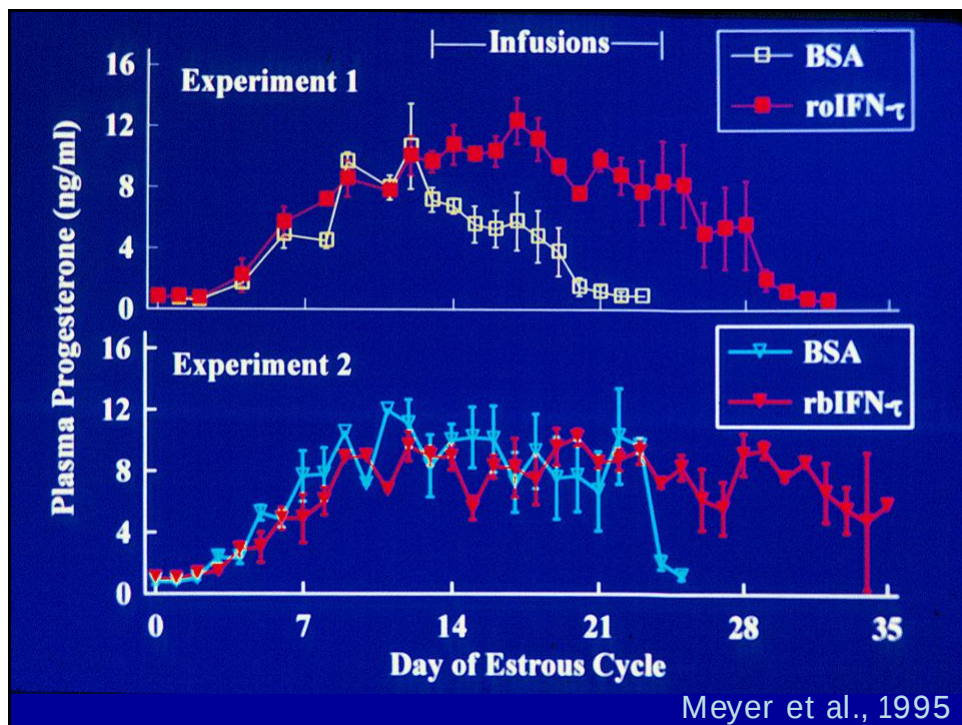
Effect of embryo removal and intrauterine infusion of embryonic homogenates on the lifespan of the bovine corpus luteum

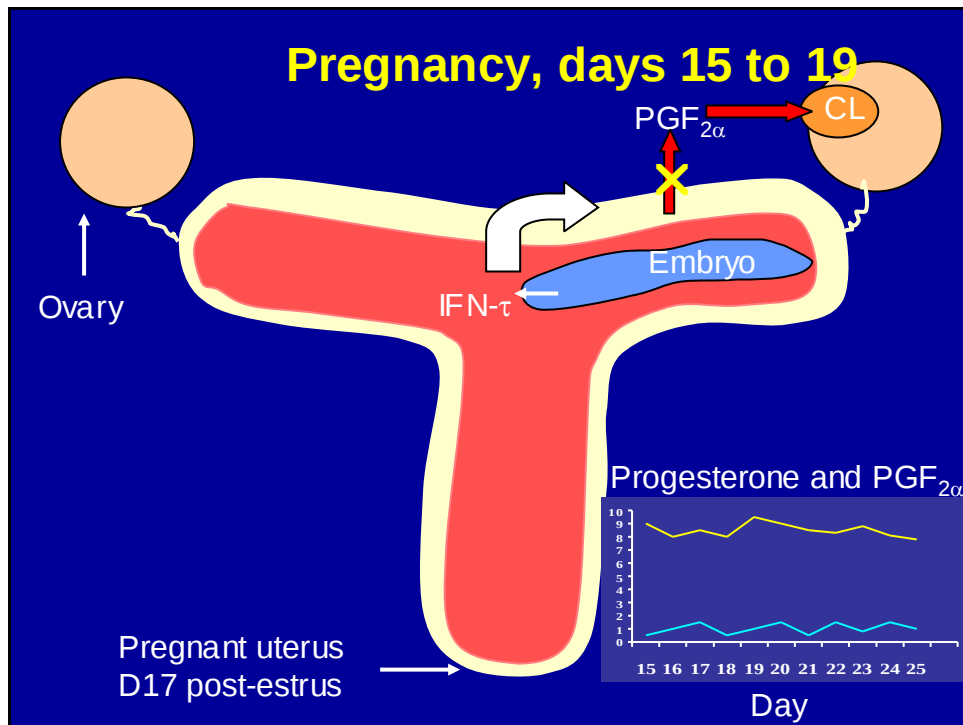


Northey and French, 1980

INTERFERON- τ

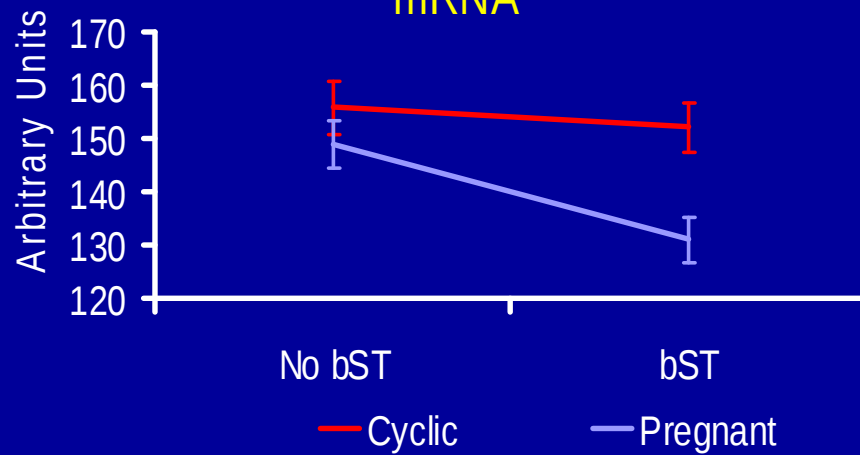
- The pregnancy recognition signal in ruminants.
- A cytokine belonging to type I Interferon family.
- Produced by mono-nucleate cells of trophoblast of the conceptus, detectable on day 12, peak around day 15 in sheep and 17 in cattle and still detectable by day 25 during early pregnancy in sheep and cattle (Roberts, 1996).
- Prevents viral infection and limits cell proliferation.
- Unlike other type I IFNs, IFN- τ is not induced by viral infection.





**Endometrial Gene
Expression
related to Luteolysis**

Endometrial Estrogen Receptor α mRNA

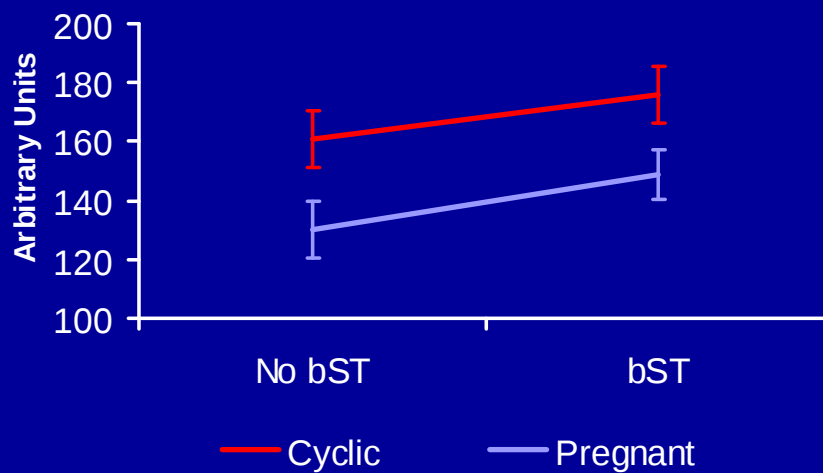


Cyclic vs Pregnant $P < 0.01$

No bST vs bST $P < 0.03$

Guzeloglu et. al., 2004a

Endometrial ER α Protein

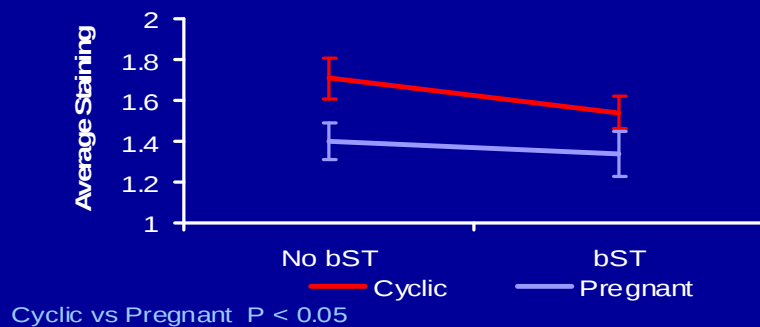
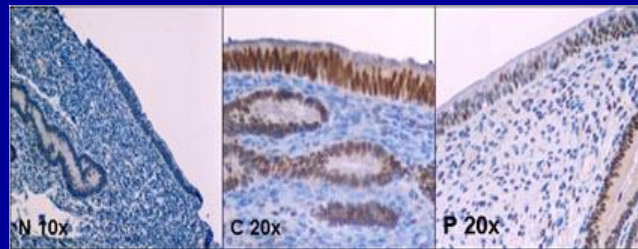


Cyclic vs Pregnant $P < 0.01$

No bST vs bST $P < 0.08$

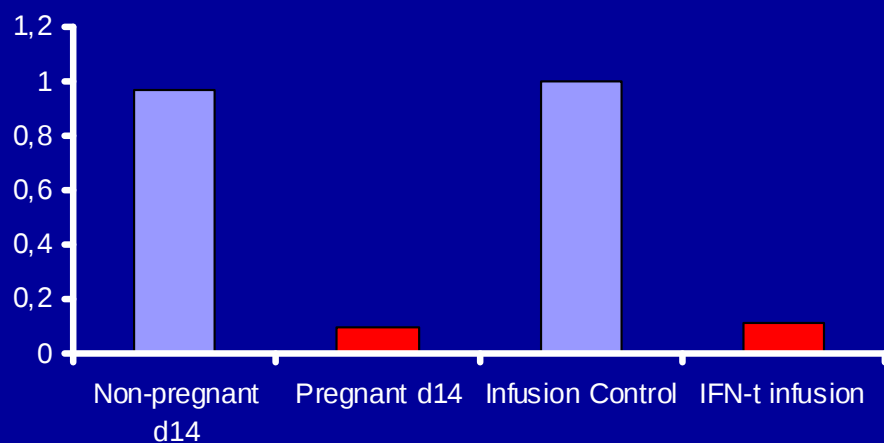
Guzeloglu et. al., 2004a

ER α Immunohistochemistry in Luminal epithelium



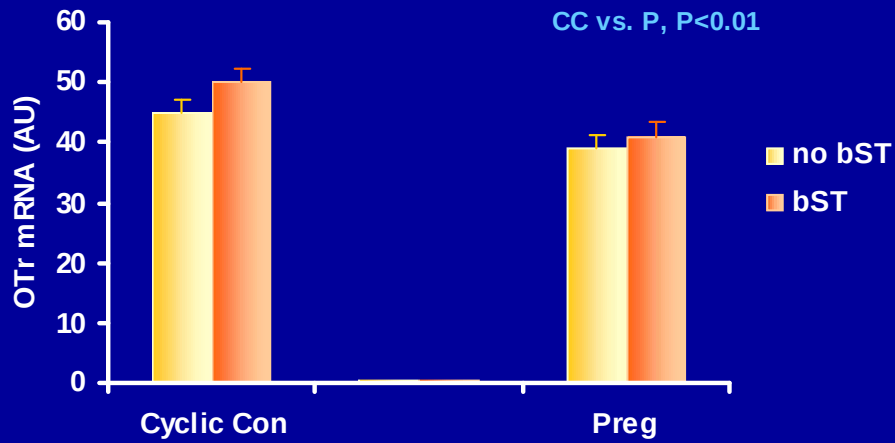
Guzeloglu et. al., 2004a

Both pregnancy and intrauterine INF- τ infusion decreased the mRNA expression of OTR in the endometrium in sheep



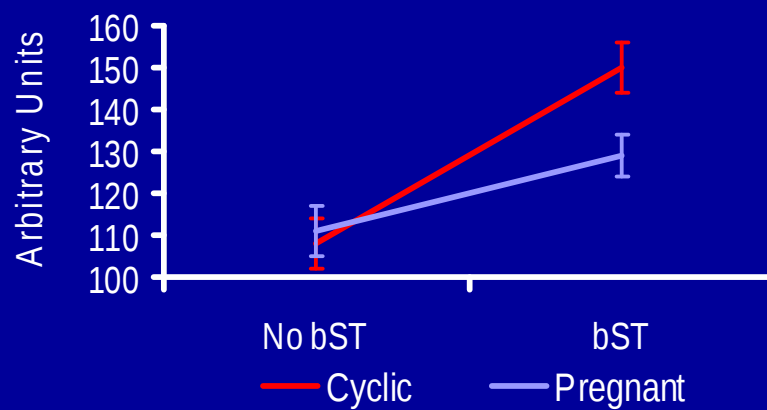
Chen et al., 2006

Endometrium OTR mRNA on D17 in Lactating Cows



Bilby et al., 2006

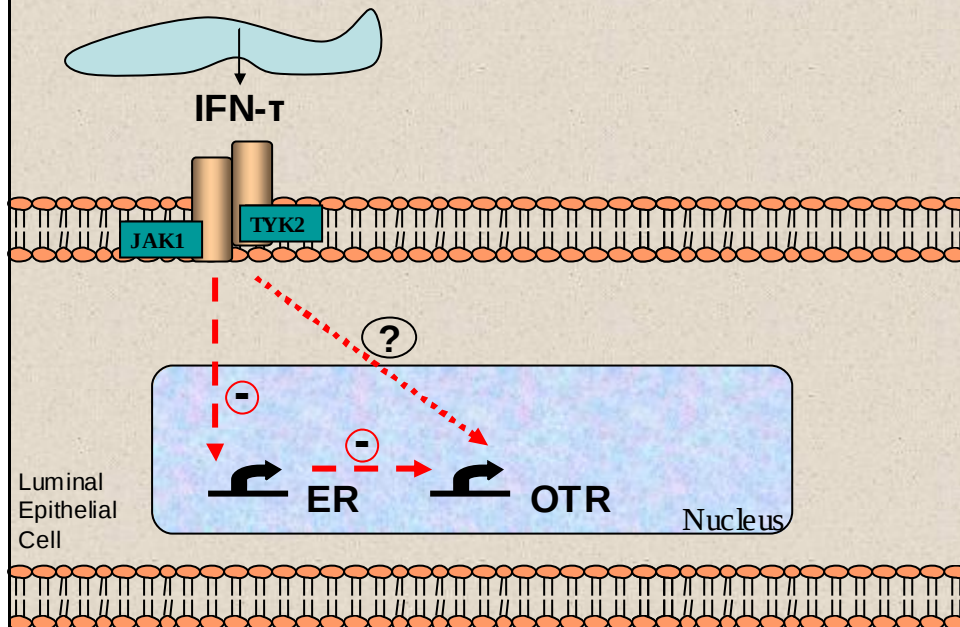
Endometrium OTR mRNA on D17 In Nonlactating Cows



bST vs No bST $P < 0.01$
Status x bST $P < 0.04$

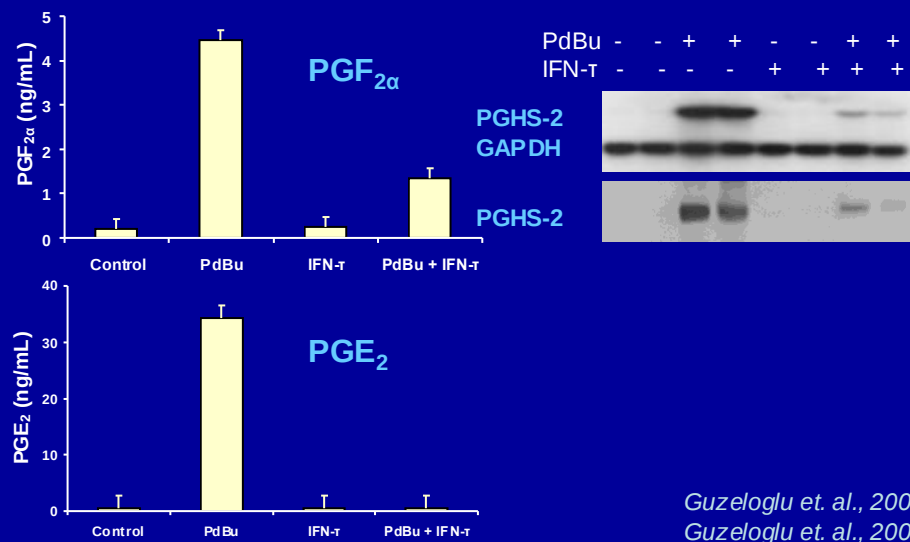
Guzeloglu et. al., 2004a

Inhibition of Luteolytic Pathway

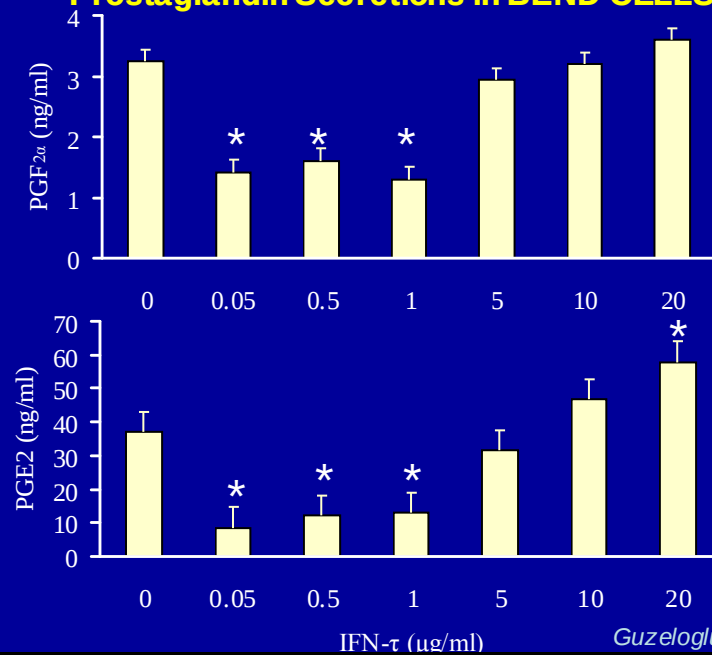


REGULATION of PGHS-2 and PROSTAGLANDIN SECRETION in BOVINE ENDOMETRIAL (BEND) CELLS

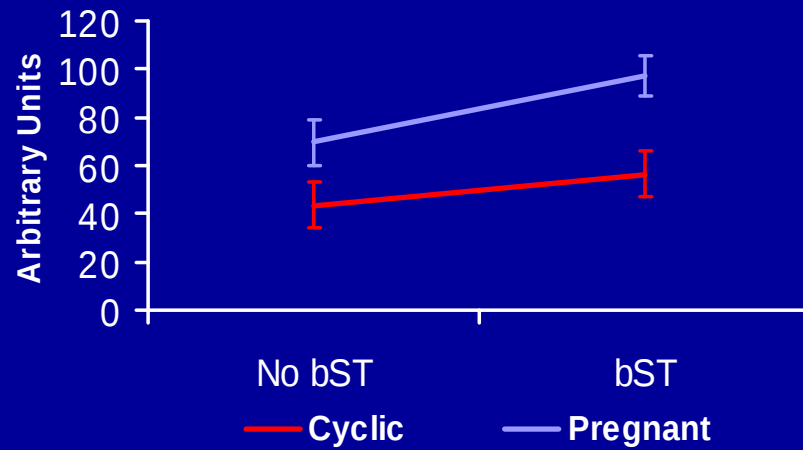
Effect of IFN- τ on PdBu-induced Prostaglandin Secretions and Expression of PGHS-2 in BEND CELLS



Effect of Different Doses of IFN- τ on PdBu-induced Prostaglandin Secretions in BEND CELLS



Endometrial PGHS-2 Protein

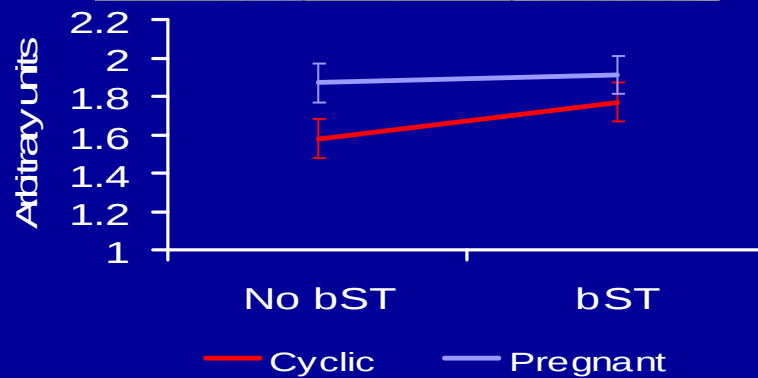
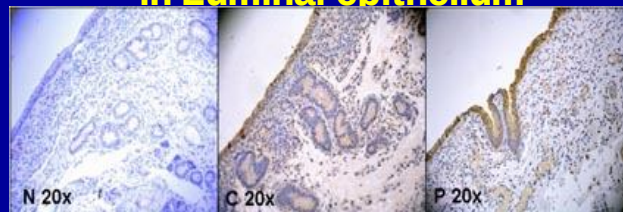


Cyclic vs Pregnant $P < 0.01$

No bST vs bST $P < 0.05$

Guzeloglu et. al., 2004a

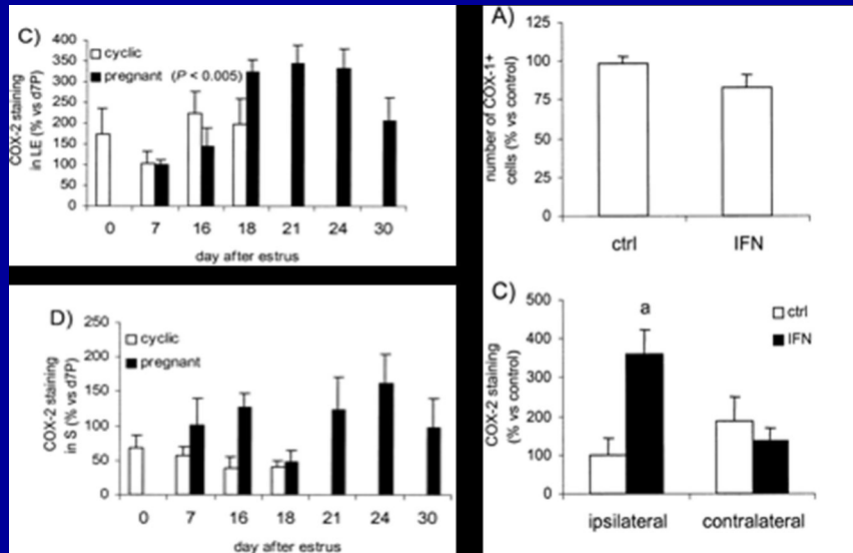
PGHS-2 Immunohistochemistry in Luminal epithelium



Cyclic vs Pregnant $P < 0.05$

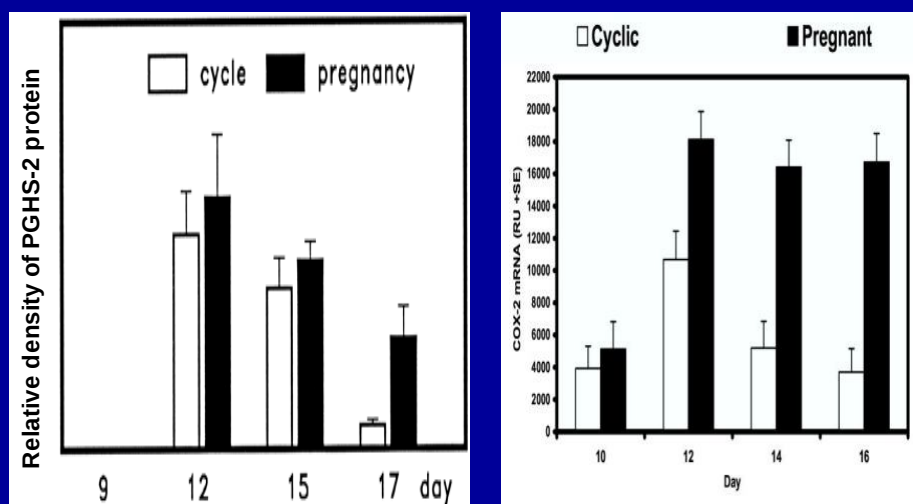
Guzeloglu et. al., 2004a

Endometrial PGHS-2 expression in endometrium in cow



Emond et al., 2004

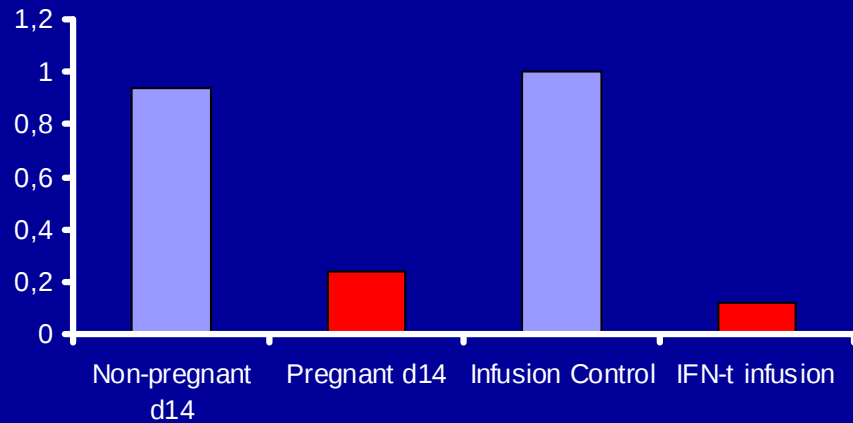
Endometrial PGHS-2 expression in endometrium in ewes



Charpigny et al., 1997

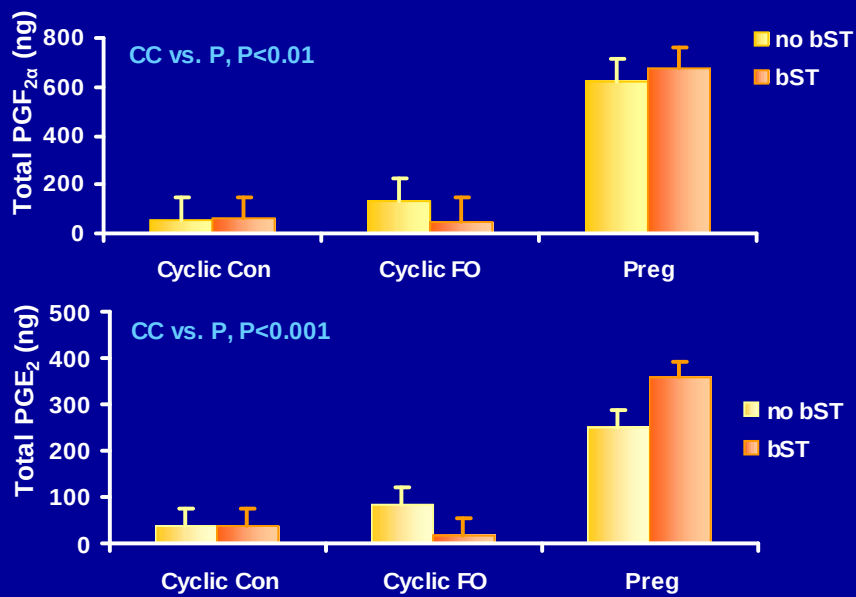
Kim et al., 2003

Both pregnancy and intrauterine INF- γ infusion decreased the mRNA expression of PGHS-2 in the endometrium in ewes



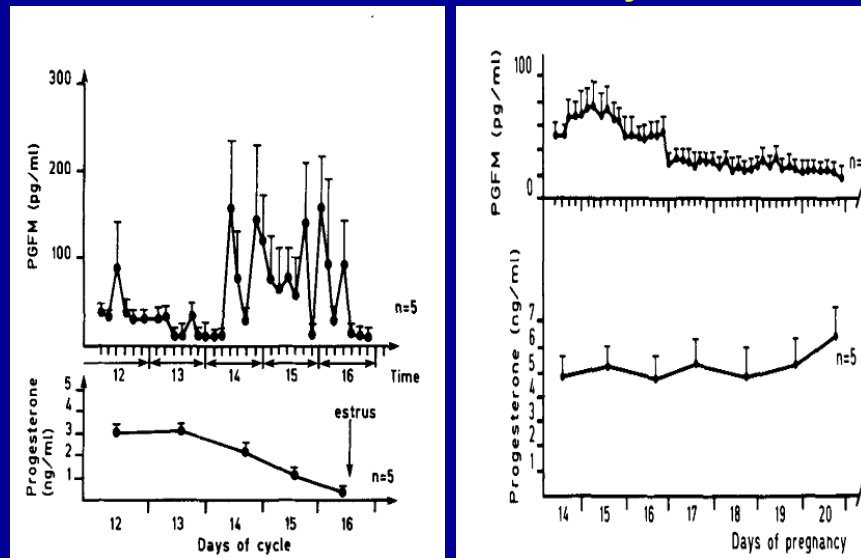
Chen et al., 2006

Total PGF_{2 α} and PGE₂ in Luminal Flushings on D17



Bilby et al., 2006

PGFM secretion in cyclic and pregnant ewes around the time of luteolysis



Lacroix and Kann, 1986

Effect of PGHS-2 inhibitors on pregnancy rates in heifers

	Control	Flunixin Meglumine
Guzeloglu et al (2007, Vet Record)	50 % (13/26)	77 % (20/26)
Flunixin Meglumine on day 15 and 16 after TAI		
	Control	Meloxicam
Guzeloglu et al (2007, RFD)	52 % (25/48)	23 % (9/37)
Meloxicam on day 15 after TAI		

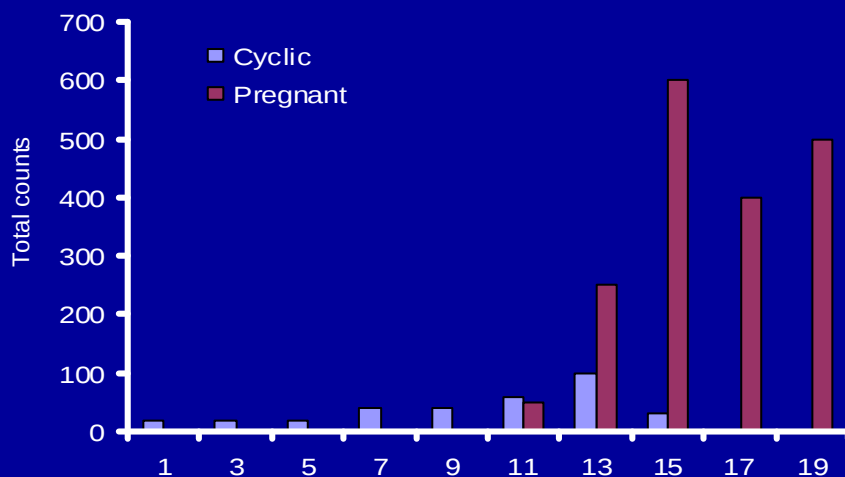
Monozygotic Twin Model Reveals Novel Embryo-Induced Transcriptome Changes of Bovine Endometrium in the Preattachment Period¹

Claudia Klein,^{3,4} Stefan Bauersachs,^{3,4,5} Susanne E. Ulbrich,⁶ Ralf Einspanier,⁷ Heinrich H.D. Meyer,⁶ Susanne E.M. Schmidt,⁴ Horst-Dieter Reichenbach,⁸ Margarete Vermehren,⁹ Fred Sinowatz,⁹ Helmut Blum,⁵ and Eckhard Wolf^{2,4,5}

In pregnant animals,

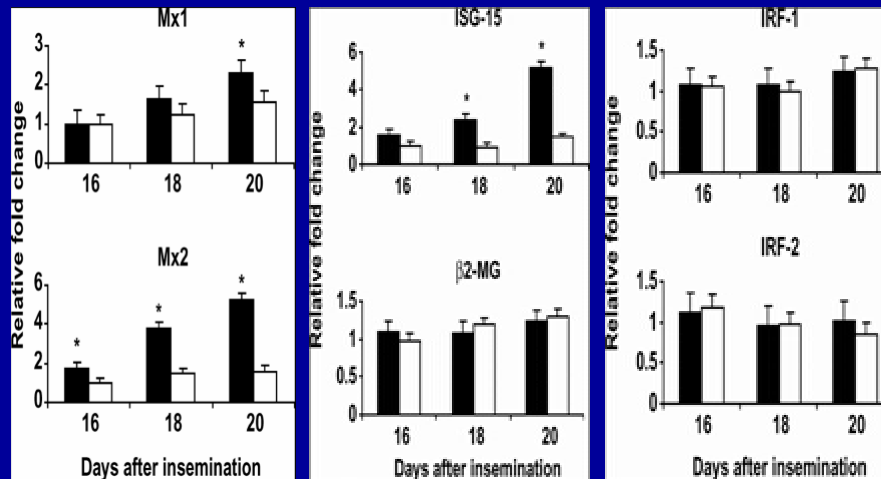
- 87 genes up-regulated in the bovine endometrium.
- About half of genes known to be induced by type I interferons.
- Functional classification of these genes points to biological processes involved in the preparation of the endometrium to implantation.
 - Modulation of maternal immune system.
 - Cell adhesion.
 - Remodeling of the endometrium.

Effect of estrous cycle and early pregnancy on uterine expression of MX mRNA in sheep



Ott et al., 1998

Regulation of Interferon-stimulated genes in peripheral blood leucocytes



Gifford et al., 2007

Summary- Conclusion

- ✓ Luteolysis during early pregnancy is inhibited by a mechanism which involves conceptus secreted protein of Interferon- τ .
- ✓ IFN- τ suppresses PGF_{2 α} peaks by suppressing expression of Estrogen and Oxytocin receptors in the endometrium.
- ✓ Pregnancy appears to increase expression of PGHS-2 in the endometrium. However, experimental studies employing intrauterine IFN- τ infusion have conflicting results.

Summary- Conclusion

- ✓ Besides inhibiting luteolysis, IFN- τ stimulates expression of genes that are involved in implantation process.
- ✓ IFN- τ also stimulates expression of some ISG's in the white blood cells, which may be indicative of a general immune response and can lead to development of early pregnancy diagnosis.
- ✓ Strategies to mimic the effects of IFN- τ may help increase the chance of pregnancy by possibly decreasing early embryonic mortality.

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