

## Early pregnancy after controlled ovarian hyperstimulation

Ilkka Järvelä  
Oulu University Hospital  
Finland

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## Disclosure of commercial and/or financial relationships with manufacturers of pharmaceuticals, laboratory supplies and/or medical devices

- None

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## Why is early pregnancy important?

- Fetal organogenesis takes place
  - 5-10: period of greatest sensitivity to teratogenesis
    - Neural tube defects, oesophageal atresia, anal atresia, exomphalos, situs inversus, acro-renal field defect etc.
- Placenta
  - Two thirds of the primitive placenta disappears by the end 1st trimester
  - Primary, secondary and tertiary villi develop
  - Secretory function

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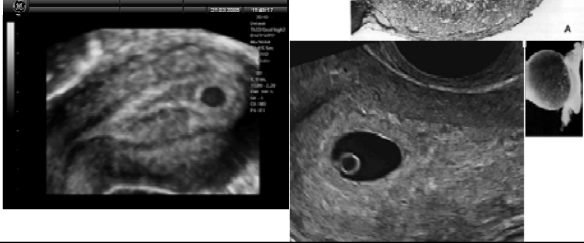
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## Pregnancy week 5

- Gestational sac
- Trophoblastic tissue surrounds the entire GS
- Yolk sac
- 5+5 heart beat



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6+6



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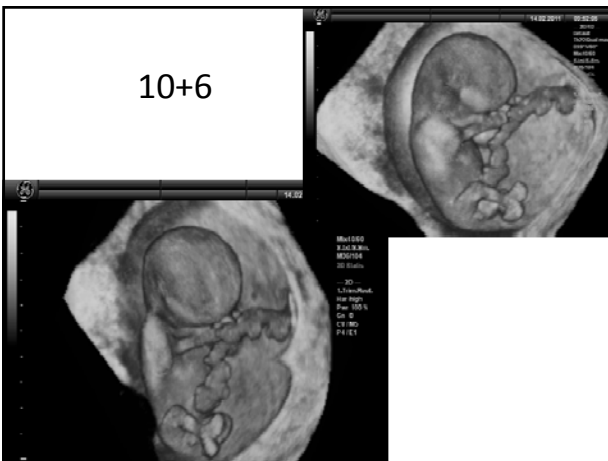
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10+6



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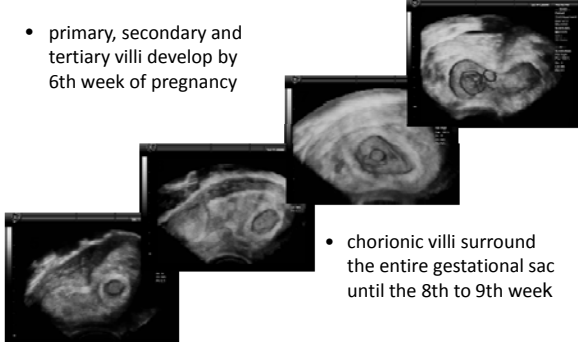
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## Placental development

- primary, secondary and tertiary villi develop by 6th week of pregnancy



- chorionic villi surround the entire gestational sac until the 8th to 9th week

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## Placenta, end of 1st trimester

- up to 10 weeks fetoplacental blood flow is limited
  - placental villi display only a few capillaries
  - fetal blood extremely viscous
- by 10-14 weeks gestation
  - two-thirds of the primitive placenta disappears



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## Placental maturation

- 1st trimester
  - increase in trophoblast tissue
    - SECRETORY FUNCTION
- 2nd and 3rd trimester
  - number of trophoblasts decline
  - remaining syncytial layer thin
    - TRANSPORT OF COMPOUNDS

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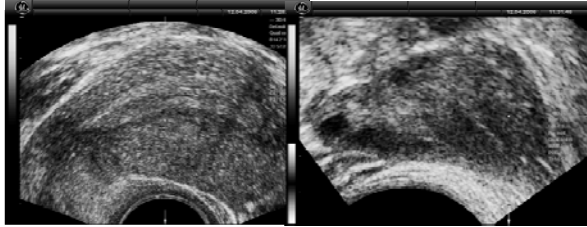
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## CORPUS LUTEUM

- Pregnancy 4 weeks



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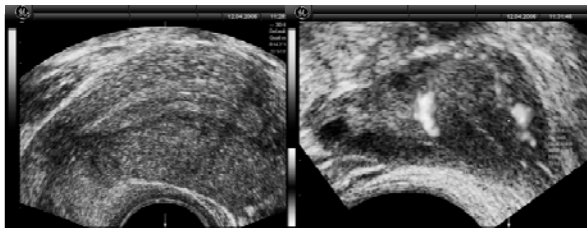
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## CORPUS LUTEUM

- Pregnancy 4 weeks



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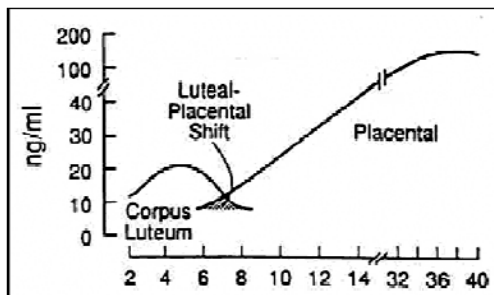
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## Luteal-placental shift



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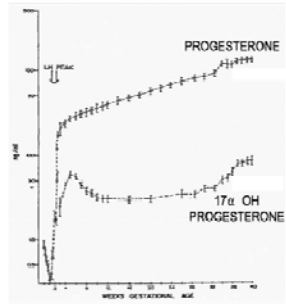
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## Progesterone

- endometrial decidualization
- smooth muscle contractility ↓
- prostaglandin (PG) formation ↓
- immune responses ↓
  - inhibits T-lymphocyte-mediated tissue rejection




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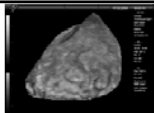
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## CL vasculature



- The capacity of the CL to produce P is closely related to the extent of its vascular network (Niswender et al., 1976; Miyazaki et al., 1998; Niswender et al., 2000; Järvelä et al., 2007).
- CL angiogenesis controlled by local secretion of growth factors (Hazzard and Stouffer, 2000)
  - vascular endothelial growth factor (VEGF) (Sugino et al., 2000; Wulff et al., 2001a,b).

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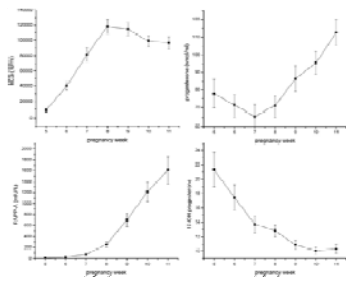
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## Early pregnancy, spontaneous conception

- 1 single corpus luteum after monofollicular ovulation
- CL rescued by trophoblastic hCG secretion after implantation
- Luteoplacental shift at 7-8 pregnancy week



Järvelä I Y et al. Hum. Reprod. 2008;23:2775-2781

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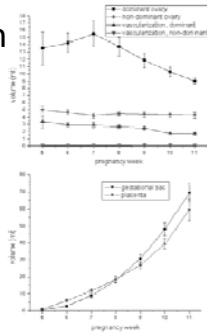
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## Early pregnancy, spontaneous conception

- Dominant ovary volume and vascularization decrease throughout the 1st trimester
- Placenta and gestational sac grow continuously



Järvelä I Y et al. Hum. Reprod. 2008;23:2775-2781

human reproduction

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## Risk of adverse perinatal outcome after fresh embryo transfer (after COH) in singleton pregnancies

- preterm birth (PTB)
- low birth weight (LBW)
- congenital anomalies
- perinatal mortality

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## Why?

- factors related to the hormone stimulation and/or IVF methods per se
  - Multiple corpora lutea?
- epigenetic modification in human embryos
- Subfertility “time to pregnancy”
  - Increases the risk for LBW, SGA, preterm delivery, malformation and neonatal mortality
- Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Söderström-Anttila V, Nygren KG, Hazekamp J, Bergh C. Hum Reprod Update. 2012 Nov 14.

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## Controlled ovarian stimulation (COH)

- COH aims to mature several FSH sensitive antral follicles during IVF/ICSI treatment
  - Agonist or antagonist protocol
- hCG injection 36h before egg collection converts follicles into corpora lutea
  - hCG resembles LH peak during spontaneous cycle
- Several corpora lutea created
  - hCG rescue?
  - function during early pregnancy?

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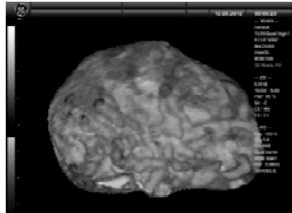
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## Pregnancy week 7 after COH



- Fetus and yolk sac
- Ovarian volume 17 ml, vascularized volume 6 ml (VI 35%)




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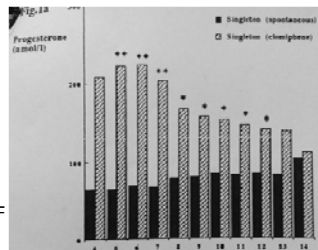
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## Progesterone

- Johnson et al 1993
  - CC+HMG or HMG alone IVF (n=62), no control group
- Johnson et al 1994
  - CC+HMG IVF (n=22)
  - GnRH-agonist HMG IVF (n=17)
- Costea et al 2000
  - GnRH-agonist HMG IVF (n=41)




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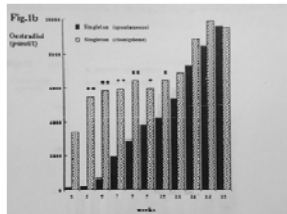
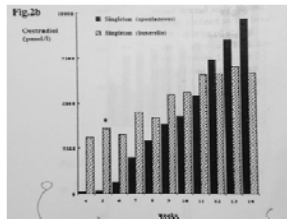
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## Estradiol

- Johnson et al 1993
  - CC+HMG or HMG alone IVF (n=62), no control group
- Johnson et al 1994
  - CC+HMG IVF (n=22)
  - GnRH-agonist HMG IVF (n=17)
  - Control group (n=18)



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## PAPP-A

- In first trimester screening for T21
- 10% lower in ART pregnancies than in control group
  - Gjerris et al 2009
  - Amor et al 2009
  - Kagan et al 2008
  
- Multiple corpora lutea (Weisz et al 2006)
- Delay in fetal and placenta development (Hui et al 2005, Maymon 2004 et al)

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## Second trimester screening

- Unconjugated estriol (uE3)
  - Decreased values
    - Barkai et al 1996
    - Frishman et al 1997
    - Wald et al 1999
    - Maymon and Shulman 2002
    - Muller et al 2003
  - Increased values
    - Rice et al 2005

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## Increased risk of blastogenesis birth defects

Halliday et al 2010

- ART 6946
  - Fresh ET 4323 after COH,
  - Thawed ET 2623 (spontaneous cycle)
- non-ART controls 2083
  
- Blastogenesis defects (adjusted OR to non-ART)
  - Fresh ET 3.65 (2.02-6.59)
  - Thawed ET 1.60 (0.69-3.69)

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## FET vs fresh ET

- Frozen-thawed embryo transfer FET
  - No COH
  - Spontaneous cycle or HRT
- CoNARTaS Wennerholm NFS 2012, Sweden Norway and Denmark, n=6653
  - PTB 0.9 (0.8-1.0)
  - LBW < 2500g 0.8 (0.7-0.9)
  - SGA 0.8 (0.7-0.9)
  - LGA 1.4 (1.2-1.6)

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## FET vs spontaneous pregnancies

- No difference (?) in
  - PTB
  - LBW
  - SGA
  - Perinatal mortality
- LGA risk increased
  
- Pelkonen HR 2010, Pinborg FS 2010, Sazonova HR 2012

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### Järvelä et al submitted

- Three groups, early pregnancy 4-11 weeks
  - Spontaneous pregnancies n=41
  - IVF/ICSI pregnancies n=40 (fresh embryo transfer after COH)
  - Frozen-thawed embryo pregnancies n=30 (natural cycle)

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### Järvelä et al submitted

- Results presented in Maribor 2013
  - Singleton pregnancies
  - Weekly visits
  - hCG, P, 17OHP, E2, PAPP-A, CL activity, CRL, GS

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### Conclusion

- COH
  - The luteal activity significantly increased for the first weeks of pregnancy
    - Effect on placentation
- Placenta
  - The placental development maybe delayed/disturbed after COH
- Association (?) with adverse outcome after fresh ET following COH

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