DECREASED OVARIAN RESERVE AS A CAUSE OF RPL

And

PGS AS TREATMENT

Dr. Yılmaz Güzel
Changes in Human Germ Cell Number

Germ Cells Number
(million)

Age

Birth
7 months
1st meiotic arrest
Puberty
Fertile (400-500 oocytes)
Menopause

400,000
38 Years
Ovary Reserve depletion rate increases dramatically - significantly decreases fertility.

51 Years
Ovary Reserve depleted (<1000)
Average age of final menstrual period.
Genç over  -->  Yağ  -->  Yaşlı over

Genetic factors:
- Genomic DNA alternation
- Mitochondrial DNA mutation
- Decreased telomerase

Microenvironmental:...
- Oxidative stress
- Advanced glycation end
- Perifollicular vascularization...

Pathological effects
- Other factors
Age is the most important factor affecting the fertility of the woman
DECREASE OF AMH AND AFC BY AGE

AMH

Seifer D. 2011

AFC

Almog B. 2011
Relationship D3 FSH IVF Delivery Rates

No live birth >18
Decline 8-11
Constant 1-7

Scott RT et al 2008
Fertility declines as woman gets older and gradual decline begins around the age 32

Very few spontaneous pregnancies after 43

The quality of the oocytes also declines with age because of the meiotic errors
OVARIAN RESERVE

Functional capability of the ovary and includes both quality and quantity of the woman’s remaining oocytes
DIMINISHED OVARIAN RESERVE (DOR)

Reproductive age woman with regular menses but reduced fecundity or decreased response to ovarian stimulation compared with age matched woman
OVARIAN RESERVE TESTS

AFC
AMH
FSH E2

Ovarian volume
DIMINISHED OVARIAN RESERVE
ESHRE STATEMENT

1) Advanced age (>40)

2) Poor response to previous ovarian stimulation

3) Abnormal ovarian reserve test (AMH<1.1, AFC <5)

Two of three

Human Rep 2011
Ovarian reserve testing is currently not considered a part of the RPL evaluation according to Practice Committee Opinion for ASRM 2012
Trisomic Pregnancy and Earlier Age at Menopause

Jennie Kline,1,3,4 Ann Kinney,2,6 Bruce Levin,5 and Dorothy Warburton7

1Epidemiology of Developmental Brain Disorders Department and 2Research Foundation for Mental Hygiene, New York State Psychiatric Institute; and 3Gertrude H. Sergievsky Center, Divisions of 4Epidemiology and 5Biostatistics in the Joseph L. Mailman School of Public Health, 6Graduate School of Arts and Sciences, and 7Departments of Genetics and Development and of Pediatrics, Columbia University, New York

We tested the hypothesis that the connection between advanced maternal age and autosomal trisomy reflects the diminution of the oocyte pool with age. Because menopause occurs when the number of oocytes falls below some threshold, our hypothesis is that menopause occurs at an earlier age among women with trisomic pregnancies than it does among women with chromosomally normal pregnancies. To determine their menstrual status, we interviewed women from our previous study of karyotyped spontaneous abortions who, in 1993, were age ≥44 years. Premenopausal women completed interviews every 4–5 mo, until menopause or until the study ended in 1997. The primary analyses compare 111 women whose index pregnancy was a trisomic spontaneous abortion with two groups: women whose index pregnancy was a chromosomally normal loss (n = 157) and women whose index pregnancy was a chromosomally normal birth (n = 226). We used a parametric logistic survival analysis to compare median ages at menopause. The estimated median age at menopause was 0.96 years earlier (95% confidence interval −0.18 to 2.10) among women with trisomic losses than it was among women with chromosomally normal losses and chromosomally normal births combined. Results were unaltered by adjustment for education, ethnicity, and cigarette smoking. Our results support the hypothesis that trisomy risk is increased with decreased numbers of oocytes. Decreased numbers may indicate accelerated oocyte atresia or fewer oocytes formed during fetal development.
Table 3

Age at Ascertained Natural Menopause in Women with Trisomic Losses Compared with Women with Chromosomally Normal Losses and Those with Live Births: Median Ages and Shifts in Median Ages

<table>
<thead>
<tr>
<th></th>
<th>NO. OF WOMEN</th>
<th>MEDIAN AGE (SE) (years)</th>
<th>Shift in Median Age (95% CI), Comparing Women with Chromosomally Normal Pregancies and Those with Trisomic Pregancies (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomic loss</td>
<td>111</td>
<td>53.36 (.52)</td>
<td>Unadjusted: .87 (−.43 to 2.17)</td>
</tr>
<tr>
<td>Chromosomally normal loss</td>
<td>157</td>
<td>54.22 (.46)</td>
<td>Adjusted: .92 (−.40 to 2.24)</td>
</tr>
<tr>
<td>Chromosomally normal live birth</td>
<td>228</td>
<td>54.38 (.40)</td>
<td>Unadjusted: 1.03 (−.20 to 2.26)</td>
</tr>
<tr>
<td>Chromosomally normal combined(c)</td>
<td></td>
<td>.96 (−.18 to 2.10)</td>
<td>Adjusted: 1.02 (−.11 to 2.14)</td>
</tr>
</tbody>
</table>

\(a\) Excludes 28 women whose data were uninformative because they began premenopausal hormone use >1 year before the intake interview.

\(b\) Adjusted for influence of education (some high school or high school graduate, some college, college graduate, postgraduate), ethnicity (white non-Hispanic, black non-Hispanic, other) and cigarette smoking (current smoker, ex-smoker, never smoked) on \(\theta_1\) (the log odds on ascertained menopause at age <50 years vs. age >50 years). These covariates were not significantly associated with \(\log \theta_3\), the slope coefficient. Education was associated with \(\theta_1\) \((P = .02)\), although the pattern was not monotonic; median age at menopause was later for college graduates than for postgraduates. Ethnicity was associated with \(\theta_1\) \((P = .02)\); median age at menopause was earlier for “other” ethnicity and black non-Hispanic than for white non-Hispanic. Cigarette smoking was not significantly associated with \(\theta_1\) \((P = .29)\); median age at menopause tended to be earlier in ex-smokers and current smokers than in those who had never smoked.

\(c\) Median age at ascertained menopause was not estimated for the two comparison groups combined. The estimate for the difference between the trisomy cohort and the two chromosomally normal cohorts combined was obtained by taking a weighted average of the individual shifts.
Diminished ovarian reserve as measured by means of baseline follicle-stimulating hormone and antral follicle count is not associated with pregnancy loss in younger in vitro fertilization patients

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a Shady Grove Fertility, Rockville, Maryland; b Reproductive Medicine Associates of Florida, Lake Mary, Florida; and c Georgetown University School of Medicine, Washington, DC

Objective: To assess the relationship between diminished ovarian reserve and pregnancy outcomes in a large cohort of women achieving pregnancy through in vitro fertilization (IVF). We evaluated antral follicle count (AFC) and baseline FSH as a measure of ovarian reserve. Secondarily, we assessed whether diminished ovarian reserve was associated with aneuploidy among spontaneous abortions.

Design: Retrospective cohort study.

Setting: Multicenter private practice.

Patient(s): All patients aged 21–44 years undergoing fresh autologous IVF cycles during 2009–2013 that resulted in positive serum hCG with recorded baseline FSH levels.

Intervention(s): None.

Main Outcome Measure(s): Live births per early pregnancy, biochemical pregnancies, clinical pregnancy losses, and aneuploidy rates in products of conception among pregnancy losses.

Result(s): A total of 9,489 cycles among 8,214 patients were analyzed. There was no association between live birth and ovarian reserve among pregnant IVF patients under the age of 35 years. Among patients 35 years of age and older, elevated baseline FSH was associated with a higher risk of pregnancy loss, which increased with increasing age. AFC was not significantly associated with pregnancy loss at any age. No associations were found between ovarian reserve measures and aneuploidy in products of conception in age-adjusted analyses, although the power to effectively evaluate this was limited.

Conclusion(s): Diminished ovarian reserve is not associated with an increase in miscarriage among younger women achieving pregnancy through IVF. Elevated FSH is associated with a higher risk of IVF pregnancy loss among older patients. We found no evidence to confirm that diminished ovarian reserve is associated with increased aneuploidy among spontaneous abortions. (Fertil Steril® 2017;108:980–7. ©2017 by American Society for Reproductive Medicine.)

Key Words: Diminished ovarian reserve, follicle-stimulating hormone (FSH), antral follicle count (AFC), live birth, pregnancy loss
Clinical outcomes according to Society for Assisted Reproductive Technology age group and ovarian reserve (FSH or antral follicle count [AFC]) group. Biochemical pregnancy losses subdivided by (A) FSH group and (B) AFC group; clinical pregnancy losses subdivided by (C) FSH group and (D) AFC group; live births subdivided by (E) FSH group and (F) AFC group; and aneuploidy rates among pregnancy loss products of conception subdivided by (G) FSH group and (H) AFC group. Error bars indicate 95% confidence intervals. *P<0.05.

Higher rates of aneuploidy in blastocysts and higher risk of no embryo transfer in recurrent pregnancy loss patients with diminished ovarian reserve undergoing in vitro fertilization

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Pacific NW Fertility, Seattle, Washington

**Objective:** To study the prediction of aneuploidy rate in blastocysts from patients with recurrent pregnancy loss (RPL) on the basis of ovarian reserve testing.

**Design:** Prospective cohort analysis.

**Setting:** Private, university-affiliated fertility clinic.

**Patient(s):** A total of 239 patients with RPL, defined as two or more clinical miscarriages, were screened for inclusion. One hundred two (102) cycles in patients with unexplained RPL resulted in at least one euploid embryo transferred. Outcomes were compared by ovarian reserve test results, with diminished ovarian reserve (DOR) defined as a cycle day 3 FSH >10 IU/mL and/or antimüllerian hormone <1 ng/mL.

**Intervention(s):** In vitro fertilization with blastocyst biopsy and aneuploidy screening of all 23 chromosome pairs.
# TABLE 2

## Cycle characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal ovarian reserve (n = 59)</th>
<th>DOR (n = 43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total amount of gonadotropins (IU)</td>
<td>3,204.5 ± 1,124.5</td>
<td>4,432.5 ± 1,562.4</td>
<td>.04</td>
</tr>
<tr>
<td>No. of mature eggs</td>
<td>12.9 (8–33)</td>
<td>8.5 (5–10)</td>
<td>.01</td>
</tr>
<tr>
<td>No. of blasts biopsied</td>
<td>5.3 (1–10)</td>
<td>3.6 (2–6)</td>
<td>.02</td>
</tr>
<tr>
<td>Aneuploid blasts (%)</td>
<td>48</td>
<td>57</td>
<td>.03</td>
</tr>
<tr>
<td>% All aneuploid blasts</td>
<td>13</td>
<td>25</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Note: Values are averages unless otherwise noted.*

*Shahine. High aneuploidy in RPL patients with DOR. Fertil Steril 2016.*
TABLE 3

Percentage of aneuploid embryos according to age.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Normal ovarian reserve (n = 59)</th>
<th>DOR (n = 43)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>45</td>
<td>59</td>
<td>.04</td>
</tr>
<tr>
<td>35–37</td>
<td>59</td>
<td>77</td>
<td>.03</td>
</tr>
<tr>
<td>38–40</td>
<td>74</td>
<td>76</td>
<td>.9</td>
</tr>
<tr>
<td>41+</td>
<td>87</td>
<td>92</td>
<td>.8</td>
</tr>
</tbody>
</table>

Note: Values are percentages.


Higher aneuploidy rates in patients < 38 years
Diminished ovarian reserve: is it a neglected cause in the assessment of recurrent miscarriage?  
A cohort study

Melahat Atasever, M.D., a Zeynep Soyman, M.D., b Emine Demirel, M.D., c Servet Gencdal, M.D., c and Sefa Kelekci, M.D. c

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# TABLE 1

Comparison of demographic characteristics and ovarian reserve test parameters between recurrent miscarriage and control groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recurrent miscarriage (n = 71)</th>
<th>Control (n = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>29.5 ± 4.5</td>
<td>29.1 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>≤30</td>
<td>42 (59.2%)</td>
<td>43 (61.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;30</td>
<td>29 (40.8%)</td>
<td>27 (38.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 ± 3.2</td>
<td>25 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean cycle length (d)</td>
<td>28.3 ± 2.2</td>
<td>28.5 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Gravidity</td>
<td>3.7 ± 0.9</td>
<td>1.7 ± 0.6</td>
<td>.001</td>
</tr>
<tr>
<td>Parity</td>
<td>0.2 ± 0.4</td>
<td>1.5 ± 0.7</td>
<td>.001</td>
</tr>
<tr>
<td>Pregnancy loss</td>
<td>3.5 ± 0.9</td>
<td>0.09 ± 0.2</td>
<td>.001</td>
</tr>
<tr>
<td>FSH (U/L)</td>
<td>8.6 ± 3.7</td>
<td>7.1 ± 1.9</td>
<td>.049</td>
</tr>
<tr>
<td>FSH ≥11 U/L</td>
<td>13 (18.3%)</td>
<td>3 (4.3%)</td>
<td>.009</td>
</tr>
<tr>
<td>LH (U/L)</td>
<td>5.2 ± 2.2</td>
<td>5.1 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>E₂ (nmol/L)</td>
<td>42.2 ± 15.1</td>
<td>45.5 ± 30.2</td>
<td>NS</td>
</tr>
<tr>
<td>E₂ ≥60 nmol/L</td>
<td>7 (9.9%)</td>
<td>12 (17.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>FSH/LH</td>
<td>1.7 ± 0.7</td>
<td>1.6 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>FSH/LH ≥3</td>
<td>4 (5.6%)</td>
<td>5 (7.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>ROV (mL)</td>
<td>6.0 ± 2.3</td>
<td>6.1 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>LOV (mL)</td>
<td>6.1 ± 2.2</td>
<td>6.0 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>MOV (mL)</td>
<td>6.0 ± 2.0</td>
<td>6.1 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>ROAFC (n)</td>
<td>4.9 ± 2.0</td>
<td>5.0 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>LOAFC (n)</td>
<td>5.1 ± 2.2</td>
<td>4.7 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>TAF (n)</td>
<td>9.4 ± 4.0</td>
<td>9.8 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>TAF ≤7</td>
<td>27 (38%)</td>
<td>19 (27.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>2.9 ± 1.7</td>
<td>3.6 ± 1.7</td>
<td>.007</td>
</tr>
<tr>
<td>AMH ≤1 ng/mL</td>
<td>14 (19.7%)</td>
<td>4 (5.7%)</td>
<td>.013</td>
</tr>
</tbody>
</table>

Note: Results are presented as mean ± SD or n (%). AMH = ant míllerian hormone; BMI = body mass index; LOAFC = left ovary antral follicle count; LOV = left ovarian volume; MOV = mean ovarian volume; NS = not significant; ROAFC = right ovary antral follicle count; ROV = right ovarian volume; TAF = total antral follicle count.

Percentage of women with diminished ovarian reserve in the recurrent miscarriage and control groups. T AFC = total antral follicle count; AMH = antimüllerian hormone.

DIMINISHED OVARIAN RESERVE MAY EXPLAIN OTHERWISE UNEXPLAINED RECURRENT PREGNANCY LOSS.  K. A. Wald, a L. R. Hickok, b L. A. Marshall, b J. D. Lamb, b L. K. Shahine. b aDept. of Ob/Gyn, University of Washington, Seattle, WA, USA; b Pacific Northwest Fertility and IVF Specialists, Seattle, WA, USA.

<table>
<thead>
<tr>
<th></th>
<th>Explained RPL Patients N=87</th>
<th>Unexplained RPL Patients N=177</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35.2 (28-43)</td>
<td>36.4 (28-44)</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI</td>
<td>23.6 (18-32.3)</td>
<td>22.6 (18.3-33.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Number of Previous Miscarriages</td>
<td>2.5 (2-5)</td>
<td>2.7 (2-5)</td>
<td>0.8</td>
</tr>
<tr>
<td>%Prior Live Births</td>
<td>38%</td>
<td>52%</td>
<td>0.07</td>
</tr>
<tr>
<td>%Patients with FSH&gt;10</td>
<td>26%</td>
<td>33%</td>
<td>0.2</td>
</tr>
<tr>
<td>%Patients with AMH &lt;1.0</td>
<td>11%</td>
<td>32%</td>
<td>0.002</td>
</tr>
<tr>
<td>%Patients with Both FSH&gt;10 and AMH &lt;1.0</td>
<td>5%</td>
<td>15%</td>
<td>0.01</td>
</tr>
<tr>
<td>% Patients with DOR</td>
<td>29%</td>
<td>48%</td>
<td>P=0.005</td>
</tr>
</tbody>
</table>

DOR: diminished ovarian reserve defined as CD3 FSH >10 mIU/mL and/or AMH <1.0 ng/mL

e14    PCRS Abstracts  
Vol. 107, No. 3, Supplement, March 2017
RECURRENT PREGNANCY LOSS

The loss of two or more pregnancies before 24 weeks of gestation

App % 2

ESHRE 2017
The Risk of Miscarriage after 2 consecutive losses  
% 17-25

The Risk of Miscarriage after 3 consecutive losses  
% 25-46
RECURRENT PREGNANCY LOSS

Genetic

Anatomic defects

Infections

Acquired and inherited thrombophilia

Endocrine
40%–50% Unexplained Including Non-APS Thrombophilias

2%–5% Genetic Factors

10%–15% Anatomic Factors

0.5%–5% Infections

17%–20% Endocrine Factors

20% Autoimmune
Parental Structural Balanced Chromosomal Rearrangements

Balanced Reciprocal (%60) or Robertsonian (%40) Translocations

Chromosomal Inversions - Insertions

Mosaicism

Single Gene Defects seldom associated with RPL
Before Translocation

After Translocation

No gain or loss of genetic information

Normal, nonhomologous, acrocentric chromosomes

Robertsonian translocation

Fragment (usually lost)

Reciprocal

Robertsonian
Segregation Reciprocal translocations

Gametes

Offspring

NORMAL/BALANCED  Adj 1  Adj 2  UNBALANCED Tert mon/tris  Interch mon/tris
Segregation Robertsonian translocations

Gametes

Offspring

NORMAL/BALANCED CARRIER

Mon 14  Tris 14  Mon 13  Tris 13

UNBALANCED
ORIGIN OF ANEUPLOIDY

Errors in germ cell proliferation (pre-meiosis)
Germ cell aneuploidy

Gonadal mosaicism

Meiosis

Errors in chromosome segregation resulting in gamete aneuploidy
Uniform aneuploidy in the resulting embryo

Mitosis

Errors in chromosome segregation during early cleavage divisions

Mosaic embryo
RECURRENT PREGNANCY LOSS

IVF + PGS

Single Euploid Embryo Transfer

Increase pregnancy rates

Decrease miscarriage rates

Prevention of the abnormal births

Decrease the time for pregnancy
In Vitro Fertilization with Preimplantation Genetic Screening

Sebastiaan Mastenbroek, M.Sc., Moniek Twisk, M.D., Jannie van Echten-Arends, Ph.D.,
Birgit Sikkema-Raddatz, Ph.D., Johanna C. Korevaar, Ph.D., Harold R. Verhoeve, M.D.,
Niels E.A. Vogel, M.D.,
Eus G.J.M. Arts, Ph.D., Jan W.A. de Vries, Ph.D.,
Patrick M. Bossuyt, Ph.D., Charles H.C.M. Buys, Ph.D.,
Maas Jan Heineman, M.D., Ph.D., Sjoerd Repping, Ph.D., and Fulco van der Veen, M.D., Ph.D.

PGS # 1

Damage of the embryo during cleavage stage following biopsy

Incomplete and limited assessment by FISH

Mosaicism of Day-3 embryo
PGS # 2

Metaphase comparative genomic hybridization

Array comparative hybridization (aCGH)

Genome wide single nucleotide polymorphism analysis

PCR based detection

Next generation sequencing (NGS)

Massive parallel sequencing (MPS)
Yang et al 2012: Only good prognosis patients (average age 31.5) 103 patients, Pregnancy rate: 70 % aCGH group. 45 % in control group (No power analysis).

Forman et al 2013: Study group 89, control group 86. SET (frozen cycle) vs 2 embryo ET on the 3rd day. Pregnancy rates 60 % bs 65 %. Designed as Noninferiority but didn’t qualified.


No randomized study per initiated cycle
Expectant management
Objective: To compare IVF outcomes between women undergoing frozen transfers of blastocysts verified as euploid by preimplantation genetic screening (PGS) with patients undergoing fresh nonbiopsied blastocyst transfers.

Design: Retrospective cohort study.
Setting: Academic medical center.
Patient(s): All patients undergoing IVF-PGS cycles between January 2010 and November 2014 were included (n = 274). Patients were compared with a control group consisting of all fresh blastocyst transfers that occurred during the same period (n = 863).

Intervention(s): Patients underwent IVF-PGS with 24-chromosome screening. Patients with euploid embryos had transfer of one to two embryos in a subsequent frozen ET cycle.

Main Outcome Measure(s): Implantation, clinical intrauterine gestation (CIG), miscarriage, biochemical pregnancy (BC), and live birth (LB) rates were compared.

Result(s): Odds ratios (ORs) were estimated for outcomes in women undergoing PGS versus controls. Among patients ≤37 years old, there were no differences in CIG and LB rates for single (adjusted ORs [aORs], 1.20 [95% confidence interval {CI}, 0.66–2.21]; 1.21 [95% CI, 0.66–2.21]) and double ETs (aORs, 1.09 [95% CI, 0.54–2.18]; 0.87 [95% CI, 0.44–1.7]). BC and miscarriage rates were also similar. For patients >37 years old, CIG and LB rates were increased for single (aORs, 3.86 [95% CI, 1.25–11.9]; 8.2 [95% CI, 2.28–29.5]) and double ETs (aORs, 9.91 [95% CI, 2.0–49.6]; 8.67 [95% CI, 2.08–36.2]) with no difference in BC and miscarriage rates. A per-retrieval analysis of the >37 group failed to demonstrate any difference in CIG or LB rates.

Conclusion(s): Among patients ≤37, IVF-PGS does not improve CIG, LB, and miscarriage rates. IVF-PGS in women >37 improved CIG and LB rates. However, per cycle, the PGS advantage in this age group does not persist. (Fertil Steril® 2016;106:597–602. ©2016 by American Society for Reproductive Medicine.)
### TABLE 2

**IVF cycle outcomes in women ≤37 years old.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PGS (n = 62)</th>
<th>Controls (n = 161)</th>
<th>P</th>
<th>PGS (n = 37)</th>
<th>Controls (n = 516)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>33.9 ± 2.8</td>
<td>32.3 ± 3.0</td>
<td>&lt;.01</td>
<td>33.9 ± 2.9</td>
<td>32.4 ± 3.3</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>0.54 ± 0.5</td>
<td>0.54 ± 0.52</td>
<td>.92</td>
<td>0.47 ± 0.40</td>
<td>0.52 ± 0.44</td>
<td>.52</td>
</tr>
<tr>
<td>Biochemical pregnancies</td>
<td>6 (9.7)</td>
<td>18 (11.2)</td>
<td>.75</td>
<td>5 (13.5)</td>
<td>62 (11.8)</td>
<td>.79</td>
</tr>
<tr>
<td>Clinical intrauterine gestations</td>
<td>34 (54.8)</td>
<td>85 (52.8)</td>
<td>.78</td>
<td>23 (62)</td>
<td>334 (64.7)</td>
<td>.75</td>
</tr>
<tr>
<td>Missed/spontaneous abortions</td>
<td>3 (4.8)</td>
<td>9 (5.6)</td>
<td>.82</td>
<td>0 (0)</td>
<td>25 (4.8)</td>
<td>.17</td>
</tr>
<tr>
<td>Live births</td>
<td>31 (50)</td>
<td>76 (47)</td>
<td>.71</td>
<td>23 (62)</td>
<td>309 (59.9)</td>
<td>.79</td>
</tr>
<tr>
<td>Twins</td>
<td>0</td>
<td>2 (1.2)</td>
<td>1</td>
<td>10 (27)</td>
<td>158 (31)</td>
<td>.65</td>
</tr>
</tbody>
</table>

*Note: Data are presented as mean ± SD and n (%). Kang. PGS and IVF outcomes. Fertil Steril 2016.*

### TABLE 3

**IVF cycle outcomes in women > 37 years old.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PGS (n = 45)</th>
<th>Controls (n = 27)</th>
<th>P</th>
<th>PGS (n = 15)</th>
<th>Controls (n = 189)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>40.8 ± 1.7</td>
<td>39.3 ± 1.5</td>
<td>&lt;.01</td>
<td>40 ± 0.85</td>
<td>39.7 ± 1.3</td>
<td>.37</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>0.62 ± 0.49</td>
<td>0.37 ± 0.49</td>
<td>.04</td>
<td>0.53 ± 0.30</td>
<td>0.37 ± 0.42</td>
<td>.18</td>
</tr>
<tr>
<td>Biochemical pregnancies</td>
<td>5 (11)</td>
<td>2 (7.4)</td>
<td>.61</td>
<td>1 (6.7)</td>
<td>23 (12.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Clinical intrauterine gestations</td>
<td>28 (62.2)</td>
<td>10 (37.0)</td>
<td>.04</td>
<td>13 (86.7)</td>
<td>97 (51.3)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Missed/spontaneous abortions</td>
<td>2 (4.4)</td>
<td>5 (18.5)</td>
<td>.051</td>
<td>1 (6.7)</td>
<td>16 (8.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Live Births</td>
<td>26 (57.8)</td>
<td>5 (18.5)</td>
<td>&lt;.01</td>
<td>12 (80)</td>
<td>81 (42.9)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Twins</td>
<td>0</td>
<td>0</td>
<td></td>
<td>5 (33.3)</td>
<td>29 (15.3)</td>
<td>.14</td>
</tr>
</tbody>
</table>

*Note: Data are presented as mean ± SD and n (%). Kang. PGS and IVF outcomes. Fertil Steril 2016.*
Cost-effectiveness analysis of preimplantation genetic screening and in vitro fertilization versus expectant management in patients with unexplained recurrent pregnancy loss

Gayathree Murugappan, M.D., Mika S. Ohno, M.D., and Ruth B. Lathi, M.D.
Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Stanford University Medical Center, Palo Alto, California

### TABLE 1

Baseline clinical probabilities from the literature: IVF–PGS versus expectant management.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IVF–PGS (n = 232)</th>
<th>Expectant management (n = 302)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate, % (n)</td>
<td>44 (102)(^c)</td>
<td>75 (226)</td>
</tr>
<tr>
<td>Live-birth rate, % (n)</td>
<td>40 (94)(^c)</td>
<td>55 (167)</td>
</tr>
<tr>
<td>CM rate, % (n)</td>
<td>7 (7)(^d)</td>
<td>24 (55)(^d)</td>
</tr>
</tbody>
</table>

Note: CM = clinical miscarriage; IVF–PGS = in vitro fertilization with preimplantation genetic screening.

\(^a\) Obtained from Hodes-Werz et al. 2012 (10).
\(^b\) Obtained from Brigham et al. 1999 (11).
\(^c\) Calculated per attempt, which was defined as an IVF cycle and oocyte retrieval ± embryo transfer.
\(^d\) Calculated per pregnancy.


### TABLE 2

Base case analysis: cost outcomes at 7% clinical management rate for IVF–PGS.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IVF–PGS</th>
<th>Expectant management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>$24,009</td>
<td>$280</td>
</tr>
<tr>
<td>Live-birth rate(^a)</td>
<td>53%</td>
<td>67%</td>
</tr>
<tr>
<td>CM rate(^b)</td>
<td>7%</td>
<td>24%</td>
</tr>
<tr>
<td>Cost per live birth</td>
<td>$45,300</td>
<td>$418</td>
</tr>
</tbody>
</table>

Note: CM = clinical miscarriage; IVF–PGS = in vitro fertilization with preimplantation genetic screening.

\(^a\) Calculated per strategy.
\(^b\) Calculated per pregnancy.

The value of PGT-A as a screening test has yet to be determined.
Conclusions

Diminished ovarian reserve may have a role in RPL

Ovarian reserve tests may help to make suggestions about the treatment options in such kind of patients

PGS not advised as a treatment in RPL societies yet

Caryotyping of the POC may have a role to explain the cause of otherwise “unexplained” RPL
NONINVASIVE PGS

THE BLASTOCYST

Cavitation:
Accumulation of the blastocoelic fluid transported by TE cells

Desmosomes:
- connect TE cells
- help maintaining TE cell integrity and stability during blastocyst expansion

The process depends on:
- Complete cellular polarization
- Formation of permeable seals (tight junctions) between TE cells forming a belt-like circular line
Noninvasive chromosome screening of human embryos by genome sequencing of embryo culture medium for in vitro fertilization

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Contributed by X. Sunney Xie, August 10, 2016 (sent for review April 28, 2016; reviewed by Eva Hoffmann and John Rasko)