

*Yesterday, today  
and forever*

**Dexeus**  
mujer

## Endometrial preparation for frozen embryo transfer ( FET )

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**Barcelona**



- 46% of embryo transfers carried out in our Department in 2017 have been FET
- FET increased 22%

# ICMART ART REPORT (2008-2010)

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- 4, 461 309 cycles → 1,144 858 babies born
- IVF ↑ 6,4% **FET ↑ 27,6%**
- ICSI 66%

*EVERS J.L.H. 2016  
Hum. Reprod. 31-7:1381-2*

# WHAT IS THE REASON FOR THIS FET INCREASE?

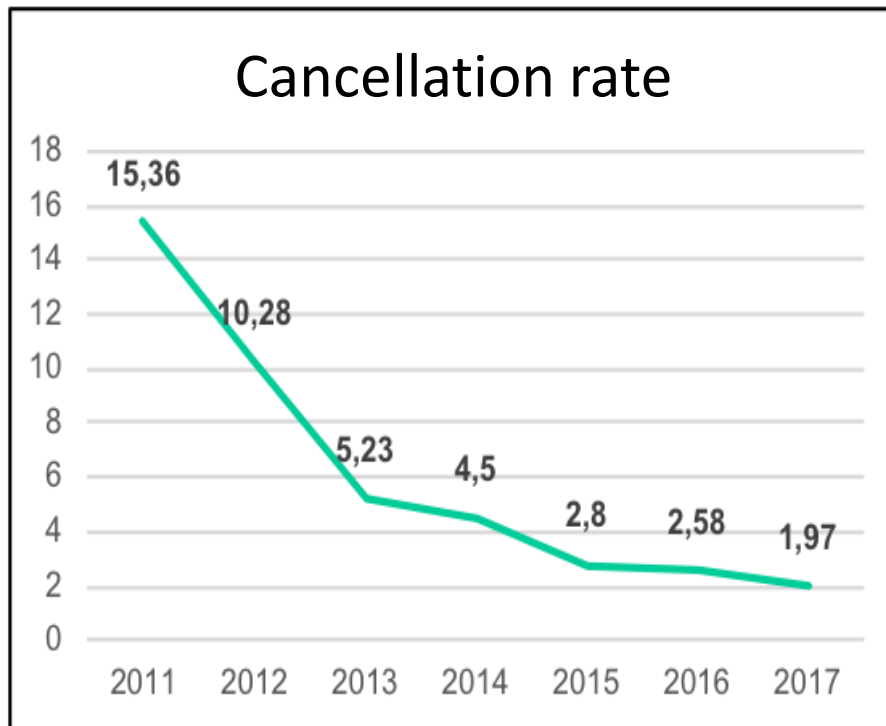
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## SET policies

Freeze all: *Blockeel et al., 2016*

- OHSS prevention, *Devroey et al., 2011*
  - PGT-A ( *Preimplantational genetic testing*)
  - High Progesterone levels: *Bosch et al., 2010; Roque et al., 2015; Healy et al., 2016*
  - Asynchrony embryo-endometrium: *Shapiro et al., 2008*
  - Bigger pregnancy rate in FET: *Shapiro et al., 2011; Roque et al., 2013*
  - TED risk: *Hansen et al., 2014*
  - Endometriosis: *Bourdon et al 2017*
  - Elective fertility preservation: *ASRM Ethics Committee 2018*
- 
- New COS protocols: Luteal phase stimulation: *Martinez et al., 2014*
  - **Improved outcomes following frozen embryo transfer does not provide a “universal license to chill”**: *Eapen and Sparks 2018*



# QUESTIONS

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1. Is there an ideal endometrial preparation treatment for FET?
2. Are hormone monitoring and measuring of endometrial thickness important?
3. What is the best method for embryo cryopreservation?
4. Is it better to freeze blastocysts?
5. Is there a higher miscarriage rate in FET?
6. Are there greater obstetric and neonatal complications following FET?
7. Does the cost of the treatment vary?

Is there an ideal endometrial preparation  
treatment for FET?

# PROTOCOLS FOR ENDOMETRIAL PREPARATION IN FROZEN EMBRYO TRANSFER (FET)

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**Natural Cycle- NC**

**Artificial Cycle- E2+P**

**Artificial Cycle under GnRH agonist - E2+P**



# NATURAL CYCLE

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- *Endometrial preparation depends on endogenous hormonal production by a developing follicle and an ovulatory cycle. Ovulation happens 36-40 hours after LH serum peak (Andersen et al., 1995). Embryo transfer 3-5 days after ovulation.*
- *Disadvantages:*
  - ***Need for monitoring***
  - ***21 hours gap between serum LH peak and urine tests***
  - ***30% false negatives in urine tests, sometimes difficult to read***
  - ***Intercycle variability***

## Frozen–thawed embryo transfers in natural cycles with spontaneous or induced ovulation: the search for the best protocol continues

M. Montagut<sup>1</sup>, S. Santos-Ribeiro<sup>2,3</sup>, M. De Vos<sup>2</sup>, N.P. Polyzos<sup>2</sup>,  
P. Drakopoulos<sup>2</sup>, S. Mackens<sup>2</sup>, A. van de Vijver<sup>2</sup>, L. van Landuyt<sup>2</sup>,  
G. Verheyen<sup>2</sup>, H. Toumaye<sup>2</sup>, and C. Blodkeel<sup>2,4,\*</sup>



|                        | Unadjusted OR<br>(95% CI) | Adjusted OR<br>(95% CI) |
|------------------------|---------------------------|-------------------------|
| BMI                    | 1.02(1.00-1.05)           | 1.02 (1.00-1.05)        |
| Oocytes retrieved      | 1.06 (1.04-1.08)          | 1.04 (1.02-1.06)        |
| Fresh cycle pregnancy  |                           |                         |
| Not pregnant           | Reference                 | Reference               |
| Pregnant               | 1.64 (1.30-2.07)          | 1.35 (1.06-1.71)        |
| Type of FET            |                           |                         |
| mNC-FET+LPS            | Reference                 | Reference               |
| NC-FET+LPS             | 1.73(1.36-2.21)           | 1.67 (1.31-2.12)        |
| NC-FET                 | 2.40 (1.80-3.19)          | 2.18 (1.64-2.90)        |
| Double embryo transfer | 1.27 (1.03-1.57)          | 1.23 (0.98-1.54)        |
| Blastocyst transfer    | 2.02 (1.60-2.54)          | 2.25 (1.74-2.91)        |
| Endometrial thickness  | 1.09 (1.04-1.15)          | 1.08 (1.03-1.14)        |
| Embryo Quality 1       | Reference                 | Reference               |
| Embryo Quality 2       | 0.63 (0.51-0.78)          | 0.47 (0.37-0.60)        |
| Embryo Quality 3       | 0.43 (0.26-0.70)          | 0.35 (0.21-0.59)        |
| Embryo Quality 4       | 0.09 (0.03-0.24)          | 0.14 (0.05-0.38)        |

# Programming the endometrium for deferred transfer of cryopreserved embryos: hormone replacement versus modified natural cycles



Eva R. Groenewoud, M.D., Ph.D.,<sup>a</sup> Bernard J. Cohlen, M.D., Ph.D.,<sup>b</sup> and Nicholas S. Macklon, M.D., Ph.D.<sup>c,d</sup>

<sup>a</sup> Department of Obstetrics and Gynaecology, Noordwest Ziekenhuis, Den Helder, The Netherlands; <sup>b</sup> Isala Fertility Centre, Isala, Zwolle, The Netherlands; <sup>c</sup> London Women's Clinic, London, United Kingdom; and <sup>d</sup> Department of Obstetrics and Gynaecology, Zealand University Hospital, Roskilde, Denmark



Updated meta-analyses comparing live birth NC-FET vs. AC-FET.

Groenewoud. *Hormone replacement cycles and modified natural cycles. Fertil Steril* 2018.

## Summary NC-FET versus AC-FET:

- No difference in clinical and ongoing pregnancy rates and live birth rates between both endometrial preparation methods.
- No difference in costs between both treatment entities.
- No optimal minimal monitoring regimen in NC-FET has been determined.
- Routine use of luteal phase support in NC-FET has not been shown to be advantageous but increases treatment burden.
- Minimal duration of both estrogen and progesterone supplementation need further clarification.
- Further studies comparing the various routes of estrogen and progesterone administration are necessary.

Summary, NC-FET vs. AC-FET.

Groenewoud. *Hormone replacement cycles and modified natural cycles. Fertil Steril* 2018.

## ARTIFICIAL CYCLE E2+P

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- *Endometrial preparation depends on exogenous hormonal administration. Warming and embryo transfer depends on progesterone administration.*
- *Disadvantages :*
  - **Less physiological**
  - **Multiple medical administration routes. Costs.**
  - **Does not guarantee avoiding spontaneous ovulation risk (1.9-7.4 %).**
- *Advantages:*
  - **Scheduling**

## ARTIFICIAL CYCLE E2+P + GnRH AGONIST (A-AC)

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- *Endometrial preparation depends on exogenous hormonal administration. Agonist GnRH in previous cycle to avoid spontaneous ovulation*
- *Disadvantages :*
  - **Less physiological**
  - **Multiple medical administration routes. Costs. Secondary effects: tiredness, hot flushes,...**
- *Advantages:*
  - **Scheduling**

2017



**Cochrane  
Library**

Cochrane Database of Systematic Reviews

## Cycle regimens for frozen-thawed embryo transfer (Review)

Ghobara T, Gelbaya TA, Ayeleke RO

Ghobara T, Gelbaya TA, Ayeleke RO.

Cycle regimens for frozen-thawed embryo transfer.

*Cochrane Database of Systematic Reviews* 2017, Issue 7. Art. No.: CD003414.

DOI: 10.1002/14651858.CD003414.pub3.

[www.cochranelibrary.com](http://www.cochranelibrary.com)

**18 RCT: 3815 women**

# CONTROVERSIAL ISSUES IN FROZEN EMBRYO TRANSFER: ESTROGENS SUPPLEMENTATION



## Frozen embryo transfer: a review on the optimal endometrial preparation and timing

S. Mackens<sup>1</sup>, S. Santos-Ribeiro<sup>1,2</sup>, A. van de Vijver<sup>1</sup>, A. Racca<sup>1,3</sup>, L. Van Landuyt<sup>1</sup>, H. Tournaye<sup>1</sup>, and C. Blockeel<sup>1,4,\*</sup>

2 WEEKS



Empyrical, reproduces natural cycle (*Lutjen et al., 1984*)

5-7 days



- Enough for endometrial preparation (*Naboth et al., 1984*)
- Cost benefit
- Higher miscarriage rate (*Borini et al., 2001*)

> 2 WEEKS



No Compromise on pregnancy (*Soares et al., 2005*)

# VARIABLES ASSOCIATED WITH LIVE BIRTH AFTER A FROZEN-THAWED BLASTOCYST TRANSFER: MULTIPLE LOGISTIC REGRESSION ANALYSIS



| Parameters   | Odds ratio | 95% CI    |
|--|------------|-----------|
| Age>35 y at retrieval                              | 0.72       | 0.56-0.93 |
| Good-quality embryo transfer                       | 1.74       | 1.20-2.53 |
| Days of estradiol administration ( $\leq 2$ I ref) |            |           |
| 22 – 28  | 0.86       | 0.63-1.16 |
| 29 – 35  | 0.65       | 0.45-0.95 |
| 36 – 48  | 0.49       | 0.26-0.92 |

*Bourdon, et al. 2018*

*Human Reproduction 33-5:905-913*



# CONTROVERSIAL ISSUES IN FROZEN EMBRYO TRANSFER: ADMINISTRATION ROUTES



## Progesterone supplementation in the frozen embryo transfer cycle

*Israel Ortega<sup>a</sup> and Juan Antonio García Velasco<sup>a,b</sup>*

### KEY POINTS

- NC-FTET is the favored option for women with normal ovulatory menstrual cycles and may be programmed either associated with daily blood or urine LH measurements or triggering ovulation with hCG, showing comparable reproductive outcomes.
- In AC-FTET, estrogen and progesterone are sequentially administered, being the option of choice for women with irregular menstrual cycles.
- Nowadays, no differences between the different formulations of progesterone have been observed.
- Final decision must be based on individualization of the treatment based on patient characteristics prior to FTET.

## H.U.Dexeus - STUDY MATERIAL - I



|                            | FET IVF<br>(n=2300) | FET DON<br>(n=993) | p     |
|----------------------------|---------------------|--------------------|-------|
| <b>Clinical Preg</b> (n/%) | 759 (33%)           | 361 (36.4%)        | n.s.  |
| <b>Miscarriage</b> (n/%)   | 235 (31%)           | 96 (26%)           | n.s.  |
| <b>Ectopic</b> (n/%)       | 6 (0.79%)           | 6 (1.66%)          | n.s.  |
| <b>Livebirth</b> (n/%)     | 505 (22%)           | 253 (25.5%)        | 0,031 |

## H.U.Dexeus - STUDY MATERIAL - II

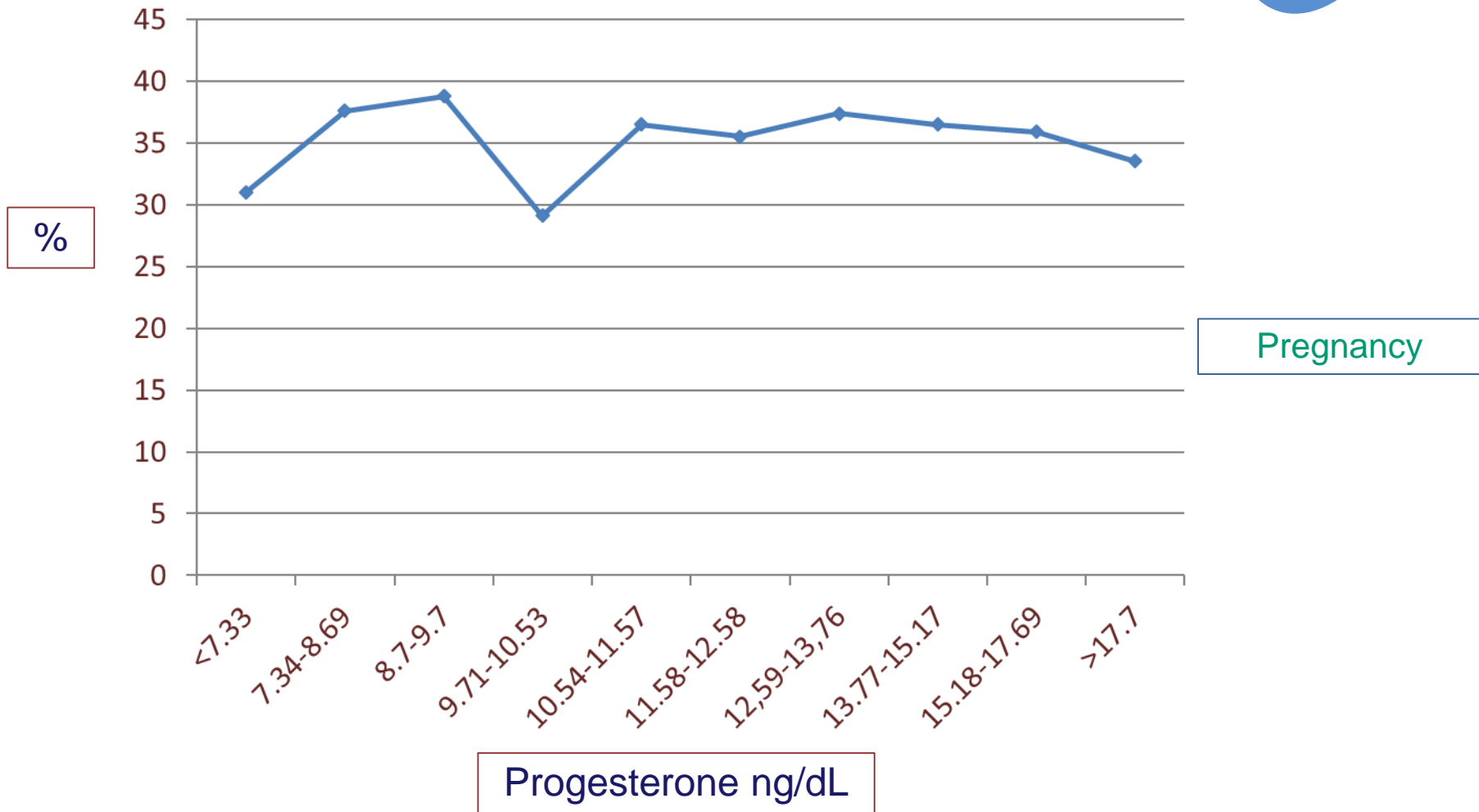


|                               | <b>NATURAL<br/>(n=219)</b> | <b>E2+P<br/>(n=388)</b> | <b>AGONIST<br/>(n=2686)</b> | <b><i>p</i></b> |
|-------------------------------|----------------------------|-------------------------|-----------------------------|-----------------|
| <b>Clinical Preg.<br/>n/%</b> | 73 (33.3%)                 | 132 (34%)               | 915 (34.1%)                 | n.s.            |
| <b>Miscarriage<br/>n/%</b>    | 13 (17.8%)                 | 42 (31.8%)              | 276 (30.2%)                 | n.s.            |
| <b>Ectopic<br/>n/%</b>        | 1 (1.3%)                   | 4 (3.03%)               | 7 (0.77%)                   | n.s.            |
| <b>Livebirth<br/>n/%</b>      | 57 (26%)                   | 84 (21.6%)              | 617 (23%)                   | n.s.            |

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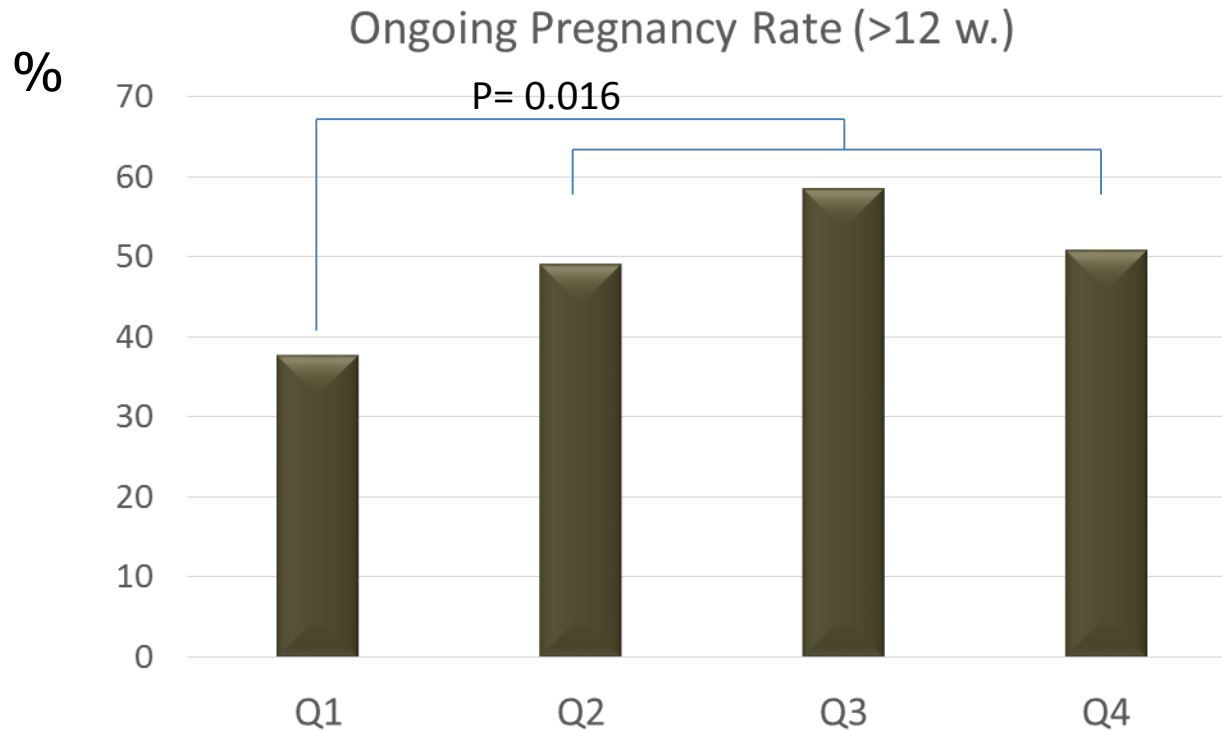
Are hormone monitoring and measuring of  
endometrial thickness important?

# H.U.Dexeus FET RESULTS ACCORDING TO PROGESTERONE SERUM LEVELS



No association was found between Progesterone levels and pregnancy probability in FET (p=0.727)

# LOW SERUM PROGESTERONE ON THE DAY OF ET IS ASSOCIATED WITH A DIMINISHED OPR IN ARTIFICIAL ENDOMETRIAL PREPARATION CYCLES



P4 < 9.2 ng/ml vs.  $\geq$ 9.2 ng/ml  
(OR: 0.297; 95%CI: 0.113-0.779); P = 0.013.

# THE IMPACT OF A THIN ENDOMETRIAL LINING ON FRESH AND FROZEN-THAW IVF OUTCOMES: AN ANALYSIS OF OVER 40 000 EMBRYO TRANSFERS

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**STUDY DESIGN, SIZE, DURATION:** This study is a retrospective cohort analysis of all Canadian IVF fresh and frozen-thaw ET cycles. A total of 24 363 fresh and 20 114 frozen-thaw IVF-ET cycles were reported during this timeframe.

**MAIN RESULTS AND THE ROLE OF CHANCE:** In fresh IVF-ET cycles, clinical pregnancy and live birth rates decreased ( $P < 0,0001$ ) and pregnancy loss rates increased ( $P = 0,01$ ) with each millimeter decline in endometrial thickness **below 8 mm**. In frozen-thaw ET cycles, clinical pregnancy ( $P = 0,007$ ) and live birth rates decreased ( $P = 0,002$ ) with each millimeter decline in endometrial thickness **below 7 mm**. With no significant difference in pregnancy loss rates. The likelihood of achieving and endometrial thickness  $\geq 8$  mm decreased with age (89,7, 87,8 and 83,9% in women  $< 35$ , 35-39 and  $\geq 40$ , respectively) ( $P < 0,0001$ )

*K.E. Liu, et al. 2018*

*Human Reproduction, pp.1-6*

## H.U.Dexeus - STUDY MATERIAL - III



|                           | <b>NATURAL<br/>(n=219)</b> | <b>E2+P<br/>(n=388)</b> | <b>AGONIST<br/>(n=2686)</b> |
|---------------------------|----------------------------|-------------------------|-----------------------------|
| <b>Estradiol</b> pg/ml    | 140 ± 72.5*                | 243 ± 106               | 231 ± 101                   |
| <b>Progesterone</b> ng/ml | 14 ± 32                    | 13 ± 10                 | 12.4 ± 9,3                  |
| <b>End. thickness</b> mm  | 11.1 ± 2,1                 | 10.4 ± 2,1*             | 10.8 ± 2,1                  |

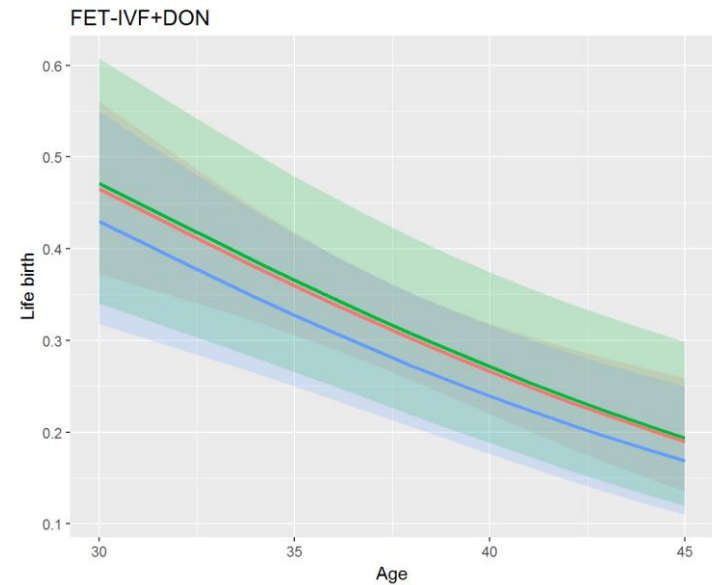
\* p<0.05



# H.U.Dexeus - PREGNANCY RATE-LOGISTIC REGRESSION



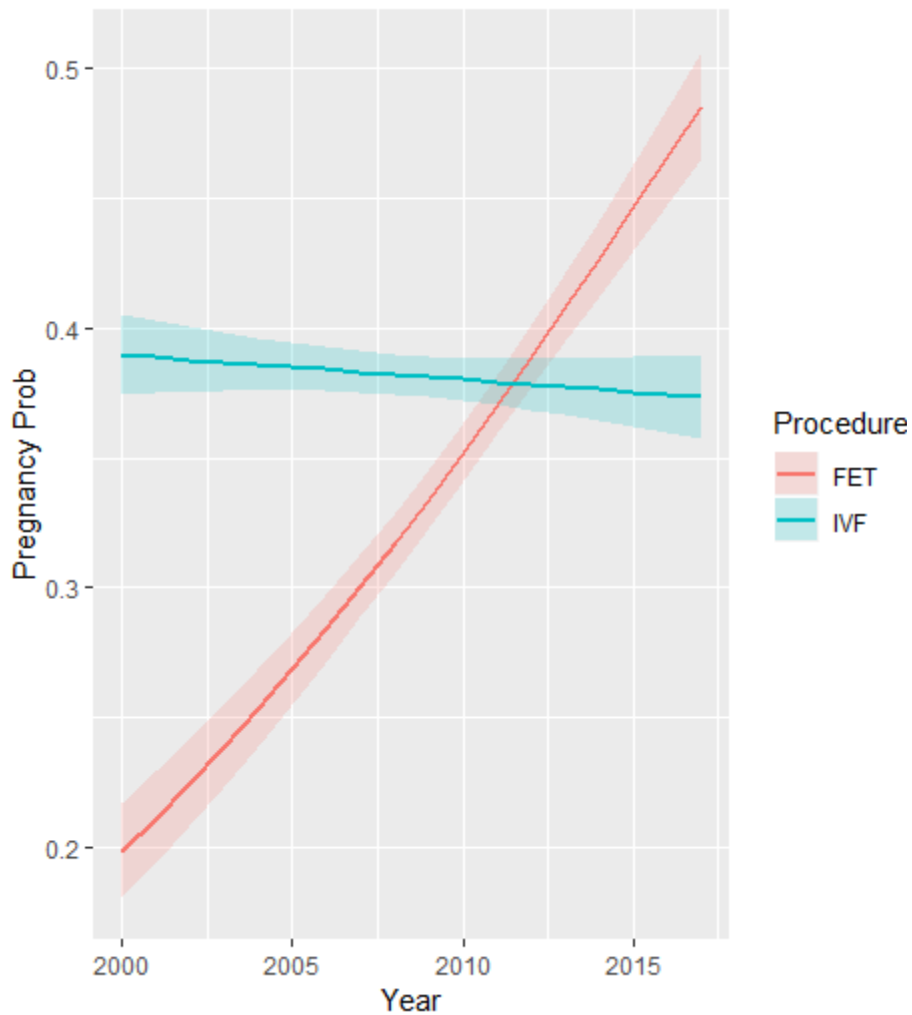
|                                  | OR 95% CI          |
|----------------------------------|--------------------|
| Intercept                        | 1.45 [0.20; 10.52] |
| FET-Don                          | 4.76 [0.67; 34.07] |
| FET-IVF                          | 1                  |
| Age at oocyte retrieval          | 0.95 [0.91; 0.99]* |
| Age at FET                       | 0.98 [0.94; 1.02]  |
| Oocytes inseminated              | 1.01 [0.99; 1.03]  |
| Treatment-Natural                | 1.03 [0.66; 1.57]  |
| Treatment- E2+P                  | 0.87 [0.62; 1.20]  |
| Treatment-Agonist                | 1                  |
| Embryo stage-Cells               | 0.60 [0.45; 0.78]* |
| Embryo stage-Blastocyst          | 1                  |
| Freezing procedure-Slow          | 0.24 [0.01; 1.31]  |
| Freezing procedure-Vitrification | 1                  |
| Embryos transferred              | 1.63 [1.36; 1.97]* |
| Endometrial thickness            | 1.04 [0.99; 1.09]  |
| Progesterone                     | 1.00 [1.00; 1.01]  |
| Estradiol                        | 1.00 [1.00; 1.00]  |
| Cells*Slow                       | 3.11 [0.55; 58.55] |
| Group*Age at oocyte retrieval    | 0.97 [0.91; 1.02]  |



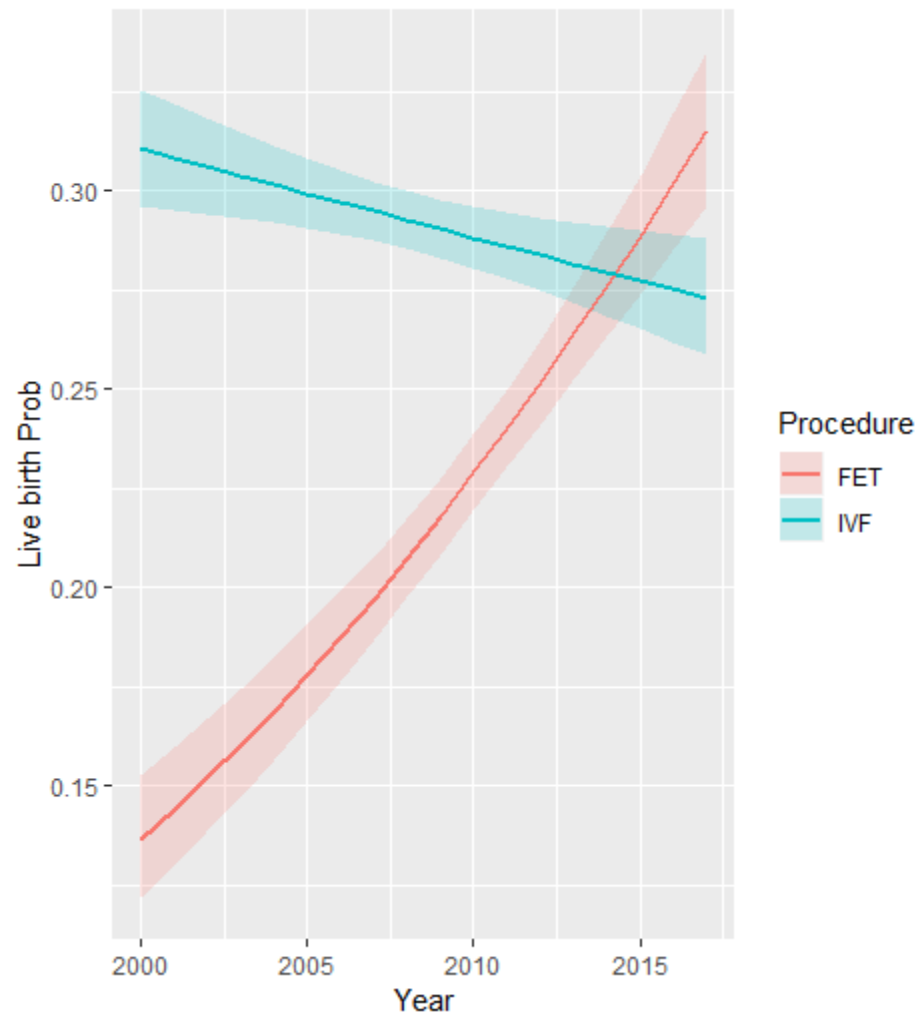
# H.U.Dexeus - IVF vs FET PREGNANCY AND LIVEBIRTH RATES



### FET-IVF PREGNANCY



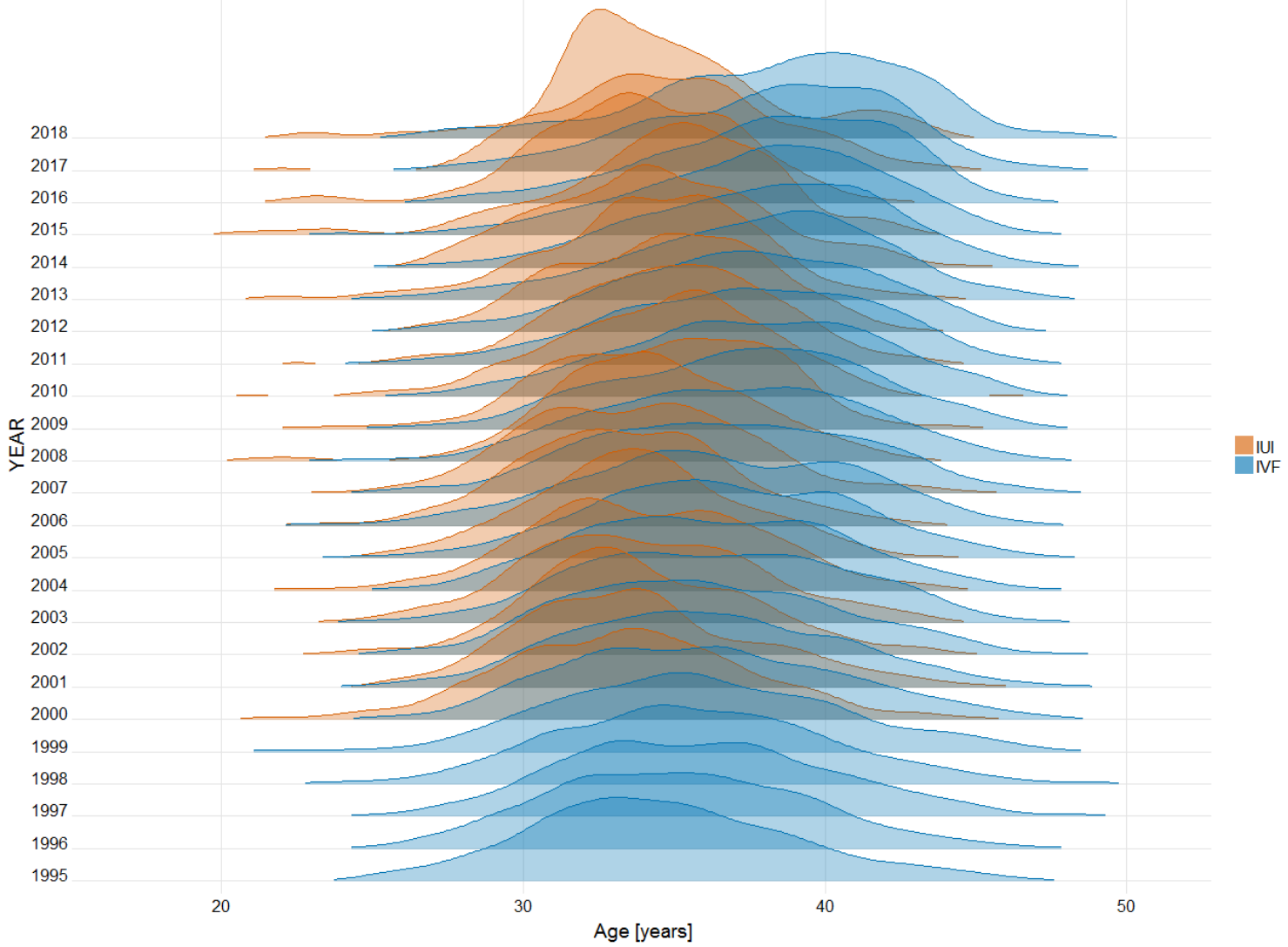
### FET-IVF LIVEBIRTH



# IUI/IVF. PATIENTS' AGE EVOLUTION



Age in Dexeus ART Patients

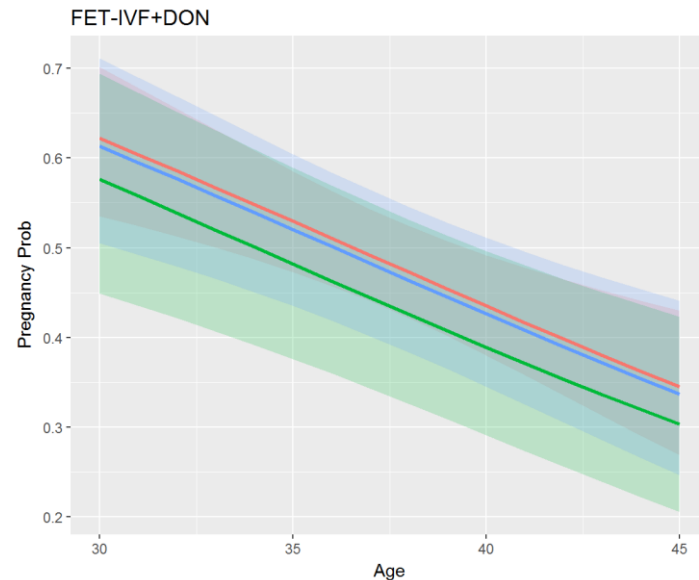


What is the best method for embryo  
cryopreservation?

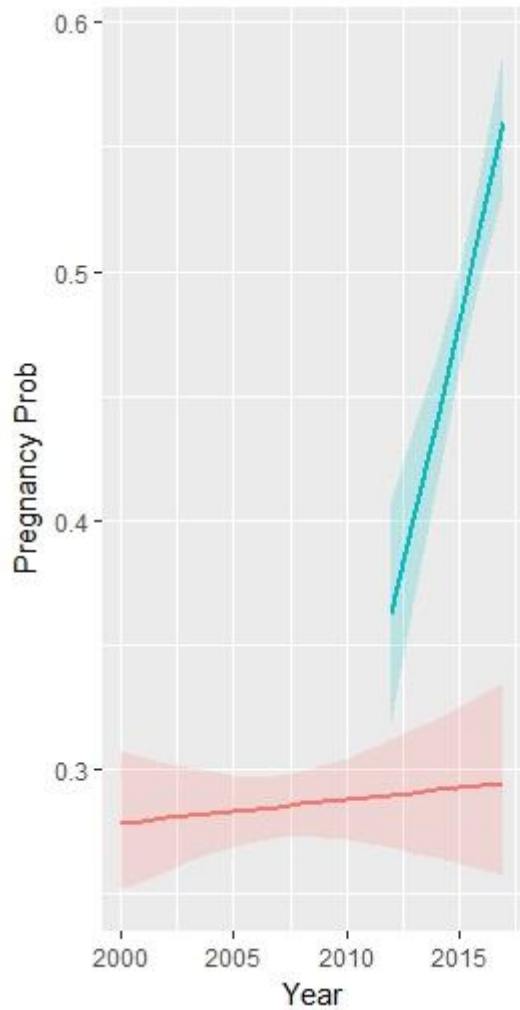
# H.U.Dexeus - LIVE BIRTH RATE - LOGISTIC REGRESSION



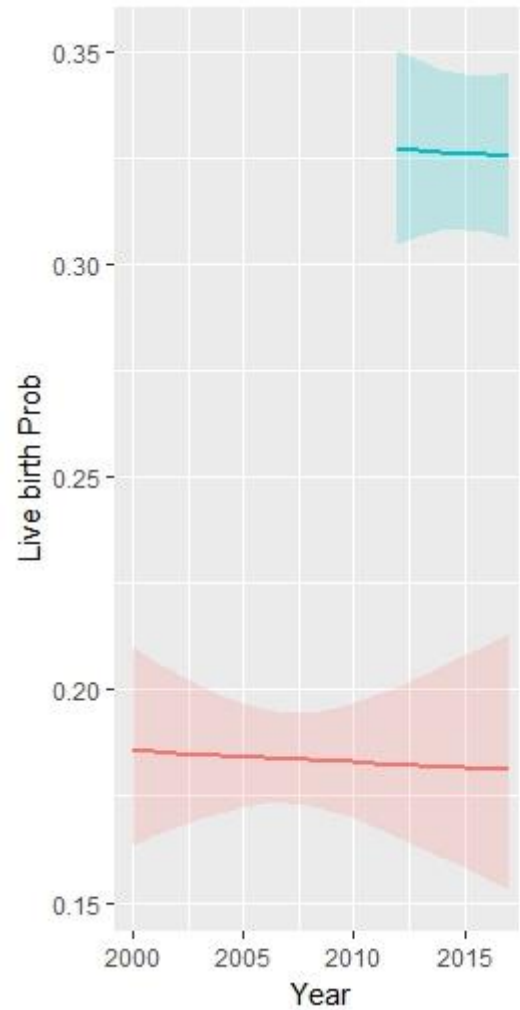
|                                  | OR 95% CI            |
|----------------------------------|----------------------|
| Intercept                        | 1.24 [0.20; 7.50]    |
| FET-Don                          | 6.01 [1.00; 36.33]*  |
| FET-IVF                          | 1                    |
| Age at oocyte retrieval          | 0.97 [0.94; 1.00]    |
| Age at FET                       | 0.99 [0.95; 1.02]    |
| Oocytes inseminated              | 1.01 [0.99; 1.03]    |
| Treatment-Natural                | 0.83 [0.55; 1.23]    |
| Treatment- E2+P                  | 0.96 [0.72; 1.29]    |
| Treatment-Agonist                | 1                    |
| Embryo stage-Cells               | 0.55 [0.43; 0.71]*   |
| Embryo stage-Blastocyst          | 1                    |
| Freezing procedure-Slow          | 0.12 [0.01; 0.67]*   |
| Freezing procedure-Vitrification | 1                    |
| Embryos transfered               | 1.65 [1.40; 1.95]*   |
| Endometrial thickness            | 1.04 [0.99; 1.08]    |
| Progesterone                     | 1.00 [0.99; 1.01]    |
| Estradiol                        | 1.00 [1.00; 1.00]    |
| Cells*Slow                       | 6.11 [1.10; 114.56]* |
| Group*Age at oocyte retrieval    | 0.96 [0.91; 1.01]    |



# H.U.Dexeus - VITRIFICATION vs SLOW FREEZING. PREGNANCY AND LIVEBIRTH RATES



**Freezing**  
— Slow  
— Vitri



**Freezing**  
— Slow  
— Vitri

Is it better to transfer blastocysts?

# BLASTOCYST VS CLEAVAGE FET SART 2004 - 2013

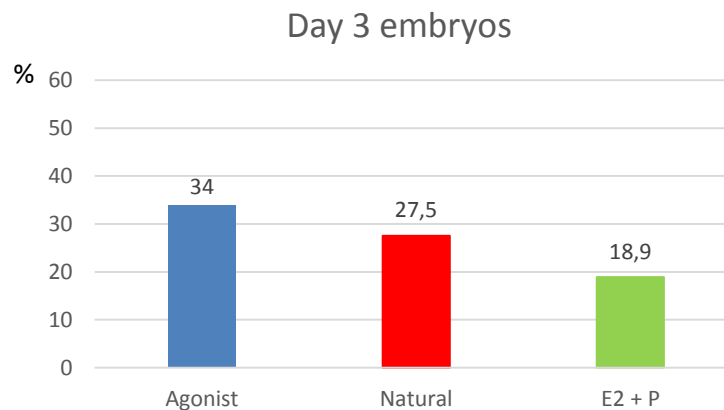
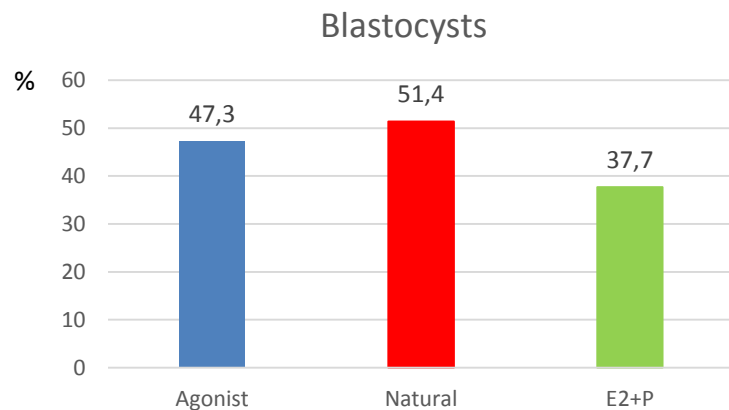


| <b>Outcome</b>                    | <b>Adjusted Odds ratios</b> | <b>Confidence interval</b> |
|-----------------------------------|-----------------------------|----------------------------|
| Live birth                        | 1.49                        | 1.44, 1.54                 |
| Clinical pregnancy rate           | 1.68                        | 1.63, 1.74                 |
| Miscarriage rate                  | 0.93                        | 0.88, 0.98                 |
| Preterm delivery <37 wk gestation | 1.16                        | 1.06, 1.27                 |

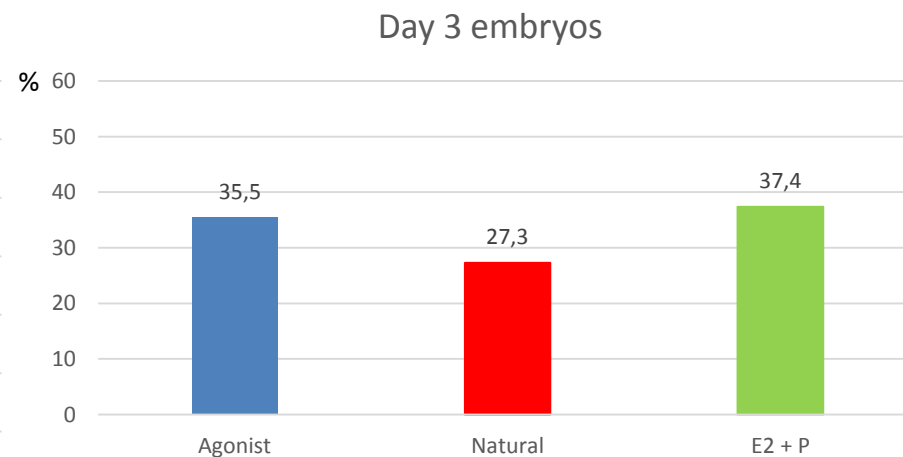
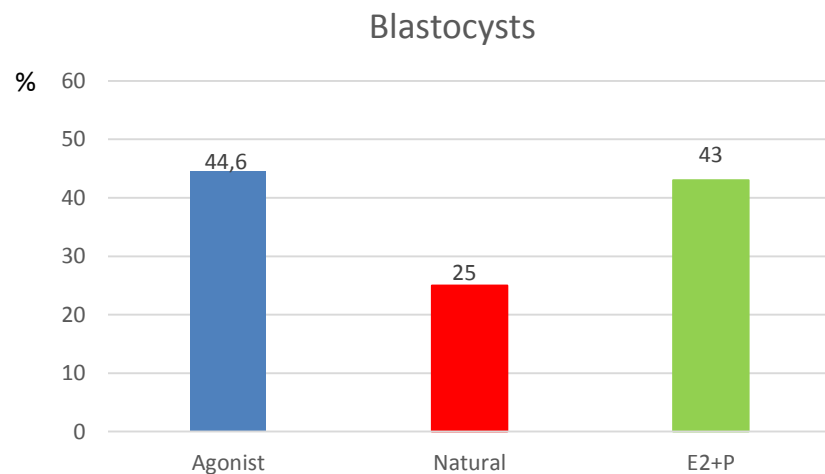
**Blastocyst (118572) vs Cleavage (117619)**



## FET-IVF

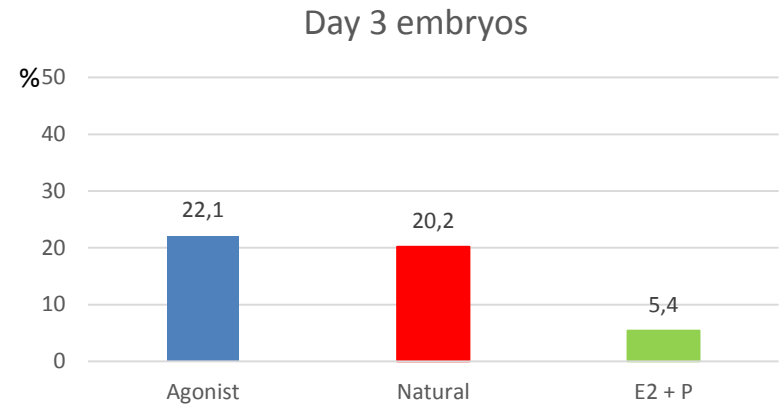
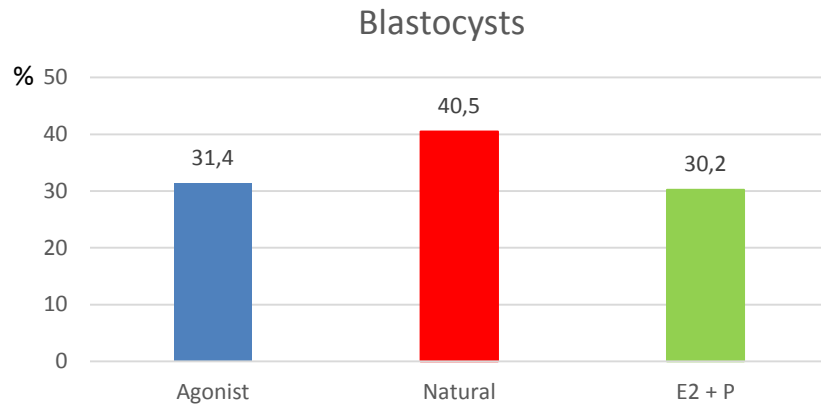


## FET-DON

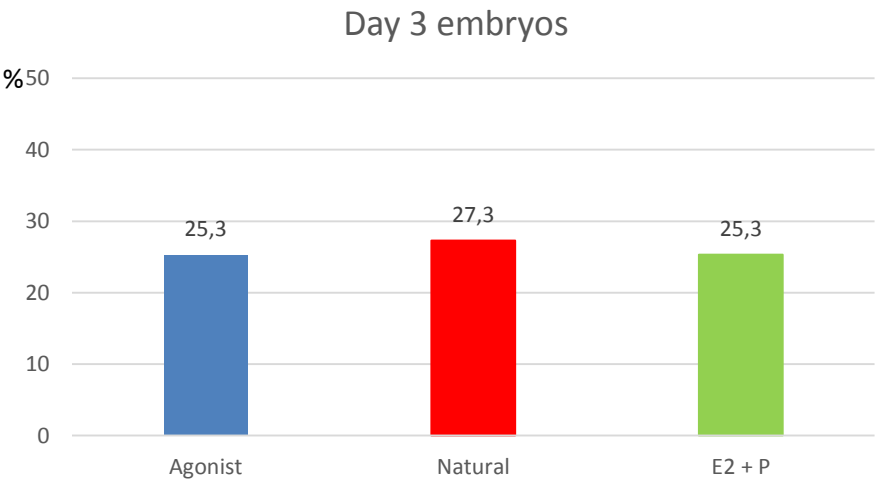
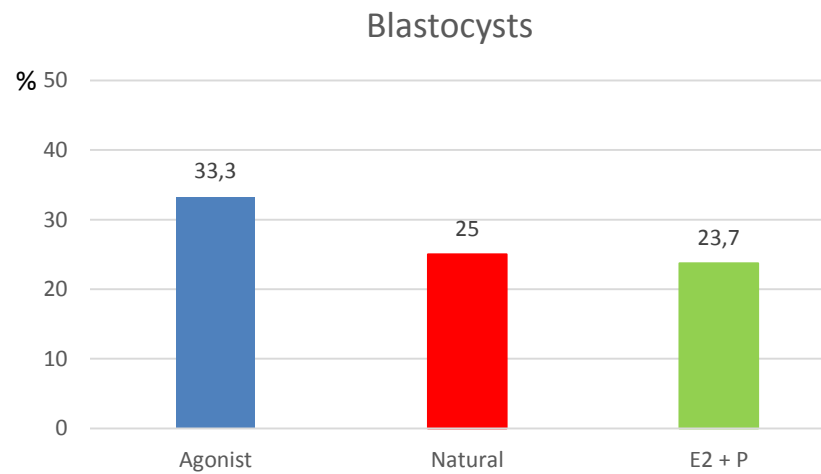




## FET-IVF



## FET-DON



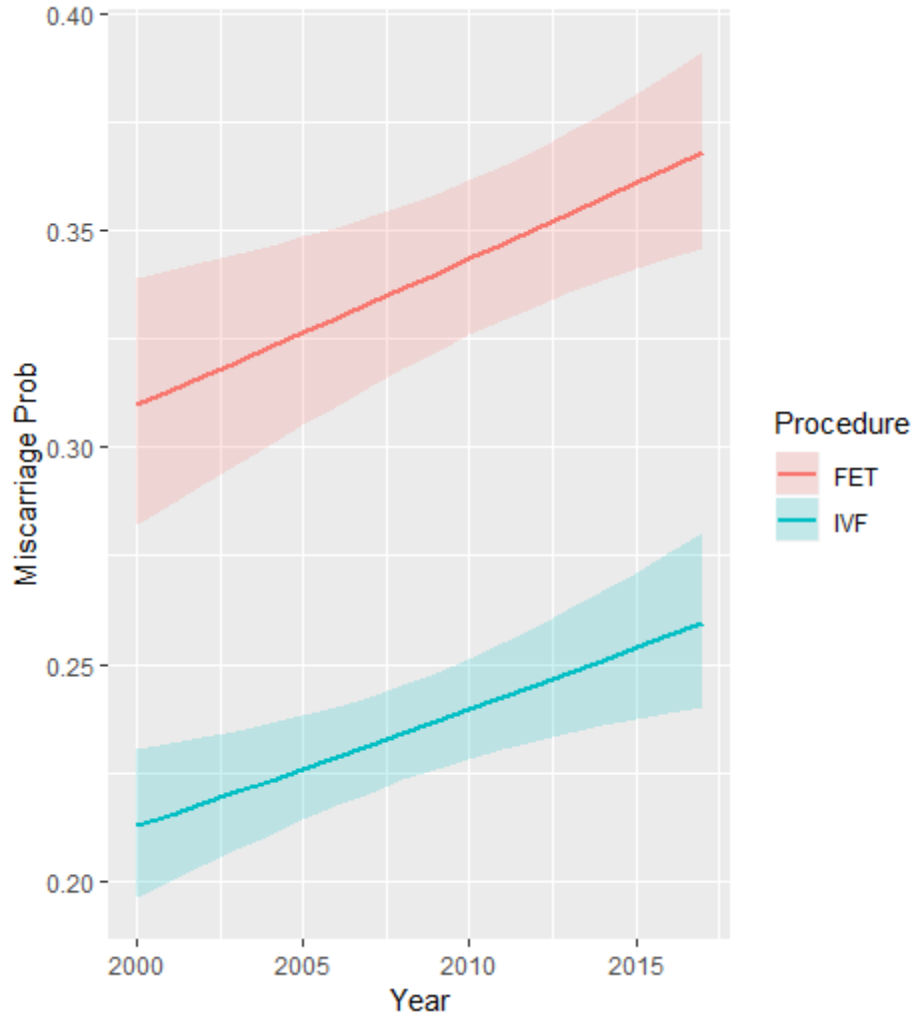
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Is there a higher miscarriage rate in FET?

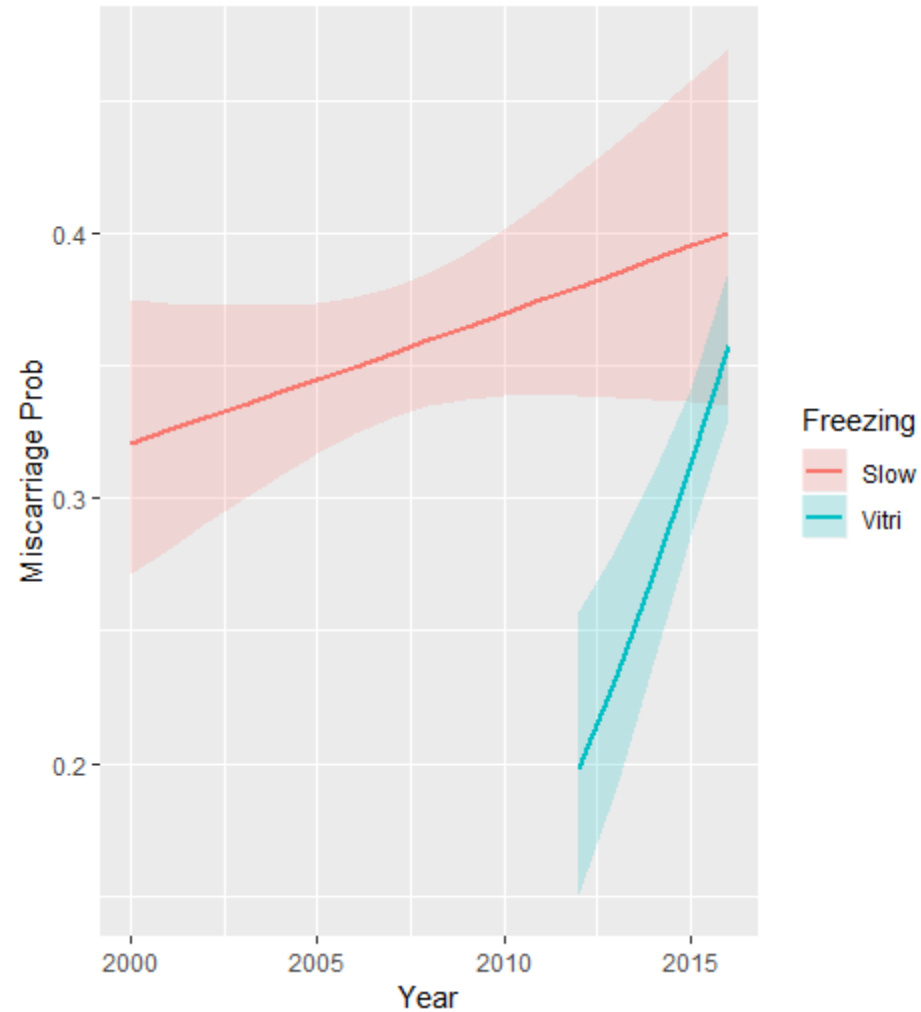
# H.U.Dexeus - MISCARRIAGE RATES IN IVF/ FET AND VITRIFICATION AND SLOW FREEZING



### FET vs. IVF MISCARRIAGE



### FET Freezing



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Are there greater obstetric and neonatal complications following FET?

# PERINATAL AND OBSTETRICAL RISKS/CONGENITAL ANOMALIES



Human Reproduction, Vol.29, No.7 pp. 1552–1557, 2014  
Advanced Access publication on May 7, 2014 doi:10.1093/humrep/deu088

human  
reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

## Major congenital anomalies in children born after frozen embryo transfer: a cohort study 1995–2006

S. Pelkonen<sup>1,\*</sup>, A.-L. Hartikainen<sup>1</sup>, A. Ritvanen<sup>2</sup>, R. Koivunen<sup>3</sup>,  
H. Martikainen<sup>1</sup>, M. Gissler<sup>2,4</sup>, and A. Tiitinen<sup>5</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Oulu University Hospital, PO Box 24, Oulu 90029 OYS, Finland <sup>2</sup>National Institute for Health and Welfare (THL), PO Box 30, Helsinki 00271, Finland <sup>3</sup>Väestöliitto Fertility Clinics Ltd, Kiviharjunte 11, Oulu 90220, Finland <sup>4</sup>NHIV, Nordic School of Public Health, Box 12133, Gothenburg SE-40242, Sweden <sup>5</sup>Department of Obstetrics and Gynecology, Helsinki University Central Hospital and Helsinki University, PO Box 140, Helsinki 00029 HUS, Finland

**Major congenital anomalies  
are similar to IVF  
Adjusted Odd Ratio (aOR) 0.95; 0.71-1.27**

## Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer?

Abha Maheshwari<sup>1,\*</sup>, Shilpi Pandey<sup>2</sup>, Edwin Amalraj Raja<sup>3</sup>,  
Ashalatha Shetty<sup>1</sup>, Mark Hamilton<sup>1</sup>, and Siladitya Bhattacharya<sup>3</sup>

<sup>1</sup>Aberdeen Maternity Hospital NHS Grampian, AB 25 2ZL, Scotland, UK <sup>2</sup>CARE Fertility Nottingham, John Webster House, 6 Lawrence Drive, Nottingham Business Park, Nottingham NG8 6PZ, UK <sup>3</sup>School of Medicine and Dentistry, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK

**Table III Summary of findings from cumulative meta-analysis.**

| Risk of outcome                     | Evidence                         | Evidence available by year | No further change in precision, magnitude or direction | More observational data needed |
|-------------------------------------|----------------------------------|----------------------------|--|--------------------------------|
| Small for gestational age           | Lower in Frozen embryo transfer  | 2010                       | 2014   | No                             |
| Low birth weight                    | Lower in Frozen embryo transfer  | 1997                       | 2014   | No                             |
| Very low birth weight               | Lower in Frozen embryo transfer  | 2013                       | 2016   | No                             |
| Large for gestational age           | Higher in Frozen embryo transfer | 2010                       | 2014   | No                             |
| High birth weight                   | Higher in Frozen embryo transfer | 2014                       | 2016   | No                             |
| Very high birth weight              | Higher in Frozen embryo transfer | 2013                       | 2014   | No                             |
| Preterm delivery                    | Lower in Frozen embryo transfer  | 2005                       | 2014   | No                             |
| Very preterm delivery               | Lower in Frozen embryo transfer  | 2016                       | 2016   | No                             |
| Antepartum haemorrhage              | No difference                    | 2010                       | 2014   | Yes                            |
| Admission to NICU                   | No difference                    | 2012                       | 2013   | Yes                            |
| Congenital anomalies                | No difference                    | 2014                       | 2016   | Yes                            |
| Perinatal mortality                 | No difference                    | 2014                       | 2014   | Yes                            |
| Hypertensive disorders of pregnancy | Higher in Frozen embryo transfer | 2015                       | 2015   | Yes                            |

# H.U.Dexeus - IVF/DON. FRESH vs FROZEN CYCLES. OBSTETRICAL AND NEONATAL COMPLICATIONS



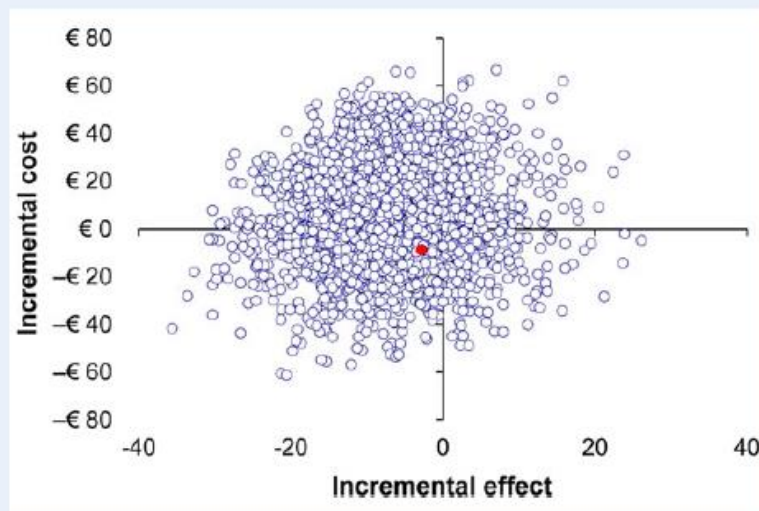
|                          | FET-DON<br>(n=52) | FET-IVF<br>(n=221) | IVF<br>(n=763) | DON<br>(n=337) | <i>p</i> |
|--------------------------|-------------------|--------------------|----------------|----------------|----------|
| NICU admission           | 1,9%              | 1,4%               | 2,6%           | 3,9%           | ns       |
| Perinatal death          | 0,0%              | 0,0%               | 0,4%           | 0,3%           | ns       |
| Postnatal death          | 0,0%              | 0,0%               | 0,3%           | 0,0%           | ns       |
| Prematurity < 28         | 0,0%              | 0,0%               | 0,1%           | 0,6%           | ns       |
| Prematurity < 34         | 0,0%              | 0,5%               | 1,4%           | 2,7%           | ns       |
| Prematurity < 37         | 7,7%              | 2,7%               | 7,2%           | 10,1%          | <.05     |
| Cesarean section         | 65,4%             | 44,3%              | 34,6%          | 62,9%          | <.001    |
| Gestational diabetes     | 23,1%             | 15,4%              | 11,7%          | 19,0%          | <.05     |
| Postpartum hemorrhage    | 15,4%             | 9,0%               | 4,5%           | 6,5%           | <.05     |
| Congenital abnormalities | 3,8%              | 5,4%               | 2,5%           | 4,7%           | ns       |
| Hypertension             | 5,8%              | 4,1%               | 2,6%           | 9,5%           | <.05     |
| Male babies              | 55,8%             | 51,6%              | 48,9%          | 53,7%          | ns       |
| Fetal weight             | 3221+493          | 3416+459           | 3141+520       | 3183+551       | <.001    |



Does the cost of the treatment vary?

**Table II Outcomes per embryo transfer.**

|                       | Overall         | Type of frozen embryo transfer cycle |                | OR (95% CI)     | P-value |
|-----------------------|-----------------|--------------------------------------|----------------|-----------------|---------|
|                       |                 | Modified natural                     | Artificial     |                 |         |
| Clinical pregnancy/ET | 167/734 (22.8%) | 94/394 (23.9%)                       | 75/340 (22.1%) | 0.8 (0.64–1.27) | 0.6     |
| Ongoing pregnancy/ET  | 101/734 (13.8%) | 57/394 (14.5%)                       | 45/340 (13.2%) | 0.8 (0.52–1.22) | 0.3     |
| Live birth/ET         | 98/734 (13.4%)  | 57/394 (14.5%)                       | 41/340 (12.1%) | 0.8 (0.53–1.25) | 0.3     |



**Figure 3** Cost-effectiveness plane based on bootstrap analysis displaying differences in LBR compared with differences in cost between modified natural cycle and artificial cycle frozen embryo transfer. The red dot represents the actual difference in LBR and costs.

# H.U.Dexeus- FROZEN THAWED EMBRYO TRANSFER (FET) COST



|                      | Agonist       | E <sub>2</sub> - P | Natural |
|----------------------|---------------|--------------------|---------|
| Cost / Cycle (€)     | 412 (↑ 206%)  | 330 (↑ 165%)       | 200     |
| Cost / Livebirth (€) | 1794 (↑ 233%) | 1524 (↑ 198%)      | 768     |

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Is hormone monitoring important?

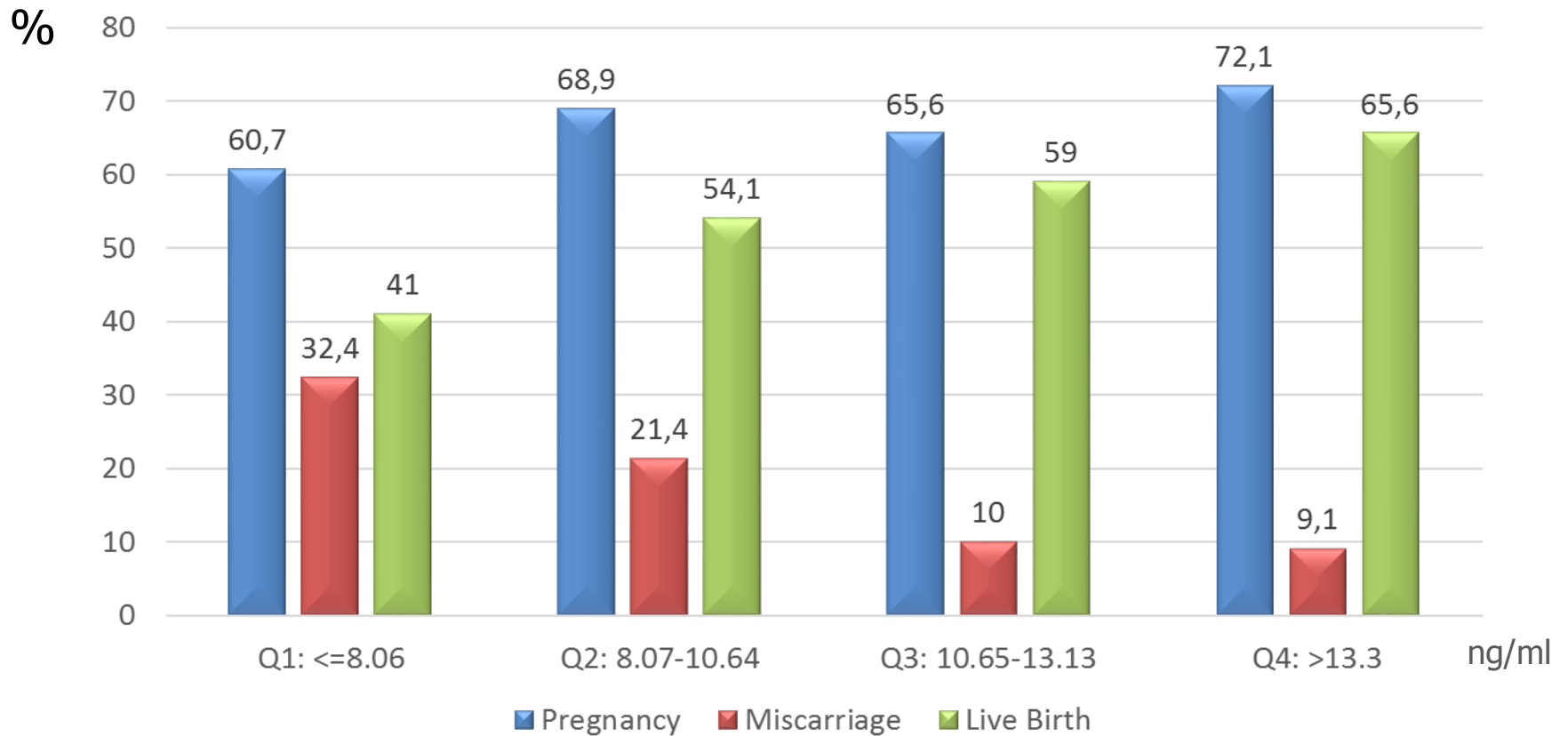
*“Low serum progesterone the day prior to frozen embryo transfer of euploid embryo is associated with significant reduction in live birth rates”.*

- 244 frozen euploid transfer
- January 2016- June 2017
- Retrospective cohort study (NCT03395665)
- Endometrial preparation:
  - Estradiol Valerate (6 mg/d)
  - Vaginal micronized Progesterone (200 mg/8h)
- A multivariate analysis to assess the relationship between serum P4 level and miscarriage and live birth (LBR) was performed, adjusted for confounding variables (maternal age at OPU, endometrial thickness, embryo quality and estradiol)

# EUPLOID BLASTOCYSTS FET



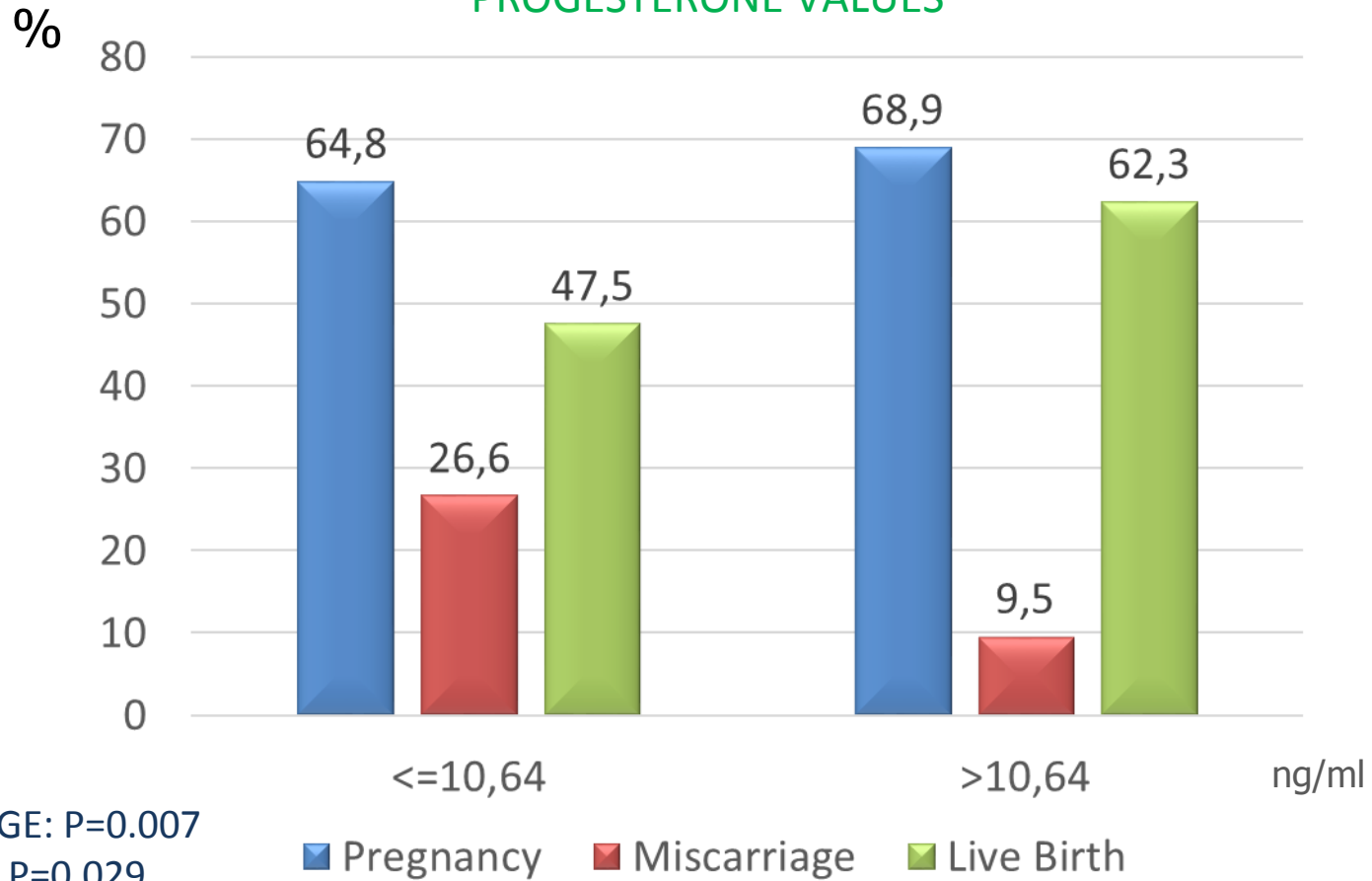
## PROGESTERONE LEVELS DAY PRIOR FET



# EUPLOID BLASTOCYSTS TRANSFERS



## PREGNANCY OUTCOMES FOR MEDIAN SERUM PROGESTERONE VALUES



*Could we reduce the miscarriage rate in patients with P4 <10.64 ng/ml (day prior FET) by increasing progesterone levels with higher doses of progesterone?*





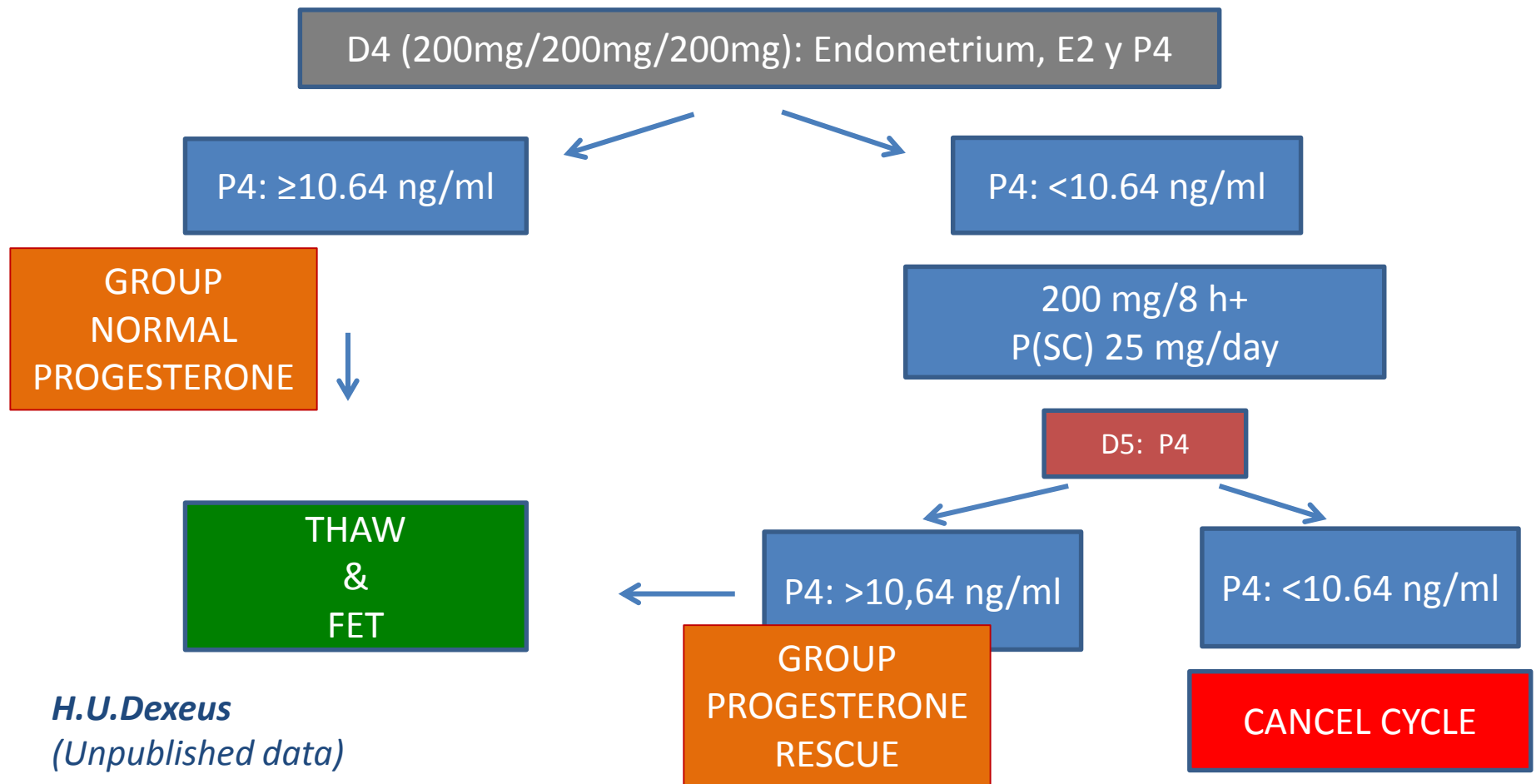
# PROSPECTIVE STUDY: EUPLOID BLASTOCYSTS FET



115 EUPLOID BLASTOCYSTS FET

## ARTIFICIAL CYCLE

a-GnRH (optional)  
Estradiol Valerate: 6 mgrs/day  
Vaginal micronized progesterone: 200/8h.



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(Unpublished data)

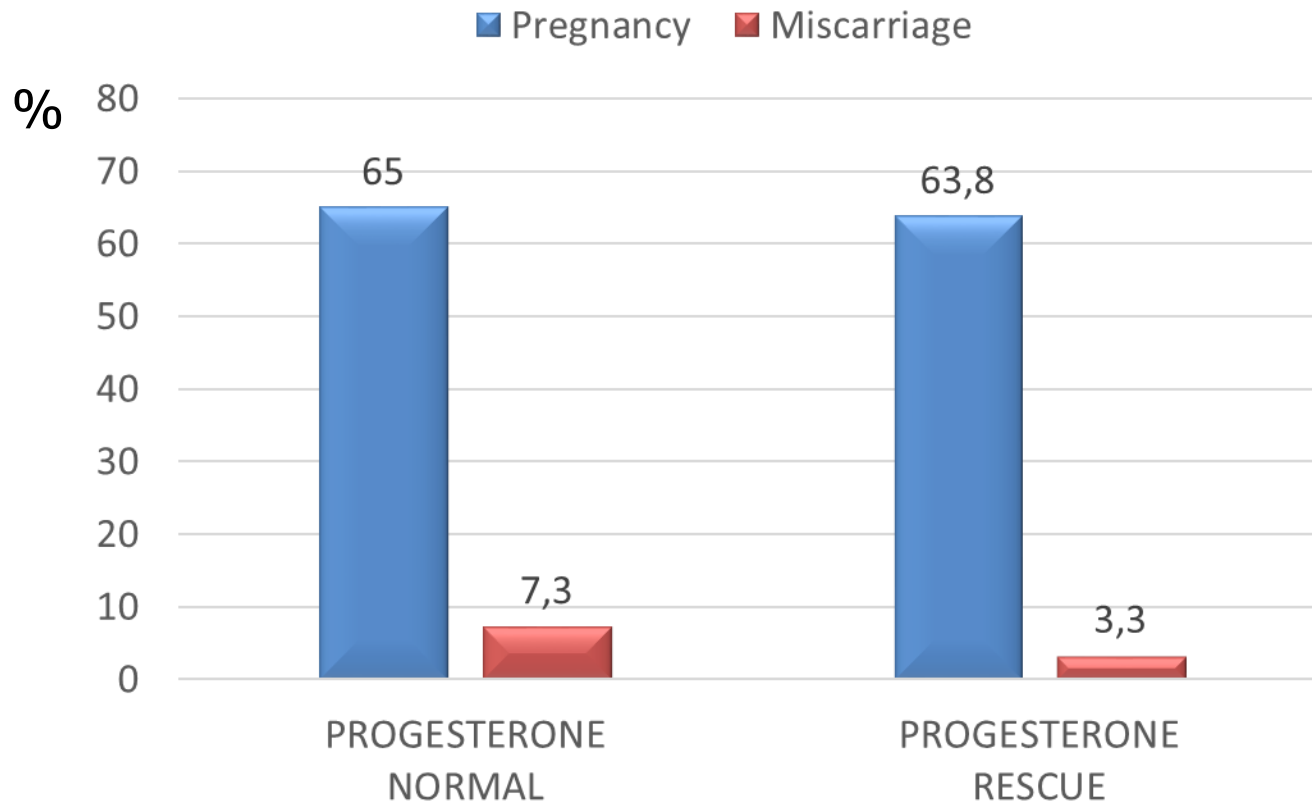
# PROSPECTIVE STUDY: EUPLOID BLASTOCYSTS FET



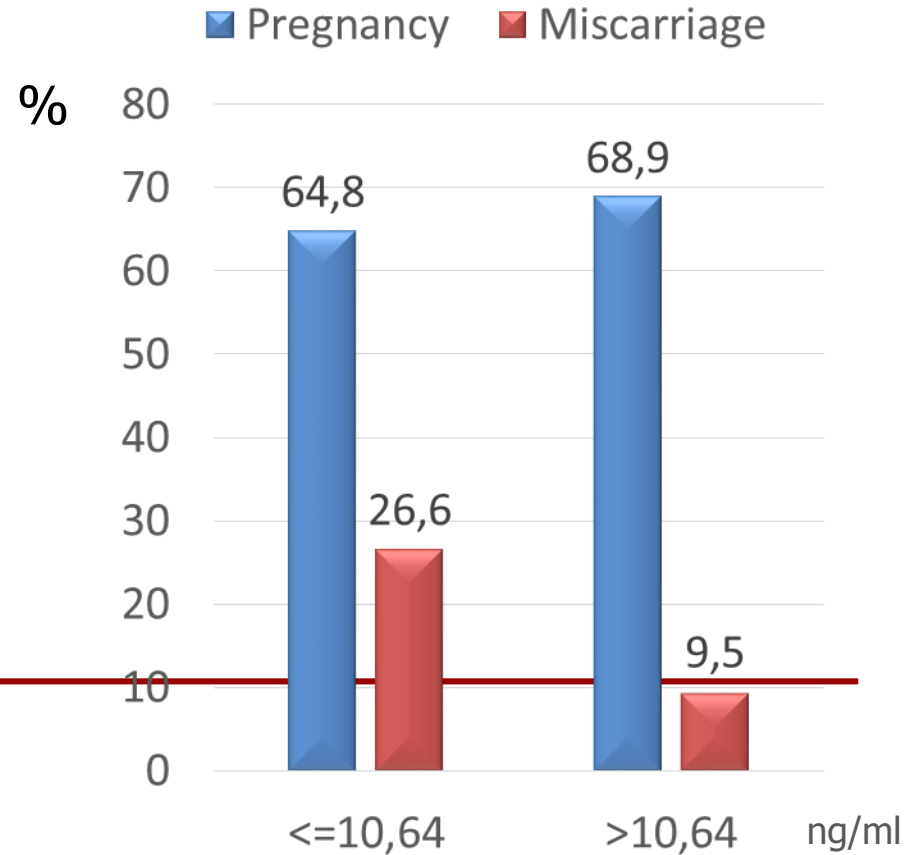
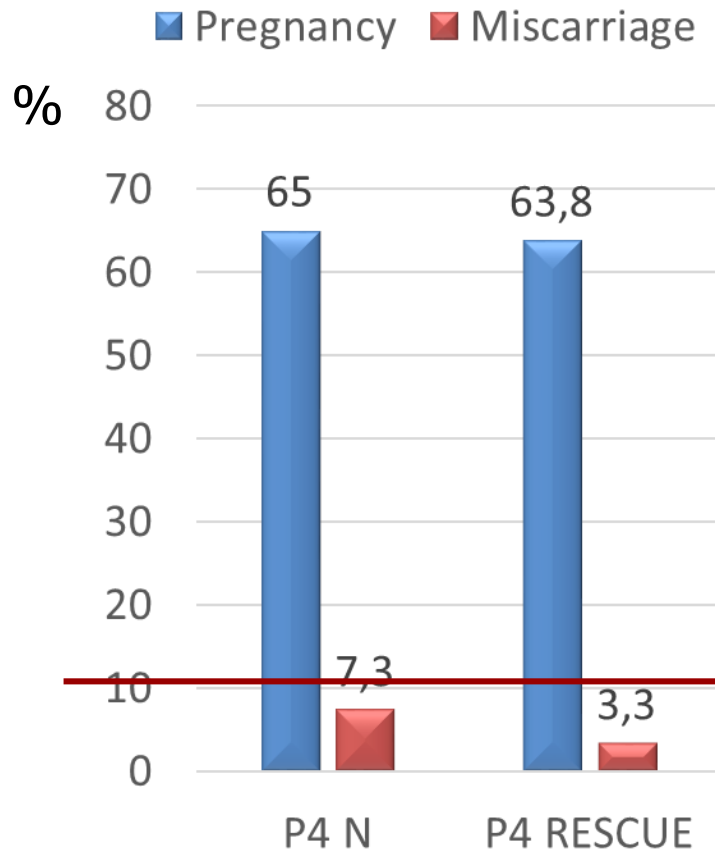
|                                    | PROGESTERONE<br>NORMAL | PROGESTERONE<br>RESCUE |
|------------------------------------|------------------------|------------------------|
| FET                                | 65 (56.5%)             | 55 (43.5%)             |
| AGE                                | 39.8 ± 4.2             | 39.1 ± 2.7             |
| BMI                                | 24.2 ± 3.6             | 24.1 ± 2.9             |
| ENDOMETRIAL THICKNESS<br>(mm)      | 10.4 ± 1.6             | 10.9 ± 1.5             |
| ESTRADIOL (pg/ml)                  | 209.1 ± 73.7           | 223.1 ± 130.9          |
| P4 PRE-FET DAY (ng/ml)             | 15.0 ± 7.1             | 8.5 ± 1.5              |
| P4 FET DAY (ng/ml)                 |                        | 20.8 ± 10.5            |
| EUPLOID BLASTOCYSTS<br>TRANSFERRED | 1.1 ± 0.3              | 1.1 ± 0.3              |
| TRANSFER SCORE                     | 9.5 ± 0.8              | 9.1 ± 1.2              |

**H.U.Dexeus**  
(Unpublished data)

# PROSPECTIVE STUDY: EUPLOID BLASTOCYSTS FET



# PROSPECTIVE STUDY: EUPLOID BLASTOCYSTS FET



## TAKE-HOME MESSAGES!!

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- Strong trend towards FET
- There is no actual evidence of the superiority of one single endometrial preparation over the others
- According to treatment there is no consensus about dosage or administration routes. So, we should not forget about novel administration routes
- TREATMENT ELECTION: depends on age, menstrual cycle type, costs, medical secondary effects, physician and PATIENT preferences
- Low progesterone levels on the day prior to FET are associated with a decreased livebirth rates
- Low progesterone levels can be rescued with a daily s.c. administration of progesterone decreasing miscarriage rates and improving livebirth rates

*Yesterday, today  
and forever*

**Dexeus**  
mujer



Thank you for your attention  
Muchas gracias por su atención

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