The uterus and IVF
Embryo Pregnancy

The uterus and IVF

Biology of endometrial receptivity

E2 and P4 effects: The donor-egg IVF lesson

Luteal E2

Late follicular P

Practical measures to optimize endometrial receptivity:

Before IVF
Minimize A Fluid in endom
Too thin end.

Intercourse and endom. receptivity

Uterine contractility

Androgens

Pregnancy

Contractility
E2 and P4 effects
the donor-egg IVF
lesson

The menstrual
cycle

Donor egg IVF: A model to study
the endometrial effects of E2 and
progesterone

The oocyte
donor

A model to
study the
effects of
E2 and P

The recipient

Estrogen and
Progesterone treatment

[Diagram showing menstrual cycle, oocyte donor, and recipient with E2 and progesterone effects indicated.]
Endometrial glands

Endometrial stroma

Day 20

Day 24

E2/progesterone effects on endometrial morphology

E2/progesterone effects on endometrial morphology

E2/progesterone effects on endometrial morphology

- No effect on endometrial morphology

Donor-egg IVF: a model for priming frozen embryo transfers

1. E2 from day 25 of previous cycle
   - Oral: mic E2 2-4 mg BID
   - Trans derm.: 0.1-0.2 mg 2x/wk
   - Add vag E2 if necessary

2. Measure serum P last day on E2 only

3. ET on P day 3-4

Morphometric analysis of endometrium in case of high E2 levels

Basir GS et al.

E2 < 20,000 pmol/L
Nat. cycle

E2 > 20,000 pmol/L
Moderate COH

E2 > 20,000 pmol/L
High responders w/ gland-stromal dyssynchrony:
Delayed glandular development
Oedematous stroma
Simon C. et al.  
_Fertil Steril_ 1998;70:234-9

86 High responders  
previous failed IVF  
>3 good quality embryos

- 24 Step down  
- 62 Regular protocol

<table>
<thead>
<tr>
<th></th>
<th>Step-dn</th>
<th>Std</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.6</td>
<td>33.9</td>
<td>NS</td>
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<tr>
<td>Amps</td>
<td>22.4</td>
<td>31.6</td>
<td>NS</td>
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<tr>
<td>E2</td>
<td>1919</td>
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<td>Oocytes</td>
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<td>0.001</td>
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<td>E.Trans.</td>
<td>3.3</td>
<td>3.4</td>
<td>NS</td>
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<tr>
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<td>2.5</td>
<td>3.1</td>
<td>NS</td>
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<tr>
<td>PR</td>
<td>64.2</td>
<td>24.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impl R</td>
<td>29.3</td>
<td>8.5</td>
<td>0.02</td>
</tr>
<tr>
<td>OHSS</td>
<td>0</td>
<td>12.9</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Supplementing luteal E2?

Not supported by donor-egg IVF data (mock cycles).


Not supported by early IVF data

Smitz J. Human Reprod 1992;7:168-75
Smitz J. Human Reprod 1993;8:40-5

Motivated by fear of mid-luteal drop in E2 levels

Hung E. Human Reprod 2000;15:1903-8  Trend only
Sahara F.I. Human Reprod 1999;14:2777-82

Are IVF results better when hCG is used for luteal support?

No: Martinez F. Gynecol Endocrinol 2000;14:316-20  PRS, n = 310
**Farhi et al.**  
*Fertil Steril* 2000;73:761-6

Prospective randomized study in 271 IVF patients whose E2>2500pg/ml

<table>
<thead>
<tr>
<th>E2</th>
<th>Micronized E2 (2mg BID), starting 7 days after ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>P4</td>
<td>50mg im Q day +50 mg vag BID</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>P</em></td>
<td><em>P+E2</em></td>
</tr>
<tr>
<td>n patients</td>
<td>142</td>
<td>129</td>
</tr>
<tr>
<td>n cycles</td>
<td>149</td>
<td>136</td>
</tr>
<tr>
<td>long GnRH-a</td>
<td>113</td>
<td>101</td>
</tr>
<tr>
<td>short GnRH-a</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>emb transf</td>
<td>3.8</td>
<td>3.7</td>
</tr>
<tr>
<td>PR</td>
<td>23.4</td>
<td>33.8</td>
</tr>
<tr>
<td>long GnRH-a</td>
<td>25.6</td>
<td>39.6*</td>
</tr>
<tr>
<td>Impl rate</td>
<td>9.6</td>
<td>14</td>
</tr>
</tbody>
</table>
Supplementing luteal E2?


Prospective randomized study in 81 IVF patients (85 cycles)

**E2** Micronized E2 (2mg BID), starting day3 of menses until luteal phase

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 27)</th>
<th>E2 (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>25.90%</td>
<td>48.30%</td>
</tr>
<tr>
<td>IR</td>
<td>10%</td>
<td>26%</td>
</tr>
</tbody>
</table>

No impact on fertilization rate
Late follicular P

Late luteal elevation of plasma progesterone

P elevation associated with IVF poorer outcome

P elevation only affects the endometrium

P elevation has no impact on IVF outcome
Silverberg KM. J Clin Endocrinol Metab. 1991;73:797-803.
Late follicular P

Late luteal elevation of plasma progesterone

<table>
<thead>
<tr>
<th>Weak</th>
<th>Intermediate</th>
<th>Strong</th>
</tr>
</thead>
<tbody>
<tr>
<td>P &gt; 0.9 ng/ml</td>
<td>3.20%</td>
<td>30%</td>
</tr>
<tr>
<td>P &lt; 0.9 ng/ml</td>
<td>23%</td>
<td>31%</td>
</tr>
</tbody>
</table>


Pathophysiology:

Which are the respective roles of FSH, LH and hCG on P and androgen elevation during the late follicular phase?

The designated suspect, LH, was not the culprit, FSH.
Androgens

P, Androgens T & D4

Effects of FSH

Effects of hCG
Luteinizing hormone increases estradiol secretion but has no effect on progesterone concentrations in the late follicular phase of in vitro fertilization cycles in women treated with gonadotropin-releasing hormone agonist and follicle-stimulating hormone.


Prospective randomized: (n = 40)
COH with GnRH-a and FSH 300 IU/day until foll. ≥ 15 mm

Then, either:
- FSH 225 IU
- hMG 225 IU
Sequential hMG/rFSH - mini hCG regimen

Used when OHSS is feared (PCOD)
Experience on 18 patients
No premature P elevation, normal E2 rise
Cx mucus and endom. unchanged,
Good oocytes, embryo and PR:
IVF 3/5(60%), IUI 4/13(31%), No OHSS
Prospective evaluation of the ultrasound appearance of the endometrium in a cohort of 1,186 infertile women


- 539 IUI: cl PR 19.7%
- 712 IVF: cl PR 25.4%

Endom. thickness correlated w/ E2

Odd Ratio for pregnancy only marginally affected by endometrial proliferation
Endometrial echogenicity

Early hyperechogenic changes are of poor prognosis

Renato Faechin, M.D., Claudia Righini, M.D., Jean-Marc Ayoubi, M.D., François Olivier, M.D., Dominique de Ziegler, M.D., and René Frydman, M.D.
Department of Obstetrics and Gynecology and Reproductive Endocrinology, Hôpital Antoine Béclère, Clamart, France

In Vitro Fertilization

High foll. P4 hastens endometrial changes

Fertility and Sterility
Vol. 74, No. 2, August 2000
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Printed in U.S.A.

Image digitization selection gray level analysis results

<table>
<thead>
<tr>
<th>Extent of hyperechogenic transformation (%)</th>
<th>≤ 30%</th>
<th>31-40%</th>
<th>41-50%</th>
<th>51-60%</th>
<th>61-70%</th>
<th>&gt; 70%</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>34</td>
<td>37</td>
<td>37</td>
<td>55</td>
<td>37</td>
<td>28</td>
</tr>
</tbody>
</table>

Clinical pregnancy rates according to the extent of hyperechogenic endometrial transformation assessed on the day of hCG administration (n=400).

Cause of late foll. Hyperechogenicity?
Endometrial echogenicity

Early hyperechogenic changes are of poor prognosis

High foll. P4 hastens endometrial changes

P = 0.9 ng/mL
O = ≤ 0.9 ng/mL

Endometrial echogenicity (%) vs. Clinical pregnancy rates according to the extent of hyperechogenic endometrial transformation assessed on the day of hCG administration (P<0.001).

Cause of late foll. Hyperechogenicity?
Endometrial echogenicity

Early hyperechogenic changes

6 echogenicity groups:

- ≤ 30% (n=34)
- 31-40% (n=37)
- 41-50% (n=37)
- 51-60% (n=55)
- 61-70% (n=37)
- > 70% (n=28)

High foll. P4 hastens endometrial changes
Endometrial echogenicity

Early hyperechogenic changes are of poor prognosis

Renato Fanchin, M.D., Claudia Righini, M.D., Jean-Marc Ayubbi, M.D.,
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In Vitro Fertilization

FERTILITY AND STERILITY®
Vol. 74, No. 2, AUGUST 2000
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Image digitization selection gray level analysis results

Hyperechogenicity:

Hyperech. ant. 10%
Hyperech. post. 15%
Hyperech. mean 13%
End. thickness 9.5 mm

≤ 30% 31-40% 41-50% 51-60% 61-70% > 70%
(n=34) (n=37) (n=37) (n=55) (n=37) (n=28)

Day hCG

Cause of late foll. Hyperechogenicity?

High foll. P4 hastens endometrial changes

Clinical pregnancy rates according to the extent of hyperechogenic endometrial transformation assessed on the day of hCG administration (n=200).
Early data: PI elevated in a fraction of pts (despite high E2 levels): poor prognosis.

De Ziegler et al. Fertil Steril 1991

Uterine Doppler and endometrial receptivity

De Ziegler et al. Fertil Steril 1991


Recent PI data: Low values across the board

<table>
<thead>
<tr>
<th></th>
<th>Preg (31)</th>
<th>Not Preg (125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>32.1</td>
<td>33.1</td>
</tr>
<tr>
<td>E2</td>
<td>1897</td>
<td>1837</td>
</tr>
<tr>
<td>oocytes</td>
<td>14.2</td>
<td>11.7</td>
</tr>
<tr>
<td>emb.</td>
<td>4.8</td>
<td>3.9</td>
</tr>
<tr>
<td>endom th.</td>
<td>10.7</td>
<td>10.9</td>
</tr>
<tr>
<td>PI (ret)</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>PI (ET)</td>
<td>1.09</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Sub-endometrial and endometrial blood flow
Computer assisted assessment of Endometrial Power Doppler Area (EPDA)

Neither Doppler of the spiral or uterine arteries nor endometrial thickness or volume was predictive of IVF outcome
# Uterine contractility

## Contractility of the non-pregnant uterus

<table>
<thead>
<tr>
<th>Phase</th>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End follicular phase</strong></td>
<td>4-5 UC/min</td>
<td>Mainly retrograde&lt;br&gt;Involved in sperm transport&lt;br&gt;Sub-endometrial layers</td>
</tr>
<tr>
<td><strong>Mid luteal phase</strong></td>
<td>&lt;2.5 UC/min</td>
<td>Utero-quiescence&lt;br&gt;Mild biderectonal UC</td>
</tr>
<tr>
<td><strong>Luteo-follicular transition</strong></td>
<td>2-3 UC/min</td>
<td>Antegrad&lt;br&gt;All layers involved&lt;br&gt;Often painful</td>
</tr>
</tbody>
</table>

**Retrograde transport of Tc-99 MAA**<br>Study displacement of ut content

**Frequency is primary parameter, UTZ is appropriate**

**IUP or collection of endometrial debris.**
Uterine contractility and IVF

Effects of P


UC/min

UC in menstrual cycle and IVF

Epiney et al. ASRM 2000
In IVF, high E2 levels induce a relative resistance to the uteroquiescent properties of P4.
Uterine contractility and hormonal levels

**hCG**

- E2: $r=0.04; \text{NS}$
- P: $r=0.21; \text{NS}$

**ET**

- E2: $r=0.03; \text{NS}$
- P: $r=-0.55; P<0.001$
Endometrial movement was obvious in 36.4% (44/121) of cases

<table>
<thead>
<tr>
<th></th>
<th>active movement</th>
<th>no movement seen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preg.</td>
<td>45.4% (20/44)</td>
<td>15.6% (12/77)</td>
</tr>
</tbody>
</table>
Biology of endometrial receptivity

Endometrial ultra structure

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pinopodes</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nat cycle</td>
<td>20-21</td>
<td>20</td>
</tr>
<tr>
<td>COH</td>
<td>18-19</td>
<td>19</td>
</tr>
<tr>
<td>E2/P</td>
<td>22</td>
<td>21-22</td>
</tr>
</tbody>
</table>


Ovulation

Implant.

Biology of endometrial receptivity

Pinopodes
Effects of the Yuzpe regimen of emergency contraception on markers of endometrial receptivity


Population
19 women underwent a control and study cycle

Treatment
On day of LH surge:
100 mg EE
1 mg norgestrel

EMB 9 ds after LH surge

<table>
<thead>
<tr>
<th></th>
<th>Yuzpe</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 19)</td>
<td>(n = 19)</td>
<td></td>
</tr>
<tr>
<td><strong>Ultrasounds</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endom. Thick.</td>
<td>7.58</td>
<td>9.79</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Endometrium (HSCORE)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b3 integrins</td>
<td>1.75</td>
<td>1.19</td>
<td>NS</td>
</tr>
<tr>
<td>Glycodelin</td>
<td>2.39</td>
<td>3.32</td>
<td>NS</td>
</tr>
<tr>
<td>LIF</td>
<td>2.33</td>
<td>2.05</td>
<td>NS</td>
</tr>
<tr>
<td>MUC-1</td>
<td>2.30</td>
<td>3.16</td>
<td>0.05</td>
</tr>
<tr>
<td>ER</td>
<td>1.58</td>
<td>0.82</td>
<td>0.009</td>
</tr>
<tr>
<td>PR</td>
<td>0.01</td>
<td>0.02</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Serum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>102.89</td>
<td>140.14</td>
<td>0.007</td>
</tr>
<tr>
<td>P (ng/ml)</td>
<td>13.12</td>
<td>13.65</td>
<td>NS</td>
</tr>
<tr>
<td>Glycodelin (mcg/ml)</td>
<td>3.65</td>
<td>3.65</td>
<td>NS</td>
</tr>
</tbody>
</table>
Serum CA 125 concentrations as predictor of pregnancy

CA 125: glycoprotein also produced in the endometrium and measurable in peripheral blood. Could it predict endom. receptivity?

 Predictor of pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Non-pregnant</th>
<th>Pregnant</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 75</td>
<td>40 (53.3%)</td>
<td>35 (46.7%)</td>
<td></td>
</tr>
<tr>
<td>day hCG -2</td>
<td>6.04</td>
<td>14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>day hCG -1</td>
<td>5.92</td>
<td>14.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>day retrieval</td>
<td>5.9</td>
<td>15.94</td>
<td>&lt;0.001</td>
</tr>
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</table>


Explanation for the discrepancy may lie in assay specificity

- Predictor of pregnancy


### Intercourse and endom. receptivity

**From: Cicinelli and de Ziegler Human Reprod 2000**

### Positive effects

<table>
<thead>
<tr>
<th>Frozen emb transfers</th>
<th>Fresh IVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercourse</td>
<td>No intercourse</td>
</tr>
<tr>
<td># cycles</td>
<td>91</td>
</tr>
<tr>
<td># embryos</td>
<td>168</td>
</tr>
<tr>
<td>Early PR</td>
<td>15.4</td>
</tr>
</tbody>
</table>

### No effects

**From: Cicinelli and de Ziegler Human Reprod 2000**


<table>
<thead>
<tr>
<th></th>
<th>Intercourse</th>
<th>No intercourse</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td># cycles</td>
<td>242</td>
<td>236</td>
<td></td>
</tr>
<tr>
<td># emb transferred</td>
<td>654</td>
<td>689</td>
<td></td>
</tr>
<tr>
<td>Clinical preg</td>
<td>57(23.6)</td>
<td>50(21.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Ongoing preg</td>
<td>47(19.4)</td>
<td>39(16.5)</td>
<td>NS</td>
</tr>
<tr>
<td>% viable embryo</td>
<td>11.01</td>
<td>7.69</td>
<td>0.036</td>
</tr>
</tbody>
</table>
Practical measures to optimize endometrial receptivity

- The endometrium before IVF
- Minimize effects of androgens
- Fluid in the endometrium
- The “too thin” endometrium
- Uterine contractility

Ultrasound

To rule out endometrial polyps and/or submucosal fibroids

Enhanced contrast (hystero-sonogram)

“3-D” reconstruction

Built-in or off-line systems

Hysteroscopy

Can be performed during OC pretreatment phase
Practical measures to optimize endometrial receptivity

• COH induces a >doubling of plasma testosterone levels. Possibly, more in some women (PCOD)?


OC pill

Minimize FSH, possibly coasting

dexamethasone

The endometrium before IVF
Minimize effects of androgens
Fluid in the endometrium
The “too thin” endometrium
Uterine contractility

By reducing FSH stimulation, coasting may lower androgens with E2

Decreases plasma and ovarian androgens

Decreases androgen (testosterone and A4) levels by blocking the adrenal contribution
  • End-follicular phase androgens are lower
  • Absolute value of FSH driven increase unchanged

A are higher in women w/ recurrent miscarriages

A inhibit endom cell growth
Practical measures to optimize endometrial receptivity

- The endometrium before IVF
- Minimize effects of androgens
- Fluid in the endometrium
- The “too thin” endometrium
- Uterine contractility

Aqueous fluid

Look for hydrosalpinx
Consider salpingectomy or tubal ligation

<table>
<thead>
<tr>
<th>n cycle</th>
<th>Dx TF</th>
<th>Hydro (UTZ)</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n Pt</td>
<td>843</td>
<td>327</td>
<td>71</td>
</tr>
<tr>
<td>ECF +</td>
<td>57(6.8%)</td>
<td>40(12%)</td>
<td>5(7%)</td>
</tr>
<tr>
<td>ECF-</td>
<td>786(93.2%)</td>
<td>287(87.8%)</td>
<td>66(93%)</td>
</tr>
<tr>
<td>p</td>
<td>Levi et al. ASRM 2000, # O-036</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Mucoid fluid

Sometimes (rarely) encountered throughout the menstrual cycle, unknown etiology.
Empirical approach:
D&C to R/o mucoid tumor and course of broad spectrum antibiotics
Practical measures to optimize endometrial receptivity

- The endometrium before IVF
- Minimize effects of androgens
- Fluid in the endometrium
- The “too thin” endometrium
- Uterine contractility

Verify quality of measurements

- Measure “between” rather than “during” uterine contractions
- If < 5 mm, differ ET

Exclude

- Endometritis
- s/p RT
- Enzymatic induction (donor-egg IVF and frozen embryo transfers)

Consider vaginal E2

- Estrace vaginal cream: 1g gel/0.1 mg E2
- Oral Estrace tablets 1-2 mg (as safe as oral E2 despite E2 levels >1000 pg/ml)
Practical measures to optimize endometrial receptivity

- The endometrium before IVF
- Minimize effects of androgens
- Fluid in the endometrium
- The “too thin” endometrium
- Uterine contractility

Low dose aspirin


Vasodilators

- NO donors
- Phosphodiesterase inhibitors

<table>
<thead>
<tr>
<th></th>
<th>aspirin</th>
<th>placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>35.9</td>
<td>35.4</td>
<td>NS</td>
</tr>
<tr>
<td>foll</td>
<td>19.8</td>
<td>10.2</td>
<td>.05</td>
</tr>
<tr>
<td>oocytes</td>
<td>16.2</td>
<td>8.6</td>
<td>.05</td>
</tr>
<tr>
<td>emb trans</td>
<td>3.3</td>
<td>3.3</td>
<td>NS</td>
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<tr>
<td>impl rate</td>
<td>17.8</td>
<td>9.2</td>
<td>.05</td>
</tr>
<tr>
<td>clin PR</td>
<td>45</td>
<td>28</td>
<td>.05</td>
</tr>
<tr>
<td>PI (ut art) d2</td>
<td>1.98</td>
<td>2.01</td>
<td>NS</td>
</tr>
<tr>
<td>PI (ut art) d hCG</td>
<td>1.22</td>
<td>1.96</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Practical measures to optimize endometrial receptivity

- The endometrium before IVF
- Minimize effects of androgens
- Fluid in the endometrium
- The “too thin” endometrium
- Uterine contractility

If UC frequency is excessive before ET:

- Delay ET until blastocyst
- Early onset of progesterone
- Use utero relaxant

Candidates:
- Betamimetics (terbutaline, ritodrine)
- NO donors (terbutaline, nitroprussiate)
- Ca channel blockers
- Xylocain

Epiney et al. ASRM 2000
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Day ET: 29%

Day retr.: 42%

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