

What gonadotropin physiology can teach us to improve ovarian stimulation

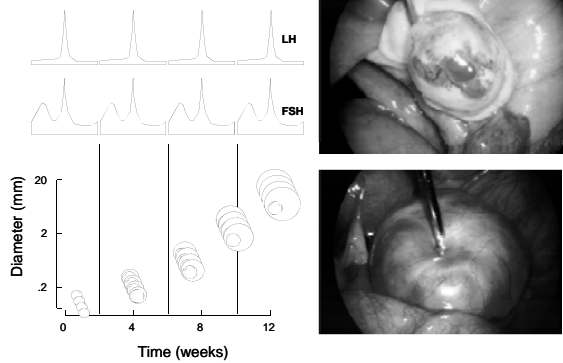
Stephen G. Hillier

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The University of Edinburgh

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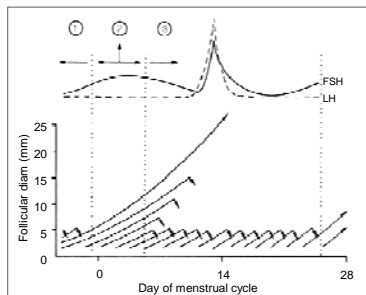


The follicle life-cycle



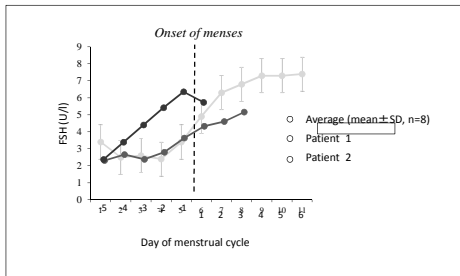
Superovulation Strategy

1. Increase the no. of 'precursor' follicles
2. Raise the stimulus for preovulatory growth
3. Override the 'selection' process

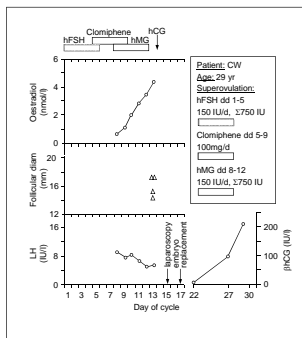


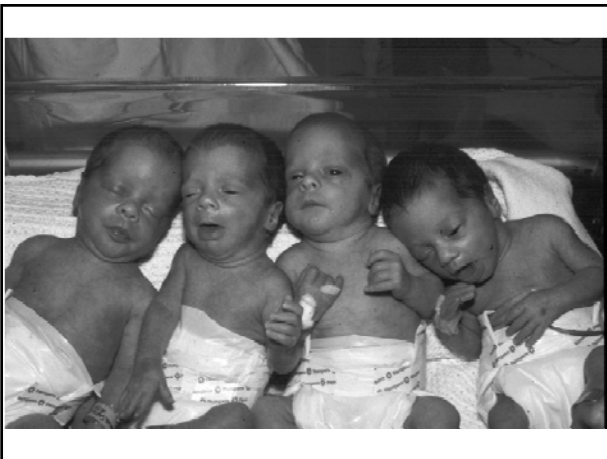
Hillier et al. 1985

Variable link between menstrual cycle onset and inter-cyclic FSH rise



The idea of an FSH 'syncromesh'





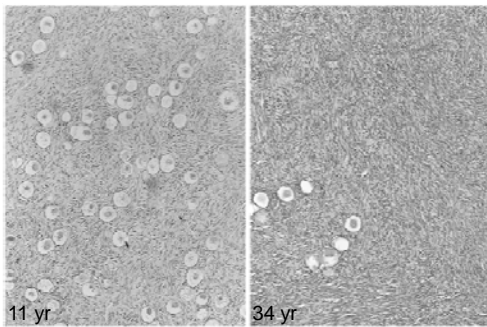
What gonadotropin physiology can teach us to improve ovarian stimulation

- Paracrine pathways
- Gonadotropic gearing
- Clinical impact

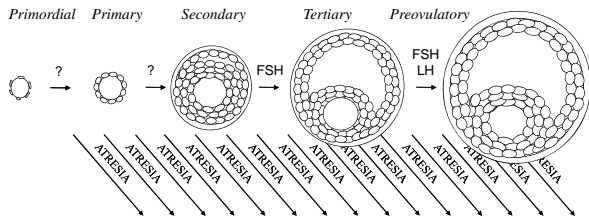
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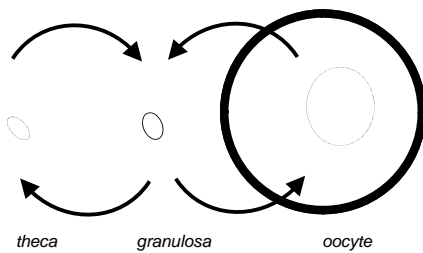
Age-related oocyte loss



Stages of folliculogenesis



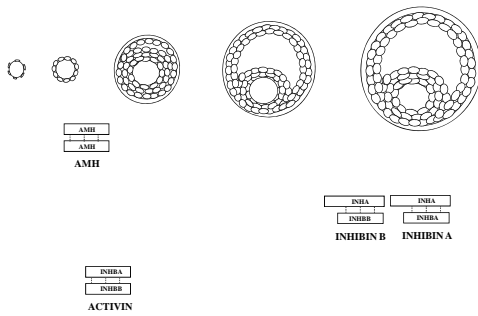
Paracrine pathways



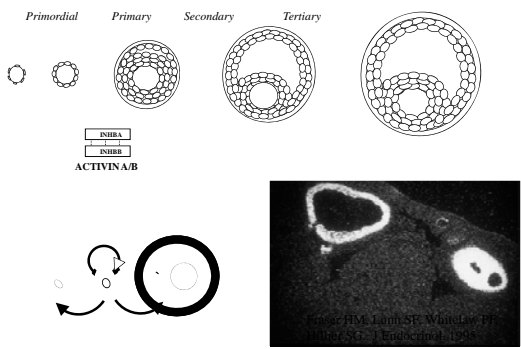
TGF β superfamily

- TGF β 1, TGF β 2, TGF β 3
- Anti-Müllerian Hormone (AMH)
- Inhibins, activins
- Bone morphogenetic proteins BMP-2, BMP-3 (osteogenin), BMP-3B (GDF-10), BMP-4 (BMP-2B), BMP-5, BMP-6 (VGR-1), BMP-7 (OP-1), BMP-8 (OP-2), BMP-15
- Embryonic growth factor GDF-1,
- Growth Differentiation Factors GDF-3, GDF-5, GDF-6, GDF-7, GDF-8 (myostatin), GDF-9
- Nodal
- Chicken dorsalin-1 (dsl-1)
- Xenopus vegetal hemisphere protein Vg1,
- Drosophila decapentaplegic protein (DPP-C)
- Drosophila protein screw (scw)
- Drosophila protein 60A
- Caenorhabditis elegans larval development regulatory growth factor daf-7
- Mammalian endometrial bleeding-associated factor (EBAF) (Lefty)
- Mammalian glial cell line-derived neurotrophic factor (GDNF)

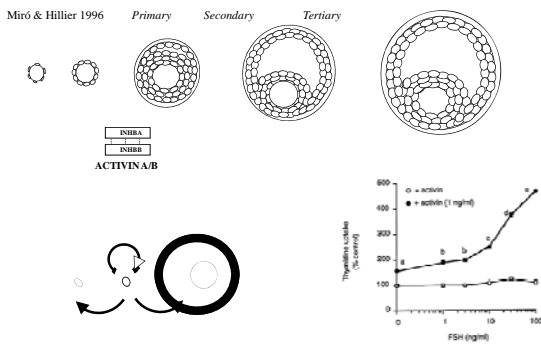
Para(auto)crine cues

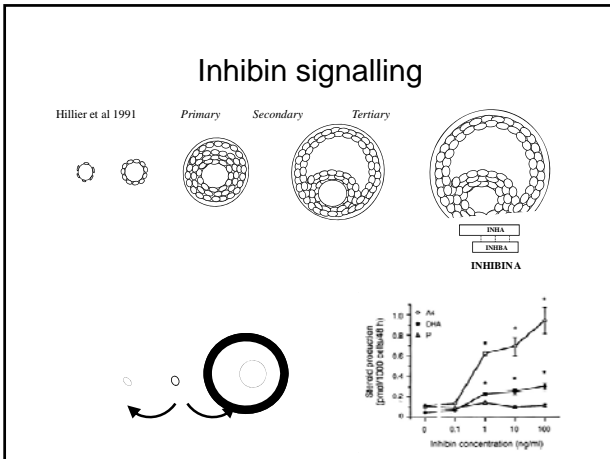


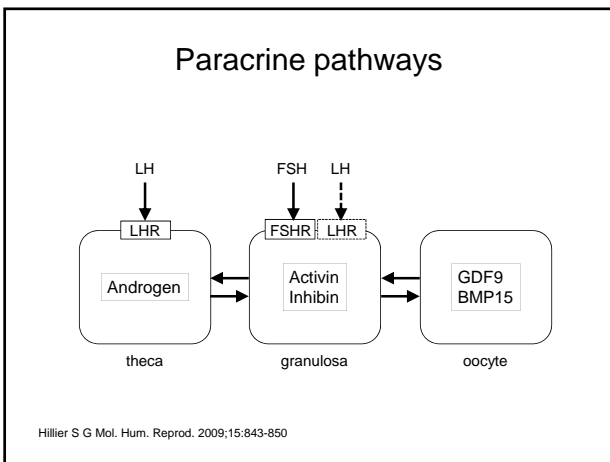
Activin signalling



Activin signalling





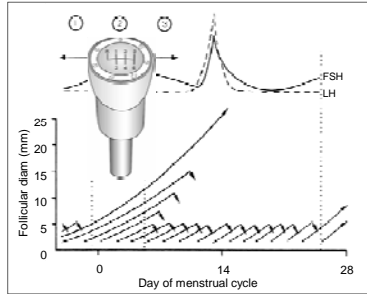


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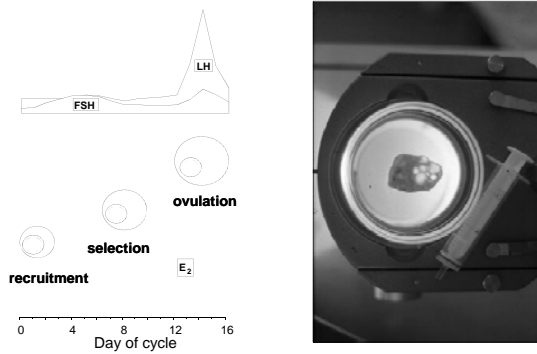
Gonadotropic gearing

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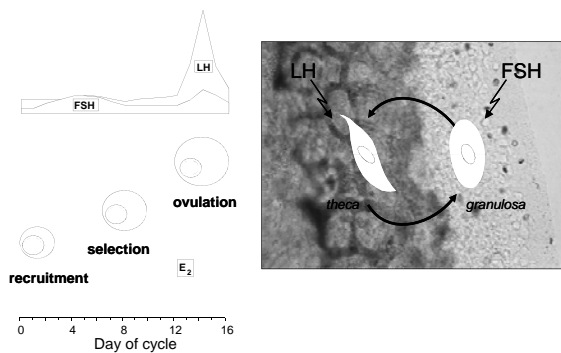


Hillier et al. 1985

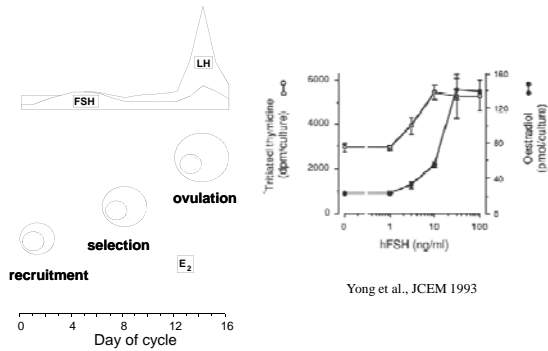
The follicle life-cycle: Recruitment



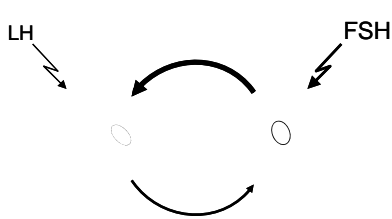
The follicular life-cycle: Recruitment



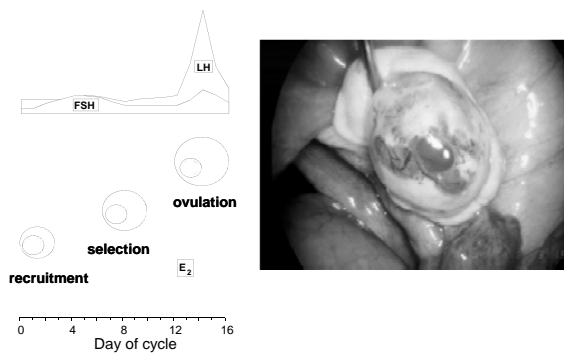
The follicular life-cycle: Recruitment



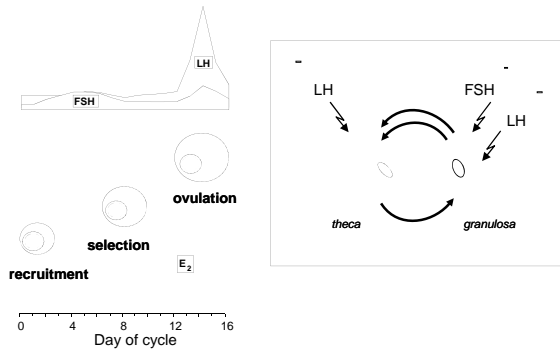
FSH drives recruitment



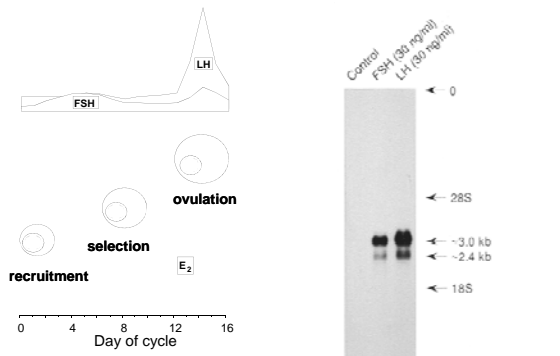
The follicle life-cycle: Selection



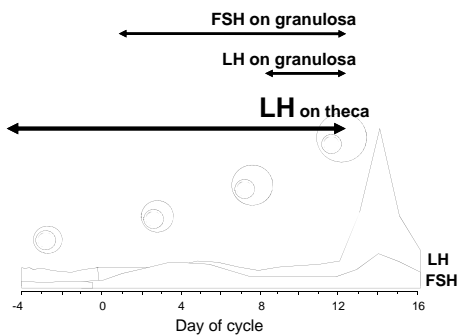
LH drives selection



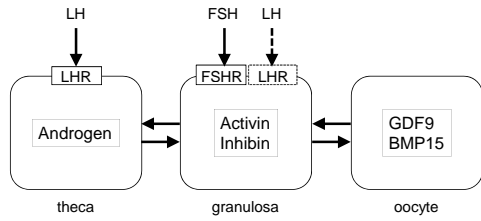
FSH-like LH action



Development-related gonadotrophin action

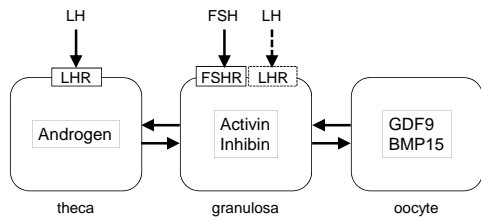


Paracrine pathways



Hillier S G Mol. Hum. Reprod. 2009;15:843-850

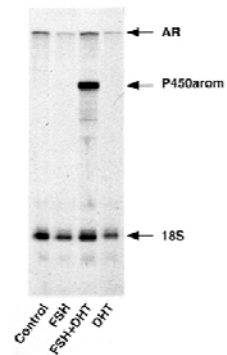
Paracrine pathways



Hillier S G Mol. Hum. Reprod. 2009;15:843-850

Androgens modulate FSH-induced gene expression in granulosa cells

Tetsuka & Hillier *ENDOCRINOLOGY* 1996

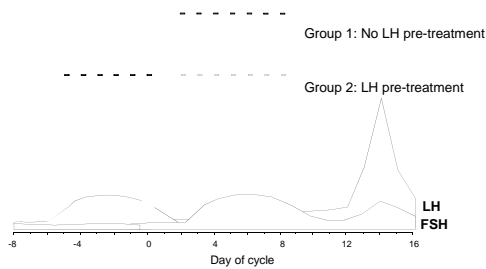


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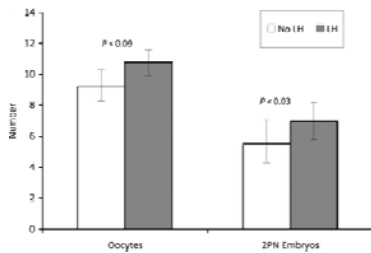
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Effects of recombinant LH treatment on folliculogenesis and responsiveness to FSH stimulation

Durnerin CI, Erb K, Fleming R, Hillier H, Hillier SG, Howles CM, Hugues JN, Lass A, Lyall H, Rasmussen P, Thong J, Traynor I, Westergaard L, Yates R; Luveris Pretreatment Group. Hum Reprod. 2008 Feb;23(2):421-6.

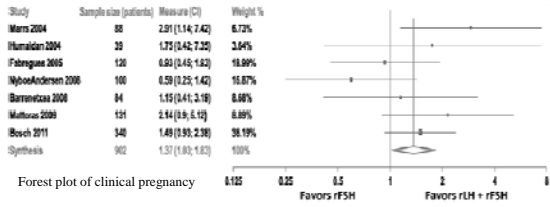


Evidence that LH-priming can improve oocyte quality



Durnerin CI, Erb K, Fleming R, Hillier H, Hillier SG, Howles CM, Hugues JN, Lass A, Lyall H, Rasmussen P, Thong J, Traynor I, Westergaard L, Yates R; Luveris Pretreatment Group. Hum Reprod. 2008 Feb;23(2):421-6.

The use of recombinant luteinizing hormone in patients undergoing assisted reproductive techniques with advanced reproductive age: a systematic review and meta-analysis.



Fertil Steril. 2012 Feb 24. [Epub ahead of print]
 Hill MJ, Levens ED, Levy G, Ryan ME, Csokmay JM, Decherney AH, Whitcomb BW.



Thank you!
