In vitro fertilization with personalized blastocyst transfer versus frozen or fresh blastocyst transfer: a multicenter, randomized clinical trial

Simón C¹,²,³,⁴, Gómez C³, Cabanillas S⁴, Vladimirov IK⁵, Castillón G⁶, Giles J⁴, Boynukalin FK⁷, Fındikli N⁷, Bahçeci M⁷, Ortega I⁸, Vidal C⁴, Funabiki M⁹, Izquierdo A¹⁰, López L¹⁰, Portela S¹¹, Frantz N¹², Kulmann¹², Taguchi S⁹, Labarta E⁴, Colucci F¹³, Mackens S¹⁴, Santamaría X⁶, Muñoz E¹¹, Barrera S¹⁵, García-Velasco JA⁸, Fernández-Sánchez M¹⁶,¹⁷,¹⁸, Ferrando M¹⁹, Ruiz M³, Mol BW²⁰, Valbuena D²,³, on behalf of the ERA RCT consortium.

<table>
<thead>
<tr>
<th>University of Valencia, Valencia, Spain.</th>
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<tbody>
<tr>
<td>Igenomix Foundation-INCLIVA, Valencia, Spain.</td>
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<tr>
<td>Igenomix, Valencia, Spain.</td>
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<td>SBALAGRM, Sofia, Bulgaria.</td>
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<tr>
<td>Bahçeci Health Group-Fulga IVF Center, Istanbul, Turkey.</td>
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<td>Oak Clinic Japan, Osaka, Japan.</td>
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<td>ProcreaTec, Madrid, Spain.</td>
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<tr>
<td>Nilo Franz Reproductive Medicine, Porto Alegre, Brazil.</td>
</tr>
<tr>
<td>Centro de Infertilidade e Medicina Fetal do Norte Fluminense, Rio de Janeiro, Brazil.</td>
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<tr>
<td>Universitair Ziekenhuis Brussels, Brussels, Belgium.</td>
</tr>
<tr>
<td>Universidad de Sevilla. Seville, Spain.</td>
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<tr>
<td>Universidad Pablo Olavide, Seville, Spain.</td>
</tr>
<tr>
<td>Monash University, Monash Medical Center, Victoria, Australia.</td>
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</table>
These data were presented in the last ASRM Congress. With this presentation, we want to show you the data obtained with the ERARCT study. Please, don’t share this presentation without previous authorization.
The Endometrial Factor in ART

Endometrial Microbiota

Endometrial Receptivity

Maternal-Embryonic Crosstalk

Decidualization

Garrido-Gomez et al., JCEM 2011
Garrido-Gomez et al., Development 2017
Garrido-Gomez et al., PNAS 2017

Vilella et al., Development 2015
Balaguer et al., MHR 2018
Balaguer et al., AJOG 2019

Diaz-Gimeno et al., F&S 2011
Ruiz-Alonso et al., F&S 2013
Garrido-Gomez et al., HR 2014
Von Grothusen et al., HR 2018
Wang W. et al. Nature Medicine, 2019 in press
Simon C. et al. HR 2019 submitted
Endometrial receptivity

Plasma membrane transformation
Molecular medicine: human endometrial transcriptome

- Riesewijk et al., 2003 (HG-U133 2.0) WOI
- Ponnapalam et al., 2004 (Home-made array) menstrual cycle
- Talbi et al., 2005 (HG-U133 2.0) menstrual cycle
Endometrial Transcriptome Dynamics at the Single Cell Level

Unciliated epithelia

log2 (rpm+1)

0 5 15

Stromal fibroblasts

Phase

1 2 3 4

Wang et al., bioRxiv online Jun. 19, 2018; doi: http://dx.doi.org/10.1101/350538, under review in Nature Medicine
ERA classifies the molecular receptivity status of the endometrium

Pre-Receptive | Receptive | Post-Receptive
Window of Endometrial Receptivity

Epithelial PR

Progesterone
Personalized embryo transfer (pET) as a treatment for RIF of endometrial origen
<table>
<thead>
<tr>
<th>YEAR</th>
<th>TITLE</th>
<th>JOURNAL</th>
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<tr>
<td>2015</td>
<td>Understanding and improving endometrial receptivity</td>
<td>Current Opinion in Obstetrics &amp; Gynecology. 27(3):187-92</td>
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<td>2015</td>
<td>Is endometrial receptivity transcriptomics affected in women with endometriosis? A pilot study</td>
<td>Reproductive BioMedicine Online. 31(5):647-54</td>
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<td>2015</td>
<td>Diagnosis of endometrial-factor infertility: current approaches and new avenues for research</td>
<td>Geburtshilfe Frauenheilkd. 76(6): 699-703</td>
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<td>2017</td>
<td>Does an increased body mass index affect endometrial gene expression patterns in infertile patients? A functional genomics analysis</td>
<td>Fertility and Sterility. 107(3):740-748.e2</td>
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<td>2017</td>
<td>Endometrial function: facts, urban legends, and an eye to the future</td>
<td>Fertility and Sterility. 108(1):4-8</td>
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<td>2017</td>
<td>Implantation failure of endometrial origin: it is not pathology, but our failure to synchronize the developing embryo with a receptive endometrium</td>
<td>Fertility and Sterility. 108(1):15-18</td>
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<td>2017</td>
<td>Meta-signature of human endometrial receptivity: a meta-analysis and validation study of transcriptomic biomarkers</td>
<td>Scientific Reports. 7(1):10077</td>
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<td>2017</td>
<td>Window of implantation transcriptomic stratification reveals different endometrial subsignatures associated with live birth and biochemical pregnancy</td>
<td>Fertility and Sterility. 108(4):703-710.e3</td>
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<td>2018</td>
<td>Inter-cycle consistency versus test compliance in endometrial receptivity analysis test</td>
<td>Journal of Assisted Reproduction and Genetics. 35(7):1307-1308</td>
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Evidence based medicine

- Meta-analysis
- Randomized Controlled Trial
- Cohort Studies
- Case-Control Studies
- Cases Series, Case Report
- Editorial, Expert Opinion

AT THE 1ST APPOINTMENT
ERA RCT – Study protocol overview

Population: IVF patients at their first appointment undergoing blastocyst transfer

### Primary objectives
- LB and cumulative LB rates at 1-year follow-up (pET versus FET and pET versus ET)

### Secondary objectives
- Implantation and pregnancy rates, biochemical and clinical miscarriages, ectopic pregnancy, obstetrical, neonatal outcomes and cost-effectiveness.

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**First IRB/EC approval**: July 2, 2013

**EC FWA#**: 00027749

**Last IRB/EC approval**: April 28, 2016

**FPFI**: October 2013

**Last LB (LPLV)**: September 2018

**Study length**: 5 years

**Recruitment length**: 4 years
ERA RCT Study Sites

16 Active sites worldwide

- N EXPECTED: 546
- IRB/EC APPROVED SITES: 16
- N RECRUITED: 569
ERA RCT Selection criteria

**Inclusion Criteria**
- Patients undergoing IVF at the first appointment
- Age ≤ 37 years
- BMI: 18.5 to 30
- Normal ovarian reserve (AFC > 8; FSH < 8)
- The stimulation protocol was decided by the doctor
- Blastocyst transfer (day 5 or 6)

**Exclusion Criteria**
- Recurrent miscarriage
- Severe male factor (< 2 million/ml)
- Implantation failure (>3 failed cycles)
- Any pathology affecting the endometrial cavity and hydrosalpinx must be previously operated.

**Post-Randomization Exclusion Criteria**
- P4 level > 1,5 ng/ml at the day of hCG administration in all groups
- Absence of blastocysts for embryo transfer
- Risk of OHSS in the fresh ET group

Note. PGT-A was NOT an inclusion criteria NEITHER an exclusion criteria
569 assessed for eligibility
- 51 did not meet selection criteria
- 43 declined to participate
- 8 double randomization by mistake
- 6 site exclusion due to data inconsistency and submitted out of deadline
- 3 inclusion error
458 randomized
- Total 111 declined randomization
- 51 did not meet selection criteria
- 43 declined to participate
- 8 double randomization by mistake
- 6 site exclusion due to data inconsistency and submitted out of deadline
- 3 inclusion error

148 allocated to personalized ET
- 7 Lost FU
- 9 did not received ET
  - 7 no blastocyst for ET
  - 2 spontaneous pregnancy
- 132 proceeded with ET
- 81 proceeded with PET
  - 1 voluntary termination of pregnancy
  - 1 protocol deviation
- 80 followed up after the first ET
- 141 ITT analysis
  - 80 per protocol analysis

154 allocated to frozen ET
- 6 Lost FU
- 148 Followed up
- 11 did not received ET
  - 2 no ET data
  - 6 no blastocyst for ET
  - 3 spontaneous pregnancy
- 137 proceeded with ET
- 45 no protocol compliance
  - 3 embryo day 3 ET
  - 1 embryo day 4 ET
  - 22 had Fresh ET
  - 5 had pET
  - 13 high P4 in COS
  - 1 ovum donation
- 92 proceeded with FET
  - 1 voluntary termination of pregnancy
- 148 ITT analysis
  - 92 per protocol analysis

156 allocated to fresh ET
- 11 Lost FU
- 145 Followed up
- 7 did not received ET
  - 1 no ET data
  - 3 no blastocyst for ET
  - 2 cancelled due to OHSS risk
  - 1 spontaneous pregnancy
- 138 proceeded with ET
- 43 no protocol compliance
  - 2 embryo day 2 ET
  - 8 embryo day 3 ET
  - 1 embryo day 4 ET and high P4 in COS
  - 6 had Frozen ET
  - 13 had Frozen ET due to OHSS risk
  - 1 had pET (n=1)
  - 12 high P4 in COS
- 95 proceeded with day ET
  - 1 voluntary termination of pregnancy
- 145 ITT analysis
  - 94 per protocol analysis
CONSORT Flow Diagram – ERA RCT

- 458 randomized
- 148 allocated to personalized ET
  - 7 Lost FU
  - 141 ITT analysis
- 154 allocated to frozen ET
  - 6 Lost FU
  - 148 ITT analysis
- 156 allocated to fresh ET
  - 11 Lost FU
  - 145 ITT analysis
**141 ITT analysis**
- 132 proceeded with ET
  - 9 did not received ET
    - 7 no blastocyst for ET
    - 2 spontaneous pregnancy
  - 51 no protocol compliance
    - 1 embryo day 3 ET
    - 5 embryo day 4 ET
    - 10 had Fresh ET
    - 7 had Frozen ET
    - 18 High P4 in COS
    - 7 no pET
    - 2 other treatment (INVO)
    - 1 protocol deviation
- 81 proceeded with PET
  - 1 voluntary termination of pregnancy
- 9 did not received ET
  - 7 no blastocyst for ET
  - 2 spontaneous pregnancy

**148 ITT analysis**
- 137 proceeded with ET
  - 45 no protocol compliance
    - 3 embryo day 3 ET
    - 1 embryo day 4 ET
    - 22 had Fresh ET
    - 5 had pET
    - 13 high P4 in COS
    - 1 ovum donation
  - 11 did not received ET
    - 2 no ET data
    - 6 no blastocyst for ET
    - 3 spontaneous pregnancy
- 92 proceeded with FET
- 92 proceeded with FET
  - 1 voluntary termination of pregnancy
- 11 did not received ET
  - 2 no ET data
  - 6 no blastocyst for ET
  - 3 spontaneous pregnancy

**145 ITT analysis**
- 138 proceeded with ET
  - 43 no protocol compliance
    - 2 embryo day 2 ET
    - 8 embryo day 3 ET
    - 1 embryo day 4 ET and high P4 in COS
    - 6 had Frozen ET
    - 13 had Frozen ET due to OHSS risk
    - 1 had pET (n=1)
    - 12 high P4 in COS
- 7 did not received ET
  - 1 no ET data
  - 3 no blastocyst for ET
  - 2 cancelled due to OHSS risk
  - 1 spontaneous pregnancy
- 95 proceeded with day ET
  - 1 voluntary termination of pregnancy
- 1 did not received ET
  - 1 no ET data
  - 3 no blastocyst for ET
  - 2 cancelled due to OHSS risk
  - 1 spontaneous pregnancy

**Analysis**
- 80 PP analysis
- 92 PP analysis
- 94 PP analysis
Demographic and clinical characteristics of the patients at baseline

<table>
<thead>
<tr>
<th></th>
<th>Personalized Embryo Transfer (n = 148)</th>
<th>Frozen Embryo Transfer (n = 154)</th>
<th>Fresh Embryo Transfer (n = 156)</th>
<th>ET (n = 156)</th>
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<tr>
<td>Age (y)</td>
<td>33 ± 3.1</td>
<td>32.8 ± 3.4</td>
<td>32.7 ± 3.3</td>
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<tr>
<td>Body-mass index§</td>
<td>22.8 ± 2.9</td>
<td>22.9 ± 2.9</td>
<td>22.6 ± 2.8</td>
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<tr>
<td>Ethnicity (%)</td>
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<tr>
<td>Caucasian</td>
<td>122 (82.4)</td>
<td>127 (82.5)</td>
<td>129 (82.7)</td>
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<td>Asian</td>
<td>12 (8.1)</td>
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<td>Latin American</td>
<td>13 (8.8)</td>
<td>11 (7.1)</td>
<td>13 (8.3)</td>
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<td>African</td>
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<td>Other or unknown</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>2 (1.2)</td>
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<td>Current smoker</td>
<td>15 (10.1)</td>
<td>12 (7.8)</td>
<td>15 (9.6)</td>
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<td>Fertility history</td>
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<tr>
<td>Duration of infertility (y)</td>
<td>3.1 ± 1.9</td>
<td>3.2 ± 2.1</td>
<td>2.9 ± 2.2</td>
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<tr>
<td>No. of previous IVF failed</td>
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<td>0</td>
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<tr>
<td>1</td>
<td>109 (73.6)</td>
<td>104 (67.5)</td>
<td>112 (71.8)</td>
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<td>2</td>
<td>20 (13.5)</td>
<td>23 (14.9)</td>
<td>22 (14.1)</td>
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<td>3</td>
<td>10 (6.7)</td>
<td>10 (6.5)</td>
<td>12 (7.7)</td>
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<tr>
<td>6</td>
<td>6 (4.0)</td>
<td>11 (7.1)</td>
<td>6 (3.8)</td>
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<td>Previous Deliveries</td>
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<td>1</td>
<td>11 (7.4)</td>
<td>16 (10.3)</td>
<td>17 (10.9)</td>
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<td>≥2</td>
<td>3 (2.0)</td>
<td>4 (2.6)</td>
<td>3 (1.9)</td>
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<td>Spontaneous clinical miscarriages</td>
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<td>1</td>
<td>23 (15.5)</td>
<td>26 (16.9)</td>
<td>24 (15.4)</td>
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<tr>
<td>≥2</td>
<td>6 (4.0)</td>
<td>3 (1.9)</td>
<td>0 (0.0)</td>
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<td>Voluntary abortions</td>
<td>3 (2.0)</td>
<td>9 (5.8)</td>
<td>8 (5.1)</td>
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<td>Previous curettages (1 or 2)</td>
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<td>12 (8.1)</td>
<td>11 (7.1)</td>
<td>10 (6.4)</td>
<td></td>
<td></td>
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<tr>
<td>8 (5.4)</td>
<td>3 (1.9)</td>
<td>4 (2.6)</td>
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<td>Ectopic pregnancies</td>
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<td>IVF indication (%)</td>
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<td>Male factor</td>
<td>65 (43.9)</td>
<td>78 (50.6)</td>
<td>50 (32.1)</td>
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<td>Tubal factor</td>
<td>20 (13.5)</td>
<td>31 (20.1)</td>
<td>33 (21.1)</td>
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<td>PCOS</td>
<td>27 (18.2)</td>
<td>20 (12.9)</td>
<td>14 (8.9)</td>
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<td>Ovarian disorders</td>
<td>4 (2.7)</td>
<td>5 (3.2)</td>
<td>7 (4.5)</td>
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<td>Endometriosis</td>
<td>21 (14.2)</td>
<td>9 (5.8)</td>
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<td>Unexplained</td>
<td>33 (22.3)</td>
<td>33 (21.4)</td>
<td>47 (30.1)</td>
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<td>Other or unknown‡</td>
<td>2 (1.3)</td>
<td>4 (2.6)</td>
<td>10 (6.4)</td>
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<td>Laboratory tests</td>
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<tr>
<td>FSH (mU/mL)</td>
<td>5.9 ± 1.9a</td>
<td>6.6 ± 2.1</td>
<td>6.9 ± 2.0b</td>
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<td>AMH (ng/mL)</td>
<td>4.4 ± 3.6</td>
<td>3.7 ± 2.7</td>
<td>3.5 ± 2.9</td>
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Cycle characteristics and embryological data. ITT analysis

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<tr>
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<th>Personalized Embryo Transfer</th>
<th>Frozen Embryo Transfer</th>
<th>Fresh Embryo Transfer</th>
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<td>AFC</td>
<td>pET (n = 141)</td>
<td>FET (n = 148)</td>
<td>ET (n = 145)</td>
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<td>14.8 ± 6.3</td>
<td>14.9 ± 6.6</td>
<td>13.1 ± 5.9</td>
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<td>Antagonist protocol</td>
<td>124 (87.9)</td>
<td>120 (81.1)</td>
<td>122 (84.1)</td>
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<td>Agonist protocol</td>
<td>10 (7.1)</td>
<td>13 (8.8)</td>
<td>12 (8.3)</td>
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<tr>
<td>Total dose of FSH</td>
<td>1696.9 ± 687.8</td>
<td>1540.2 ± 635.2</td>
<td>1666.1 ± 669.8</td>
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<td>administered (IU)</td>
<td>1167.0 ± 936</td>
<td>1202.3 ± 987</td>
<td>1165.1 ± 1042.5</td>
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<tr>
<td>Total dose of hMG</td>
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<tr>
<td>administered (IU)</td>
<td>1540.2 ± 148</td>
<td></td>
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<td>P level at the day</td>
<td>1.02 ± 0.7</td>
<td>0.93 ± 0.6</td>
<td>0.92 ± 0.8</td>
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<tr>
<td>of ovulation induction</td>
<td></td>
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<tr>
<td>Ovulation induction</td>
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<tr>
<td>hCG</td>
<td>62 (44.0)</td>
<td>57 (38.5)</td>
<td>110 (75.9)</td>
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<tr>
<td>Agonist</td>
<td>62 (44.0)</td>
<td>67 (45.3)</td>
<td>15 (10.3)</td>
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<td>Double triggering</td>
<td>7 (5.3)</td>
<td>7 (4.7)</td>
<td>7 (4.8)</td>
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<td>Oocytes retrieved</td>
<td>12.4 ± 7.6</td>
<td>11.6 ± 6.0</td>
<td>10.5 ± 6.6</td>
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<td>Fertilization technique</td>
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<td>ICSI</td>
<td>106 (75.2)</td>
<td>114 (77.0)</td>
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<td>IVF</td>
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<td>IVF/ICSI</td>
<td>21 (14.9)</td>
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<td>Fertilization rate</td>
<td>1244/1633 (76.2)</td>
<td>1197/1531 (78.2)</td>
<td>1067/1379 (77.4)</td>
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<td>Embryo Stage</td>
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<td>Cleavage stage</td>
<td>1/181 (0.6)</td>
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<td>Morula</td>
<td>2/181 (1.1)</td>
<td>1/208 (0.5)</td>
<td>1/211 (0.5)</td>
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<td>Early Blastocyst</td>
<td>12/181 (6.6)</td>
<td>11/208 (5.3)</td>
<td>5/211 (2.4)</td>
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<td>Cavitated blastocyst</td>
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<td>47/208 (22.6)</td>
<td>48/211 (22.7)</td>
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<td>Expanded Blastocyst</td>
<td>93/181 (51.4)</td>
<td>100/208 (48.1)</td>
<td>109/211 (51.7)</td>
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<td>Hatching Blastocyst</td>
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<td>49/208 (23.6)</td>
<td>43/211 (19.4)</td>
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<td>Blastocyst development</td>
<td>648/1248 (51.9)</td>
<td>636/1239 (51.3)</td>
<td>561/1093 (51.3)</td>
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<tr>
<td>rate</td>
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<td>Day of embryo development at transfer</td>
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<tr>
<td>2</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>3</td>
<td>10 (7.1)</td>
<td>4 (2.7)</td>
<td>10 (6.9)</td>
</tr>
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<td>4</td>
<td>7 (0.5)</td>
<td>4 (2.7)</td>
<td>0 (0.0)</td>
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<tr>
<td>5</td>
<td>98 (69.5)</td>
<td>112 (75.7)</td>
<td>119 (82.1)</td>
</tr>
<tr>
<td>6</td>
<td>16 (11.4)</td>
<td>17 (11.5)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Embryo Quality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“A” grade</td>
<td>48/149 (32.2)</td>
<td>70/181 (38.3)</td>
<td>56/183 (30.6)</td>
</tr>
<tr>
<td>“B” grade</td>
<td>84/149 (56.4)</td>
<td>92/183 (50.3)</td>
<td>110/183 (60.1)</td>
</tr>
<tr>
<td>“C” grade</td>
<td>17/149 (11.4)</td>
<td>21/181 (11.5)</td>
<td>17/183 (9.3)</td>
</tr>
<tr>
<td>TE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“A” grade</td>
<td>36/149 (24.2)</td>
<td>56/183 (30.6)</td>
<td>46/183 (25.1)</td>
</tr>
<tr>
<td>“B” grade</td>
<td>85/149 (57)</td>
<td>95/183 (51.9)</td>
<td>96/183 (52.5)</td>
</tr>
<tr>
<td>“C” grade</td>
<td>28/149 (18.8)</td>
<td>32/183 (17.5)</td>
<td>40/183 (21.9)</td>
</tr>
<tr>
<td>PGT-A cases</td>
<td>6 (4.3)</td>
<td>4 (2.7)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Number of transferred embryos</td>
<td>1.52 ± 0.5</td>
<td>1.61 ± 0.5</td>
<td>1.63 ± 0.5</td>
</tr>
<tr>
<td>Thawed HRT embryo transfer data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of days of E2</td>
<td>15.5 ± 3.8</td>
<td>16.6 ± 3.8</td>
<td>NA</td>
</tr>
<tr>
<td>Endogenous P levels</td>
<td>0.2 (0.0-1.4)</td>
<td>0.29 (0.05-11.03)</td>
<td>NA</td>
</tr>
<tr>
<td>Hours exogenous P. admin.</td>
<td>120 ± 14.4</td>
<td>117.8 ± 9.7</td>
<td>NA</td>
</tr>
<tr>
<td>Hours exogenous P. admin. (range)</td>
<td>65.2-163.4 (98.2)</td>
<td>66.4-151.2 (84.8)</td>
<td>NA</td>
</tr>
<tr>
<td>Time between COS and embryo transfer (months)</td>
<td>3.2 ± 2.4</td>
<td>2.1 ± 1.4</td>
<td>NA</td>
</tr>
</tbody>
</table>
Reproductive outcomes at the first embryo transfer and cumulative during 1-year follow-up*. ITT analysis

<table>
<thead>
<tr>
<th></th>
<th>pET (n = 141)</th>
<th>FET (n = 148)</th>
<th>ET (n = 145)</th>
<th>pET vs FET</th>
<th>pET vs ET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relative risk (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>No. of transfers</td>
<td>132</td>
<td>137</td>
<td>138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>83 (58.9)</td>
<td>73 (49.3)</td>
<td>84 (57.9)</td>
<td>1.22 (0.96-1.56)</td>
<td>0.12</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>88/201 (43.8)</td>
<td>80/220 (36.4)</td>
<td>97/225 (43.1)</td>
<td>1.17 (0.96-1.43)</td>
<td>0.14</td>
</tr>
<tr>
<td>LB rate</td>
<td>57 (40.4)</td>
<td>51 (34.5)</td>
<td>64 (44.1)</td>
<td>1.14 (0.90-1.44)</td>
<td>0.33</td>
</tr>
<tr>
<td>Singleton</td>
<td>49/57 (86)</td>
<td>40/51 (78.4)</td>
<td>45/64 (70.3)</td>
<td>1.31 (0.75-2.29)</td>
<td>0.32</td>
</tr>
<tr>
<td>Singleton</td>
<td>132/141 (93.6)%</td>
<td>118/148 (79.7)%</td>
<td>117/145 (80.7)%</td>
<td>2.29 (1.27-4.11)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cumulative pregnancy rate</td>
<td>132/141 (93.6)%</td>
<td>118/148 (79.7)%</td>
<td>117/145 (80.7)%</td>
<td>2.29 (1.27-4.11)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cumulative LB rate</td>
<td>88/201 (43.8)</td>
<td>80/220 (36.4)</td>
<td>97/225 (43.1)</td>
<td>1.17 (0.96-1.43)</td>
<td>0.14</td>
</tr>
<tr>
<td>Singleton</td>
<td>13/88 (14.8)</td>
<td>15/82 (18.3)</td>
<td>27/85 (31.8)</td>
<td>0.88 (0.57-1.35)</td>
<td>0.54</td>
</tr>
<tr>
<td>Multiple (all twins)</td>
<td>24/132 (18.2)</td>
<td>17/118 (14.4)</td>
<td>5/117 (4.3)</td>
<td>1.13 (0.85-1.51)</td>
<td>0.49</td>
</tr>
<tr>
<td>Singleton</td>
<td>19/132 (14.4)</td>
<td>16/118 (13.6)</td>
<td>23/117 (19.7)</td>
<td>1.03 (0.74-1.44)</td>
<td>1</td>
</tr>
<tr>
<td>Multiple (all twins)</td>
<td>1/132 (0.8)</td>
<td>1/118 (0.8)</td>
<td>1/117 (0.9)</td>
<td>0.95 (0.24-3.81)</td>
<td>1</td>
</tr>
<tr>
<td>Transfers per patient</td>
<td>2.63 ± 1.14</td>
<td>2.28 ± 0.70</td>
<td>2.62 ± 0.73</td>
<td>0.35 (-0.4-0.4)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

* denotes significance at P < 0.05.
Reproductive outcomes at the first embryo transfer and cumulative during 1-year follow-up*. Per protocol analysis

<table>
<thead>
<tr>
<th></th>
<th>pET (n = 80)</th>
<th>FET (n = 92)</th>
<th>ET (n = 94)</th>
<th>pET vs FET</th>
<th>pET vs ET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relative risk (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>58 (72.5%)</td>
<td>50 (54.3%)</td>
<td>55 (58.5%)</td>
<td>1.56 (1.07-2.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>63/110 (57.3%)</td>
<td>60/139 (43.2%)</td>
<td>58/150 (38.6%)</td>
<td>1.37 (1.03-1.82)</td>
<td>0.03</td>
</tr>
<tr>
<td>LB rate</td>
<td>45 (56.2%)</td>
<td>39 (42.4%)</td>
<td>43 (45.7%)</td>
<td>1.35 (0.97-1.86)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cumulative pregnancy rate</td>
<td>76/80 (95%)</td>
<td>65/92 (70.6%)</td>
<td>59/94 (62.8%)</td>
<td>4.18 (1.65-10.56)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cumulative LB rate</td>
<td>57 (71.2%)</td>
<td>51 (55.4%)</td>
<td>46 (48.9%)</td>
<td>1.47 (1.01-2.13)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cumulative ectopic pregnancies</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1/59 (1.7)</td>
<td>0.92 (-0.11-1.97)</td>
<td>0.09</td>
</tr>
<tr>
<td>Transfers per patient</td>
<td>3.05 ± 1.61</td>
<td>2.13 ± 0.34</td>
<td>3.5 ± 1.29</td>
<td>0.92 (-0.11-1.97)</td>
<td>0.09</td>
</tr>
</tbody>
</table>
## Obstetrical, delivery and neonatal outcomes. Per protocol analysis

<table>
<thead>
<tr>
<th></th>
<th>Personalized-Embryo Transfer. pET (n = 80)</th>
<th>Frozen-Embryo Transfer. FET (n = 92)</th>
<th>Fresh-Embryo Transfer. ET (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ovarian hyperstimulation</strong></td>
<td>80 (0.0)</td>
<td>92 (0.0)</td>
<td>94 (1.1)</td>
</tr>
<tr>
<td><strong>Obstetrical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>2 (4.4)</td>
<td>1 (2.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>HBP</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>1 (2.2)</td>
<td>1 (2.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Retrocorial hematoma</td>
<td>0 (0.0)</td>
<td>1 (2.6)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Abruptio</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vasa previa</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Still birth</td>
<td>1 (2.2)</td>
<td>1 (2.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Type of delivery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-Section</td>
<td>10 (25.0)</td>
<td>14 (40.0)</td>
<td>15 (34.9)</td>
</tr>
<tr>
<td>Vaginal</td>
<td>30 (75.0)</td>
<td>21 (60.0)</td>
<td>28 (65.1)</td>
</tr>
<tr>
<td><strong>Neonatal outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal mortality</td>
<td>0 (0.0)</td>
<td>1 (2.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38 (38.03 ± 3.1)</td>
<td>34 (38.03 ± 2.9)</td>
<td>42 (38.33 ± 1.6)</td>
</tr>
<tr>
<td>Preterm birth &lt;37 weeks</td>
<td>38 (5 (13.2))</td>
<td>34 (6 (17.6))</td>
<td>42 (4 (9.5))</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>23 (3170.6 ± 646.9)</td>
<td>30 (2868.5 ± 629.1)</td>
<td>34 (2912.6 ± 573.6)</td>
</tr>
<tr>
<td>Birth weight in singletons</td>
<td>17 (3484.4 ± 321.6)</td>
<td>14 (3362.5 ± 402)</td>
<td>22 (3210.6 ± 375.6)</td>
</tr>
<tr>
<td>Birth weight in twins</td>
<td>6 (2281.7 ± 476.7)</td>
<td>16 (2436.2 ± 444.9)</td>
<td>12 (2366.2 ± 463.2)</td>
</tr>
<tr>
<td>Birth weight &lt;2500 g</td>
<td>23 (4 (17.4))</td>
<td>30 (10 (33.3))</td>
<td>34 (6 (17.6))</td>
</tr>
<tr>
<td>Birth height (cm)</td>
<td>17 (49.9 ± 2.7)</td>
<td>27 (48.3 ± 2.6)</td>
<td>30 (48.9 ± 2.3)</td>
</tr>
<tr>
<td>APGAR score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 minute</td>
<td>28 (8.7 ± 1.5)</td>
<td>21 (9 ± 0.8)</td>
<td>18 (9.22 ± 0.7)</td>
</tr>
<tr>
<td>5 minutes</td>
<td>24 (9.5 ± 0.9)</td>
<td>16 (9.9 ± 0.2)</td>
<td>12 (9.7 ± 0.4)</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>
## Cost-effectiveness estimation per baby at home at the first attempt

<table>
<thead>
<tr>
<th></th>
<th>Personalized-Embryo Transfer pET (n = 80)</th>
<th>Frozen-Embryo Transfer FET (n = 92)</th>
<th>Fresh-Embryo Transfer ET (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of deliveries with at least 1 LB at the first attempt</td>
<td>45</td>
<td>39</td>
<td>43</td>
</tr>
<tr>
<td>IVF lab cost</td>
<td>€ 5.190</td>
<td>$ 11.825</td>
<td>€ 5.590</td>
</tr>
<tr>
<td>Drug cost</td>
<td>€ 1.700</td>
<td>$ 5.500</td>
<td>€ 1.580</td>
</tr>
<tr>
<td>Vitrification cost</td>
<td>€ 1.100</td>
<td>$ 1.375</td>
<td>€ 1.100</td>
</tr>
<tr>
<td>Estimated cost of a delivery with at least 1 LB at the first attempt</td>
<td>€ 19.555</td>
<td>$ 42.658</td>
<td>€ 23.448</td>
</tr>
<tr>
<td>Estimated cost of a delivery with at least 1 LB at the first attempt</td>
<td>€ 19.555</td>
<td>$ 42.658</td>
<td>€ 23.448</td>
</tr>
</tbody>
</table>
By ITT analysis:
- **Cumulative PR** was significantly higher in the pET group (93.6%) vs FET (79.7%) and ET (80.7%).

By PP analysis,
- LB: 14 pp and 11 pp versus FET and ET that was non statistically significant.

Statistically significant improvement in:
- **Cumulative LBR**: 16 pp and 22.1 pp versus FET and ET.
- PR: 18.2 pp and 14 pp versus FET and ET.
- IR: 14 pp and 18.4 pp versus FET and ET.
- **Cumulative PR**: 24.4 pp and 32.1 pp versus FET and ET.

Similar clinical outcome between FET and ET.

Obstetrical, delivery and neonatal outcomes were not different.
Limitations, reasons for caution

✓ The main limitation of our study is the unexpected added 20% patient drop-out rate versus 30% initially planned (16 study sites in 3 different continents).

✓ The study was powered to detect statistical differences for a 15%-percentage points increase in the primary outcomes in the pET group versus FET or ET.

✓ This is the first RCT to provide proof-of-principle evidence for the potential of using a personalized diagnosis of the endometrial factor in the work-up of the infertile couple at the first appointment.
Wider implications

IVF 1.0

Chromosomal Embryo Factor 15%

Endometrial Factor 13%

NCT03530254 (May 21, 2018)
NCT3558399 (June 15, 2018)

LIVE BIRTH RATES %

1978

2010
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Medical Manager
Diana Valbuena, MD, PhD

COLLABORATORS

Steve Quake LAB
Steve Quake
Wanxin Wang
Wenying Pan

Ruth Lathi, Stanford University

FINANCIAL SUPPORT
ERA RCT Study Sites

16 Active sites worldwide

N EXPECTED 546
IRB/EC APPROVED SITES 16
N RECRUITED 569

Participant sites
Enrolled patients (n)
Our Igenomix team

USA & Canada

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- AMADOR NAVARRO, LUCIA
- BAI, DAVIDE
- BILDA, JORGEL
- BOVER CATALA, ANA
- CAMPILLO GALINDO, INMACULADA
- CERVERO SANZ, ANA CRISTINA
- CLEMENTE OSCAR, MONICA
- DE LA FUENTE LUCENA, EUPHLEU
- DIEZ JUAN, ANTONIO
- GARCIA HERRERO, SANDRA
- GARCIA PASCUAL, M. CARME
- GIL SANCHEZ, CLAUDIA
- GOMEZ DE LA CRUZ, CARLOS ALONSO
- GOMEZ SANCHEZ, EVA MARIA
- HERNANDEZ DE DIEGO, HERMES
- HERVAS LORENTE, ARANTXA
- JIMENEZ ALMAZAN, JORGE
- RODRIGUEZ, JULIO CESAR
- MARTINEZ CONEJERO, JOSE ANTONIO
- MARIN LOPEZ DE CAJAL, LUCIA
- MARIN VALLEJO, CARLOS
- MATEU BRULL, EMILI
- MILAN SANCHEZ, MIGUEL
- MIR PARDO, PEDRO
- MIRAVET VALENCIANO, JOSE ALBERTO
- MORENO GHENO, INMACULADA
- NAVARRO DAVA, ROBERTO
- NAVARRO SANCHEZ, LUIS
- PEÑADO CORVINA, MARIA VANESSA
- RINCON BERTOLIN, ALEJANDRO
- RODRIGO VIVO, LORENA
- RUBIO LLUÉS, CAMPE
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- ESCORZA, PATRICIA
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- GARCIA MORENO, NINAR
- GOMEZ LOPEZ, MARIA
- HERRERO BAINA, MARIA
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- MADRAL SIGNEZ, TANIA
- MARTINEZ BENITO, TATYNA
- MARTINEZ ESPINOSA, SEBASTIAN
- MARTINEZ FERNANDEZ, MANUEL
- MARTINEZ HERNIO, MARIA
- MATEOS GARCIA, ACILO
- MOLES SELLER, SERA
- MORALES GARCIA, MARIA JESUS
- NETO ALFAN, JESSICA
- PEREZ SCORION, CRISTINA
- PERIS MARCO, LAURA
- POZO CRUZ, ANA MARIA
- SANDOVAL GONZALEZ ESTELA
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- GRIFFIN, MARISA
- LAYNE, NICOLE
- LOAIXEN, ALEJANDROS
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- PHAM, QUON
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- TUENNY, KENNY

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- SINGH BUTTAR, BRINDER

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- DE OLIVEIRA, PRISCILA
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- GLORIA, THIAGO
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- RIVADEÑEIRA, ANDREA

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- NAJAR, ROY
- RASBERI, ARAZ
- THORNHILL, ALAN

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