Does Preimplantation Genetic Testing for Aneuploidy Provide a Benefit to Patient Success during Assisted Reproductive Technologies?

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Problem

- Preimplantation Genetic Screening (PGS) has been offered to patients for years but has been evolving
  - Where and when we obtain material for analysis
    - Polar body biopsy
    - Day 3 blastomere biopsy
    - Trophectoderm biopsy
  - How we perform the Chromosome Analysis
    - Fluorescence in situ Hybridization (FISH)
    - Quantitative Polymerase Chain Reaction (qPCR)
    - Array Comparative Genome Hybridization (aCGH)
    - Next Generation Sequencing (NGS)

Problem

- Two techniques have fallen from favor:
  - Day 3 biopsy – harmful to the embryo
  - FISH – number of chromosomes analyzed << 23
- Recently adopted techniques are now popular:
  - Trophectoderm biopsy can be performed so that it produces negligible harm
    - Smaller biopsies are less harmful than larger biopsies
  - The use of Comprehensive Chromosome Analysis is now widely available
    - qPCR
    - aCGH
    - NGS

Problem

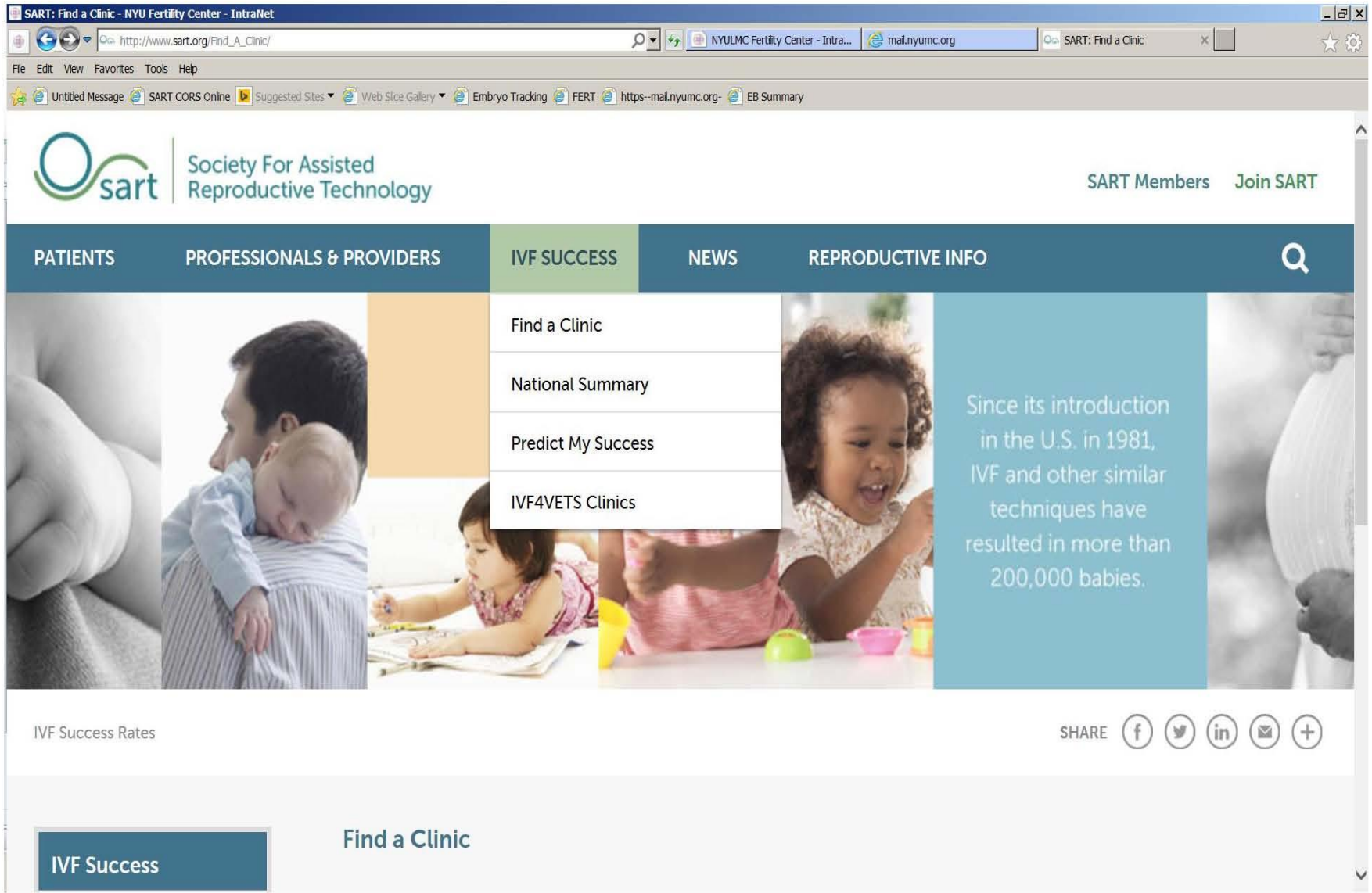
- The use of trophectoderm biopsy and comprehensive chromosome analysis

  (PGS v2.0)
- Limited randomized control trials
  - Yang et al., (2012) (N ~100; <35 years) using aCGH, eSET
  - Scott et al., (2013) (N ~150; 21-42 years; ≥2 blasts) using qPCR, DET
  - Forman et al., (2013) (N ~175; <43 years; ≥2 blasts) using qPCR, 1 vs 2 ET
  - Praised as the salvation of PGS
  - Attacked as a widely used technology with little scientific support
- Whether PGS v2.0 can provide benefits to all patients remains unclear

Purpose

- To use two approaches to investigate whether PGS v2.0 can improve outcomes for patients
  - Data from the United States (SART)
  - Projection of cumulative pregnancy rates

Data collected by SART (2014)



Primary Outcome (2014)

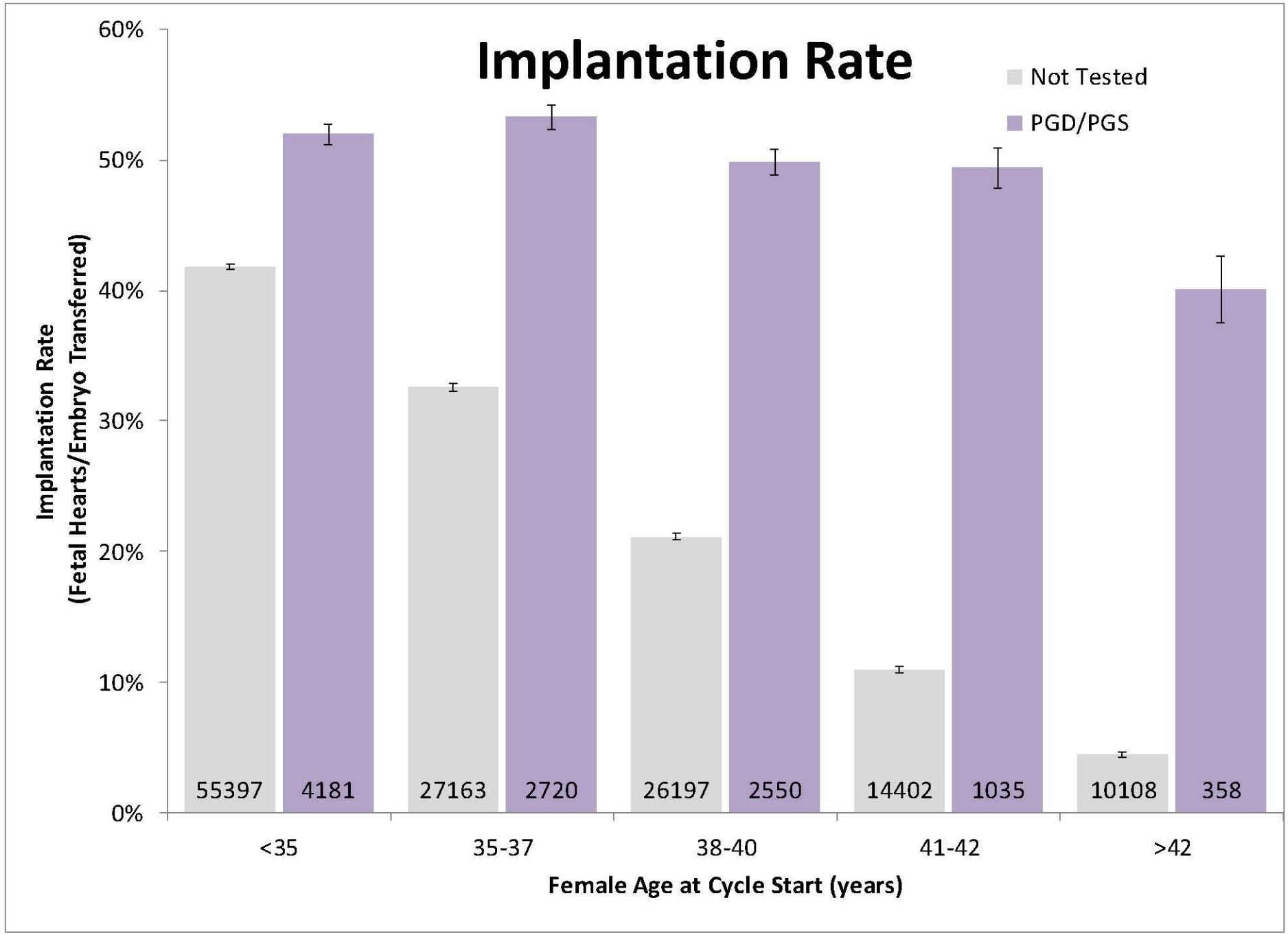
- 1st Transfer following the retrieval (**N = 94,615**)
  - Fresh transfer

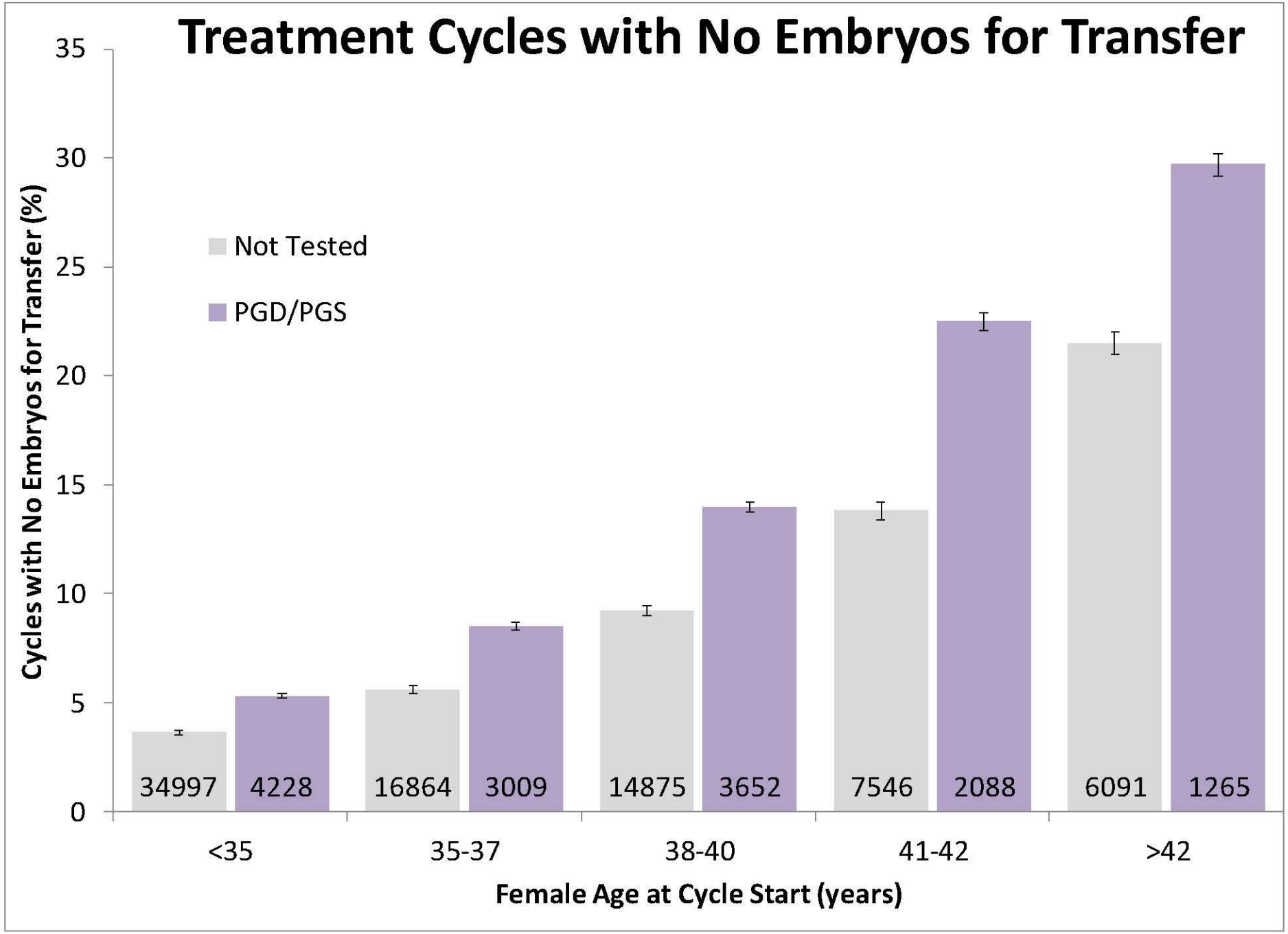
    - or -

  - 1st Frozen Embryo Transfer (if no Fresh Transfer)

    - or -

  - No transfer = Not pregnant


Implantation Rate
Not Tested
PGD/PGS
Implantation Rate
(Fetal Hearts/Embryo Transferred)
60%
50%
40%
30%
20%
10%
0%
55397
4181
27163
2720
26197
2550
14402
1035
10108
358
<35
35-37
38-40
41-42
>42
Female Age at Cycle Start (years)


Treatment Cycles with No Embryos for Transfer
Cycles with No Embryos for Transfer (%)
35
30
25
20
15
10
5
0
Not Tested
PGD/PGS
34997
4228
16864
3009
14875
3652
7546
2088
6091
1265
<35
35-37
38-40
41-42
>42
Female Age at Cycle Start (years)

Does PGS overcome the Attrition?

- Clearly, embryos with euploid biopsies (PGS) outperform embryos with no testing (presumed to be a mix of euploid and aneuploid embryos)
- Clearly, more patients have no embryos available for transfer after PGS.
- Do embryos with euploid biopsies outperform untested embryos sufficiently to compensate for the extra PGS cycles with no embryos to transfer?

Prospective Randomized Trials

- Yang et al., (2012) (N ~100) using aCGH:
  - <35 years
  - First IVF
  - 1 embryo transferred (SET)
- Scott et al., (2013) (N ~150) using qPCR:
  - 21 – 42 years
  - No more than one prior failed IVF retrieval
  - Inclusion: FSH $\leq$ 15 mIU/ml
  - Enrollment at day 5 with $\geq$ 2 blasts
  - 2 embryos transferred (when possible)(DET)
- Forman et al., (2013) (N ~175) using qPCR:
  - <43 years
  - Inclusion: FSH < 12 mIU/ml & AMH $\geq$ 1.2 ng/ml
  - Enrollment at day 5 with > 2 blasts
  - Transfer:
    - PGS – ONE euploid blast transferred
    - No PGS – TWO embryos transferred

Prospective Randomized Trials

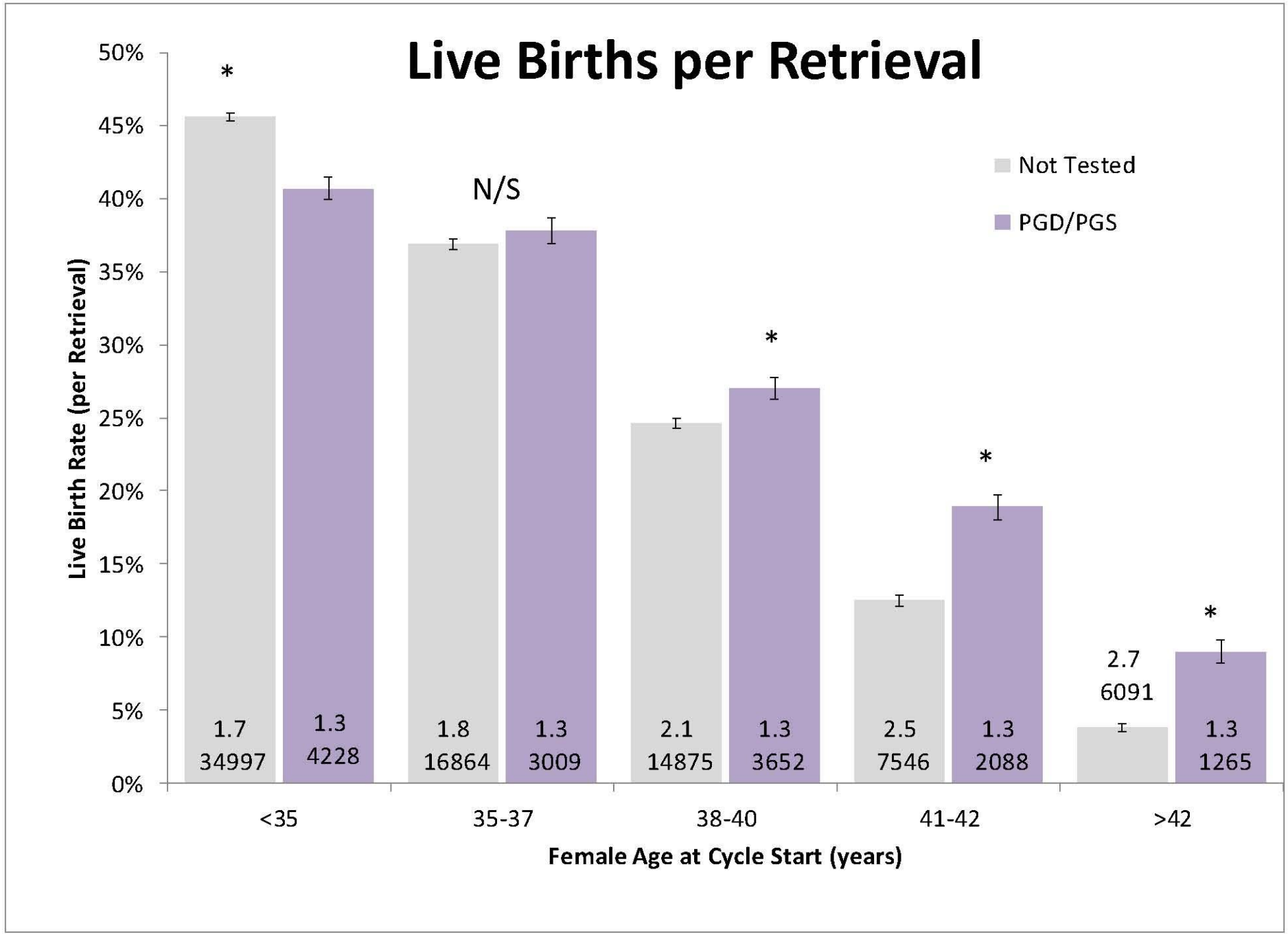
- Yang et al., (2012) (SET)
  - PGS group performed significantly better
    - Clinical pregnancy rate per transfer (71% vs. 46%)
    - Ongoing pregnancy rate per transfer (69% vs 42%)
- Scott et al., (2013) (DET)
  - PGS group performed significantly better
    - Clinical pregnancy rate per cycle (93% vs. 81%)
    - Delivery rate per cycle (85% vs. 68%)
- Forman et al., (2013) (SET versus DET)
  - PGS group was not inferior (despite SET vs. DET)
    - Ongoing pregnancy rate at 24 weeks (PGS = 61% vs. no PGS = 65%)
  - PGS group performed significantly better
    - Ongoing multiple pregnancy rate (PGS = 0% vs. no PGS = 53%)

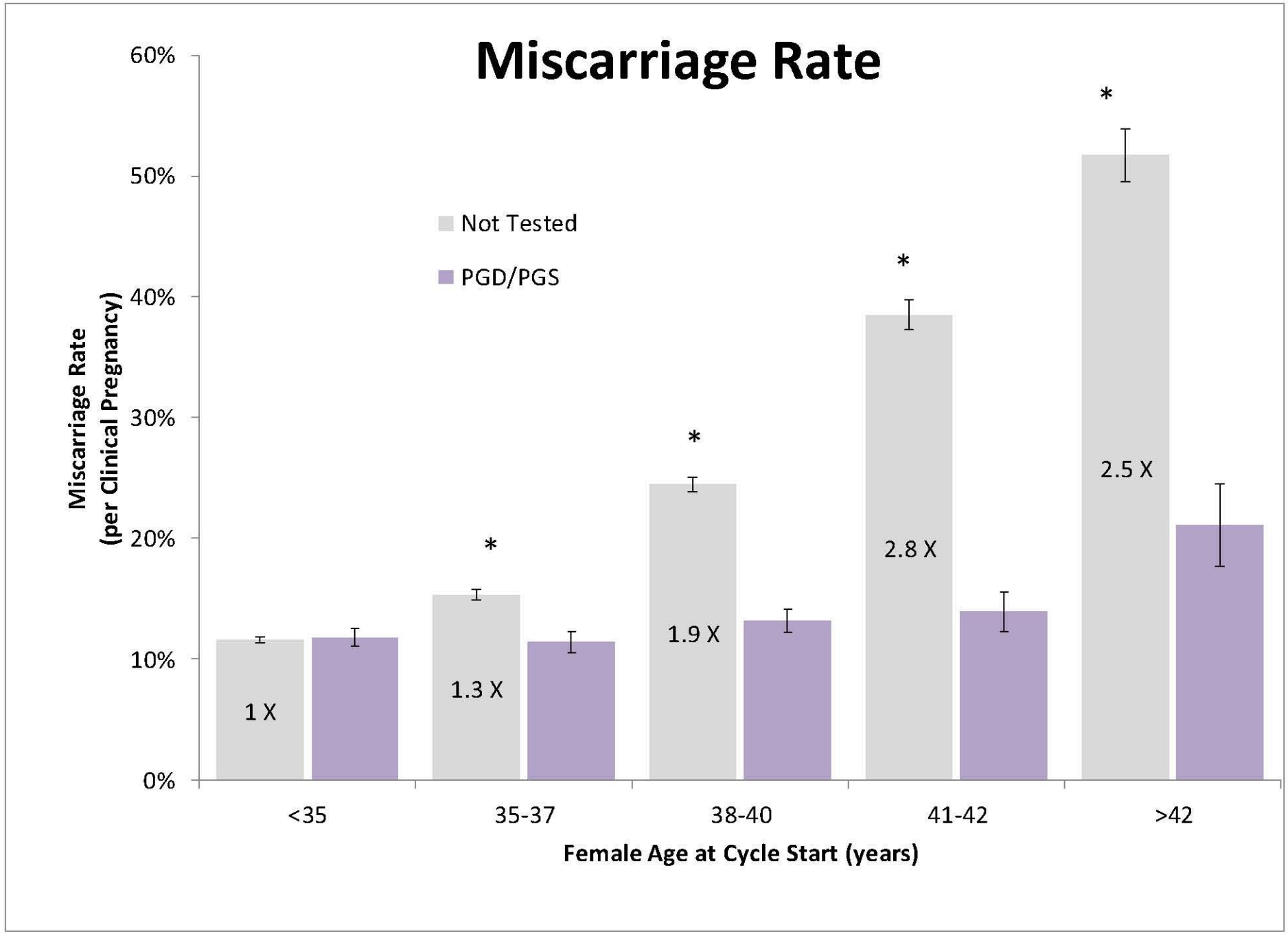
Summary of RCTs

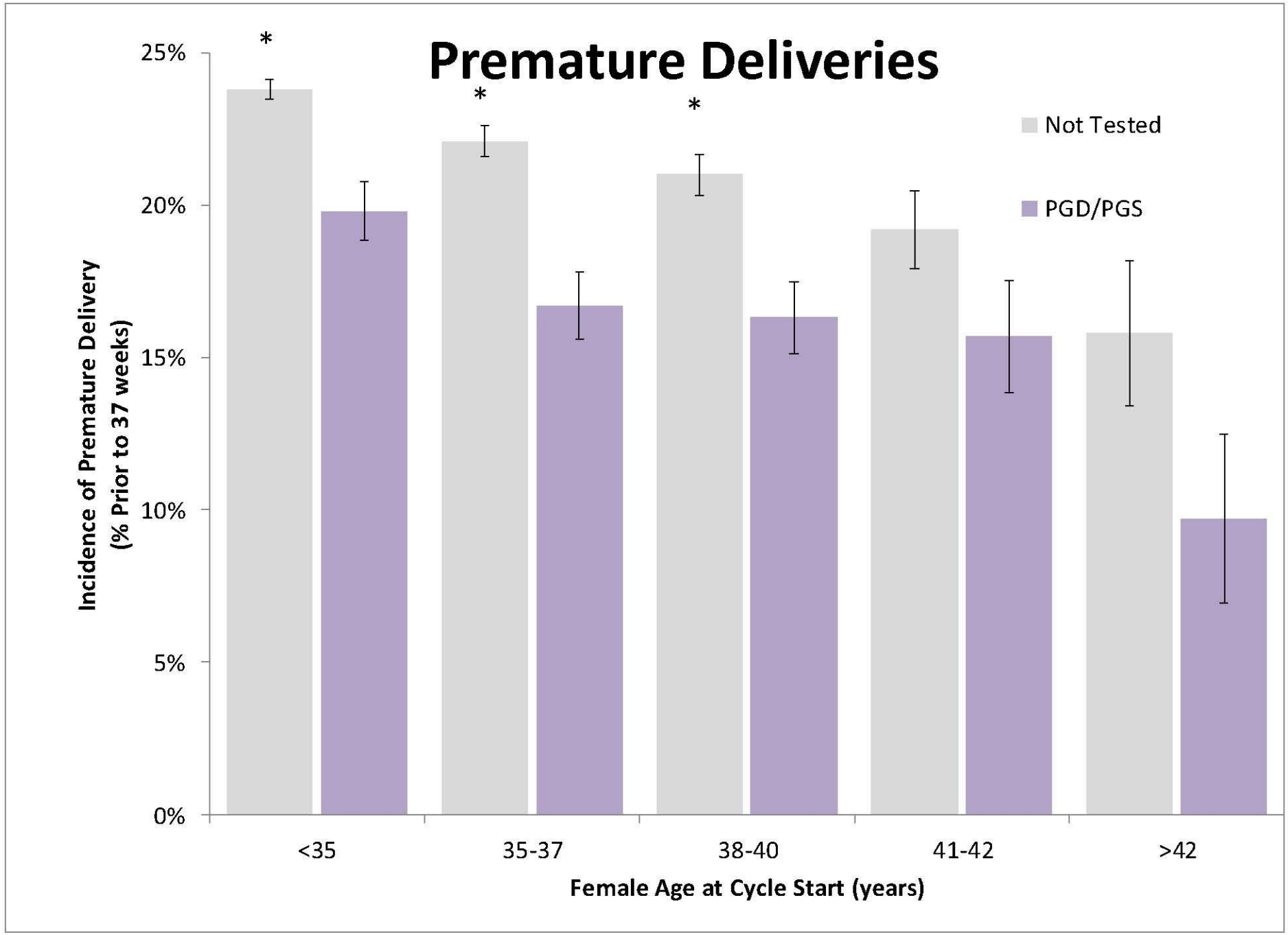
- PGS performed better when same number of embryos were transferred
- When 1 PGS embryo compared to 2 untested embryos
  - Pregnancy/Live Birth Rates – PGS not inferior
  - Multiple Pregnancy – PGS significantly fewer
- Complaints
  - Patients selected for the studies were good prognosis
  - May not be representative of the typical infertility patient

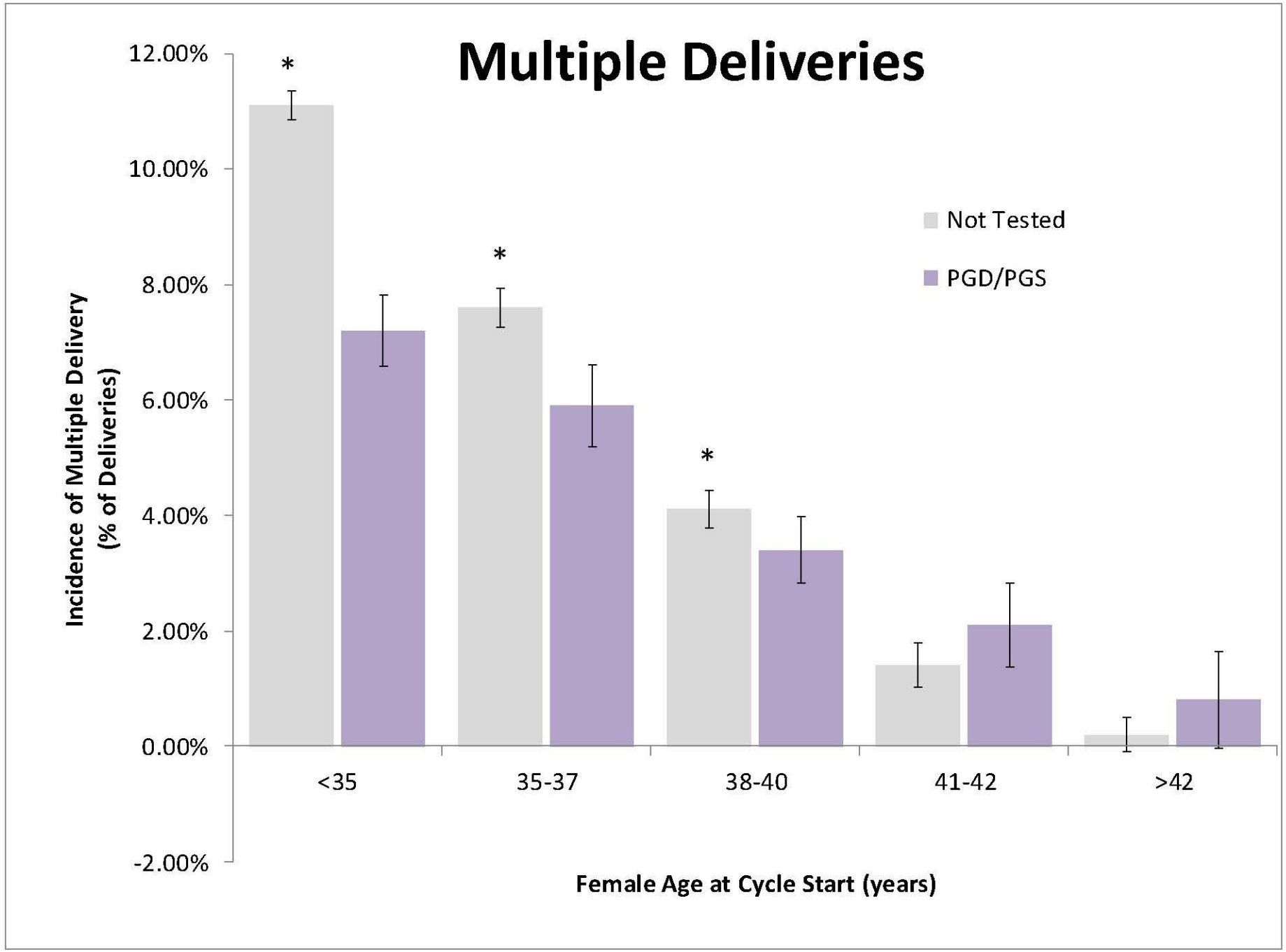
Consider a Larger Data Set

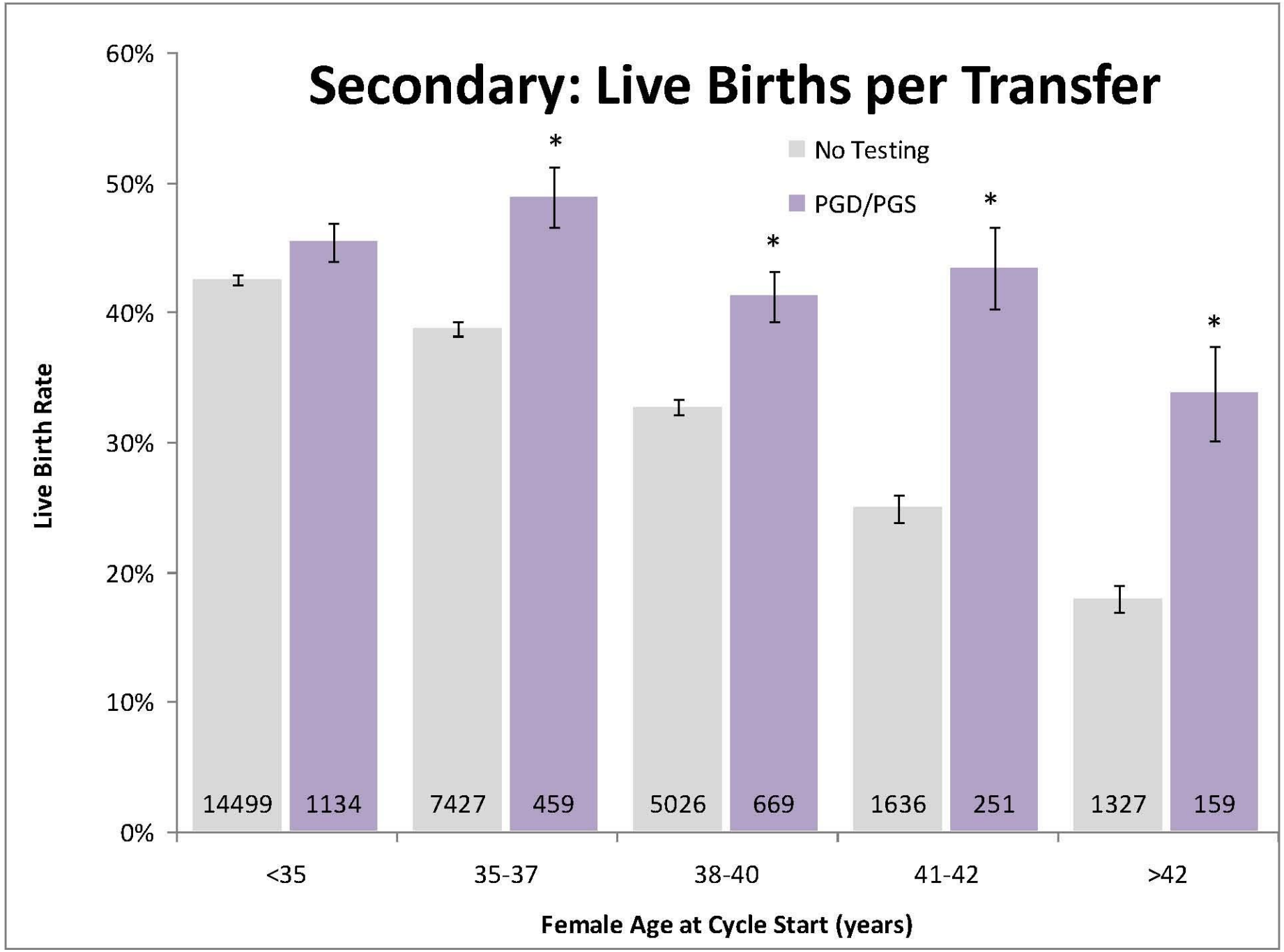
- SART Data
- Comparing PGD to no PGD per retrieval
  - PGD includes:
    - Ploidy Determination (~95%)
    - Structural Chromosomal Issues (~5%)
      - Single Gene Defects
        - » Point mutations
        - » Deletions
        - » Insertions
        - » Inversions
      - Translocations
- Not Randomized
- Not Cumulative

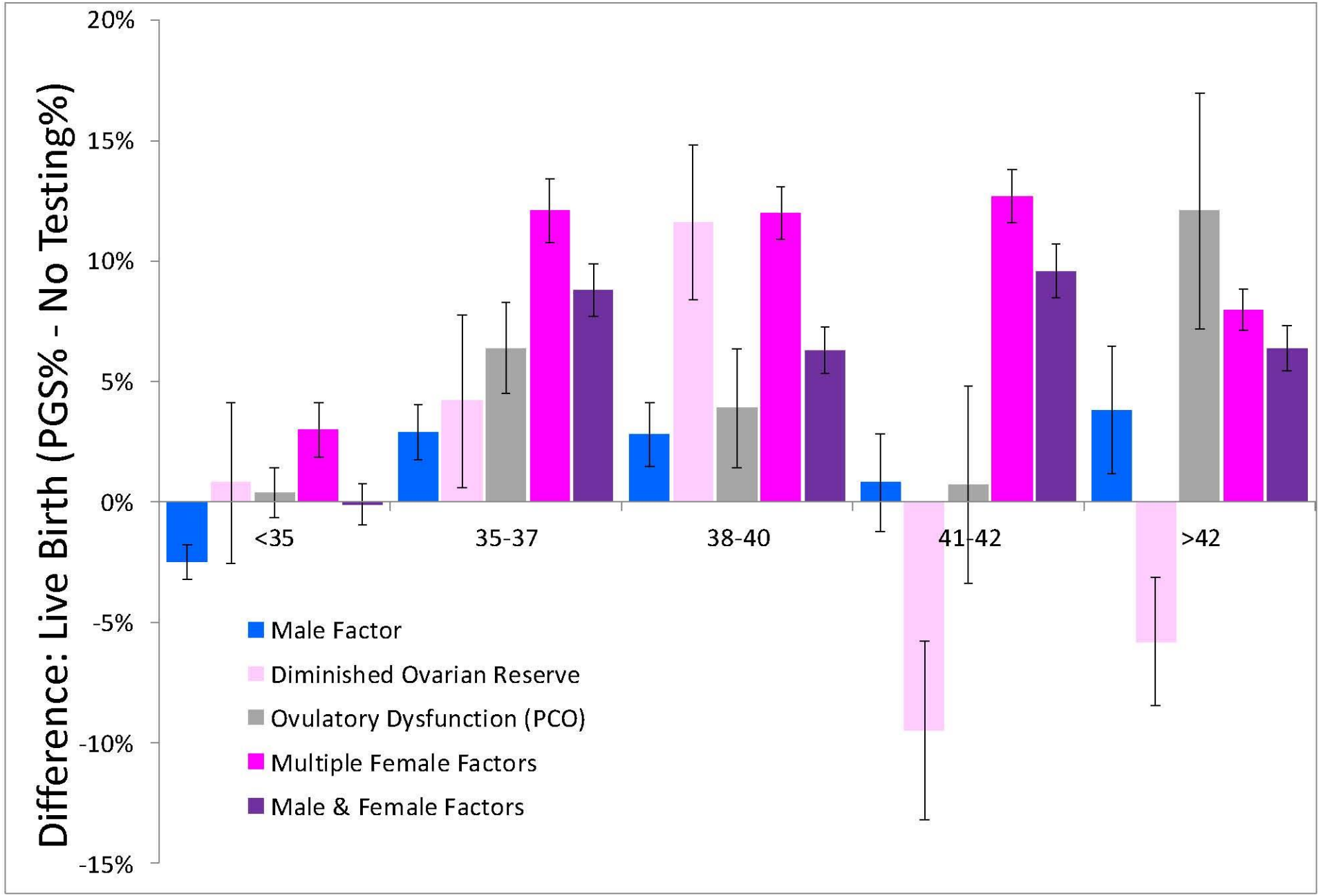

Live Births per Retrieval
Not Tested
PGD/PGS
Live Birth Rate (per Retrieval)
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
*
N/S
*
*
*
1.7
34997
1.3
4228
1.8
16864
1.3
3009
2.1
14875
1.3
3652
2.5
7546
1.3
2088
2.7
6091
1.3
1265
<35
35-37
38-40
41-42
>42
Female Age at Cycle Start (years)


Miscarriage Rate
60%
50%
40%
30%
20%
10%
0%
Miscarriage Rate
(per Clinical Pregnancy)
Not Tested
PGD/PGS
*
*
*
*
1 X
1.3 X
1.9 X
2.8 X
2.5 X
<35
35-37
38-40
41-42
>42
Female Age at Cycle Start (years)


Premature Deliveries
Not Tested
PGD/PGS
Incidence of Premature Delivery
(% Prior to 37 weeks)
25%
20%
15%
10%
5%
0%
*
*
*
<35
35-37
38-40
41-42
>42
Female Age at Cycle Start (years)


Multiple Deliveries
12.00%
10.00%
8.00%
6.00%
4.00%
2.00%
0.00%
-2.00%
Incidence of Multiple Delivery (% of Deliveries)
Not Tested
PGD/PGS
*
*
*
<35
35-37
38-40
41-42
>42
Female Age at Cycle Start (years)


Secondary: Live Births per Transfer
No Testing
PGD/PGS
Live Birth Rate
60%
50%
40%
30%
20%
10%
0%
*
*
*
*
14499
1134
7427
459
5026
669
1636
251
1327
159
<35
35-37
38-40
41-42
>42
Female Age at Cycle Start (years)


Difference: Live Birth (PGS% - No Testing%)
20%
15%
10%
5%
0%
-5%
-10%
-15%
<35
35-37
38-40
41-42
>42
Male Factor
Diminished Ovarian Reserve
Ovulatory Dysfunction (PCO)
Multiple Female Factors
Male & Female Factors

Summary of Data from SART

- Number of patient cycles examined much larger
  - Two differences in treatment
    - PGS versus NO Testing
    - 30 – 110% more embryos transferred for NO Testing
- Benefits seen for PGS patients
  - Increased Live Birth Rate (38 years and up)
  - Decreased SAb Rate (35 years and up)
  - Decreased premature deliveries (under 41 years)
- Benefits ONLY realized with PGS!

Cumulative Live Birth Rates (Modelled)

- Do cumulative live birth rates really favor “No Testing?”
  - Projections using real data
  - Compare cumulative live births between
    - PGS
    - No Testing
  - Using identical patients
  - Realistic conditions

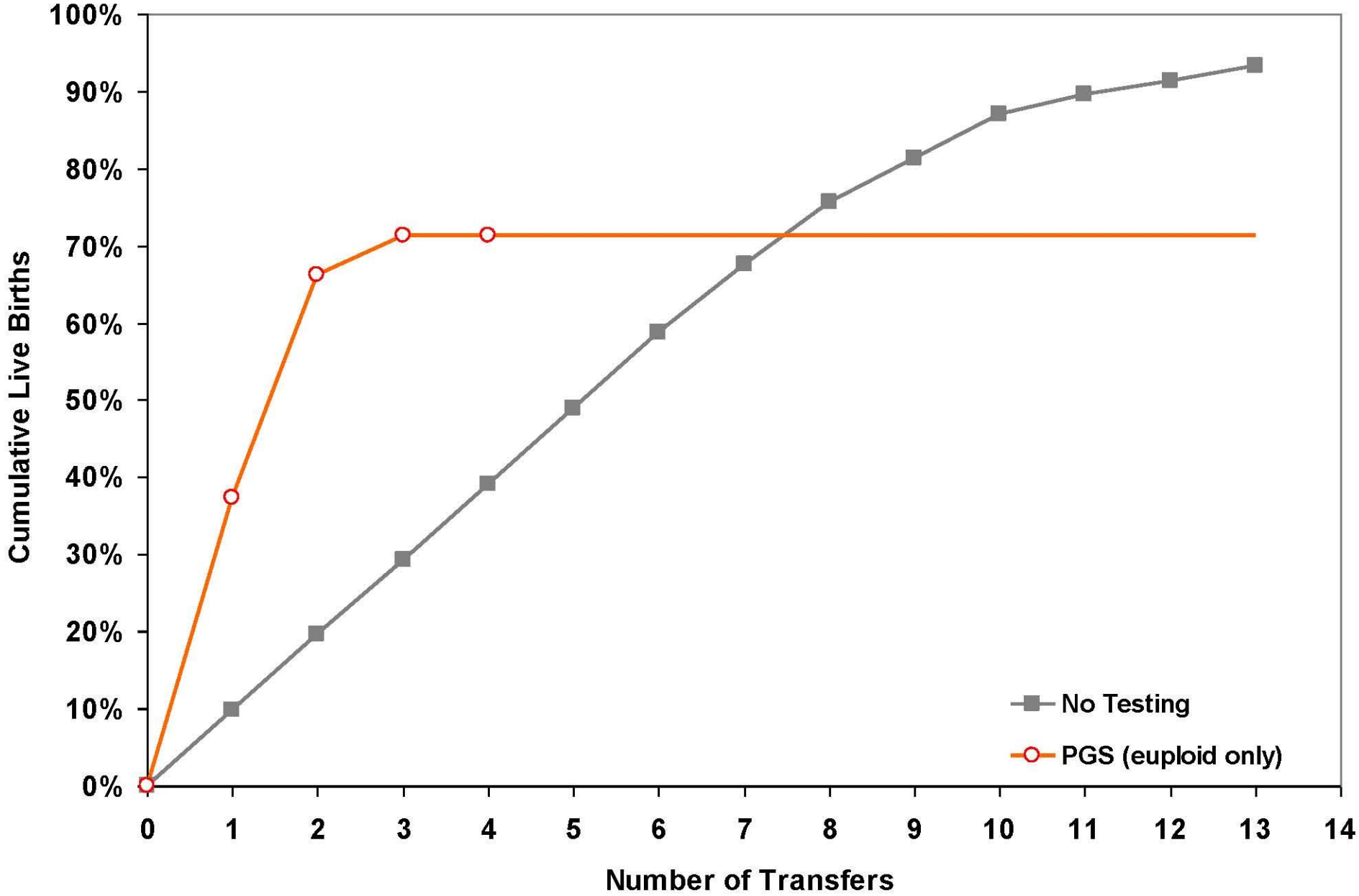
Cumulative Pregnancy Rates

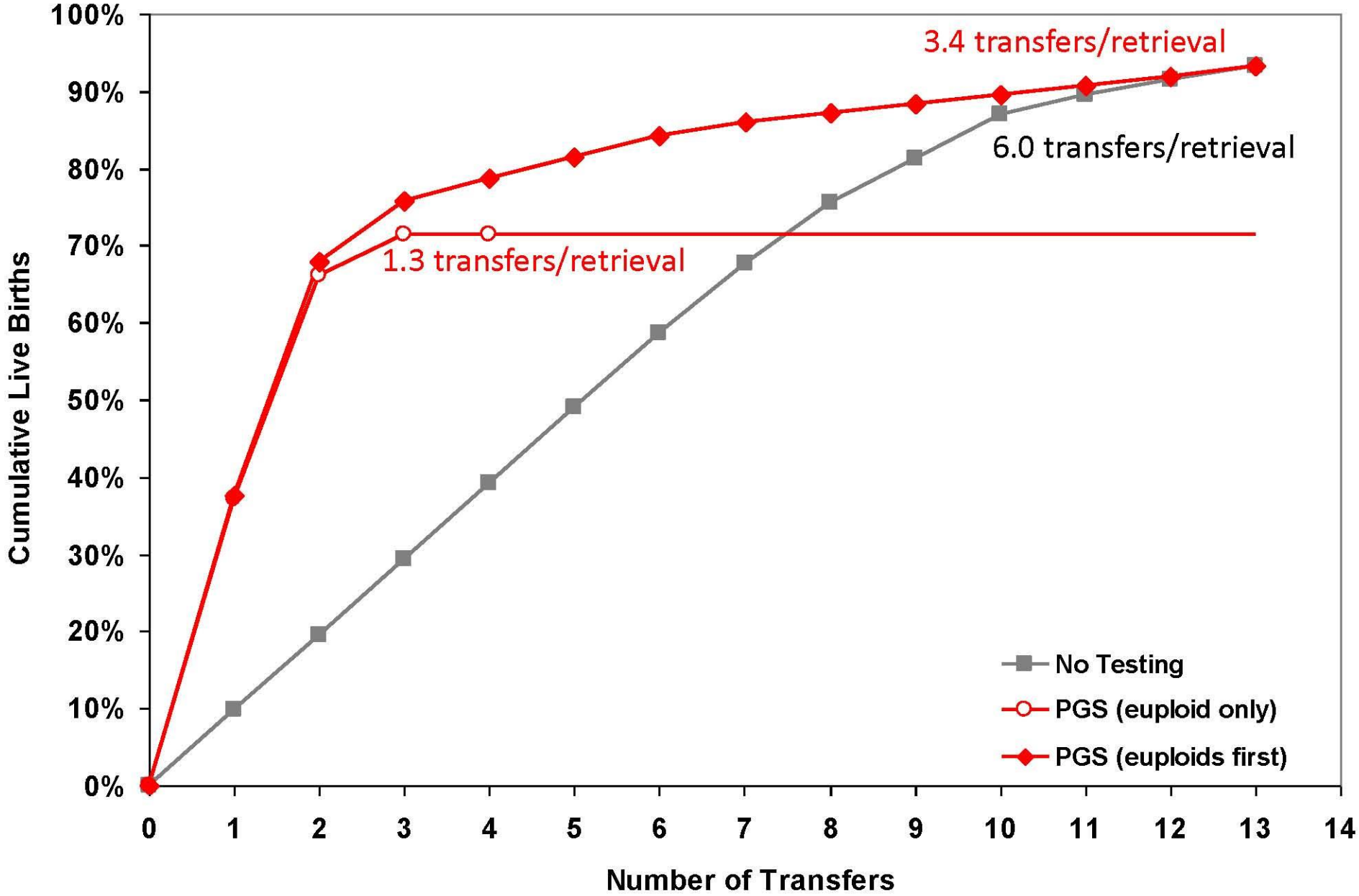
- Patients with 13 embryos for transfer
  - Patients average 2.0 embryos with euploidy
    - 10% with NO euploidy
    - 20% with ONE embryo with euploidy
    - 40% with TWO embryos with euploidy
    - 20% with THREE embryos with euploidy
    - 10% with FOUR embryos with euploidy
  - Live Birth Rates for Embryos with:
    - Euploid Biopsy = 0.414
    - Aneuploid Biopsy = 0.0404
    - Scott, Ferry, Su, Tao, Scott & Treff. *Fertil. Steril.* (2012)

Compare Cumulative Live Birth Rates

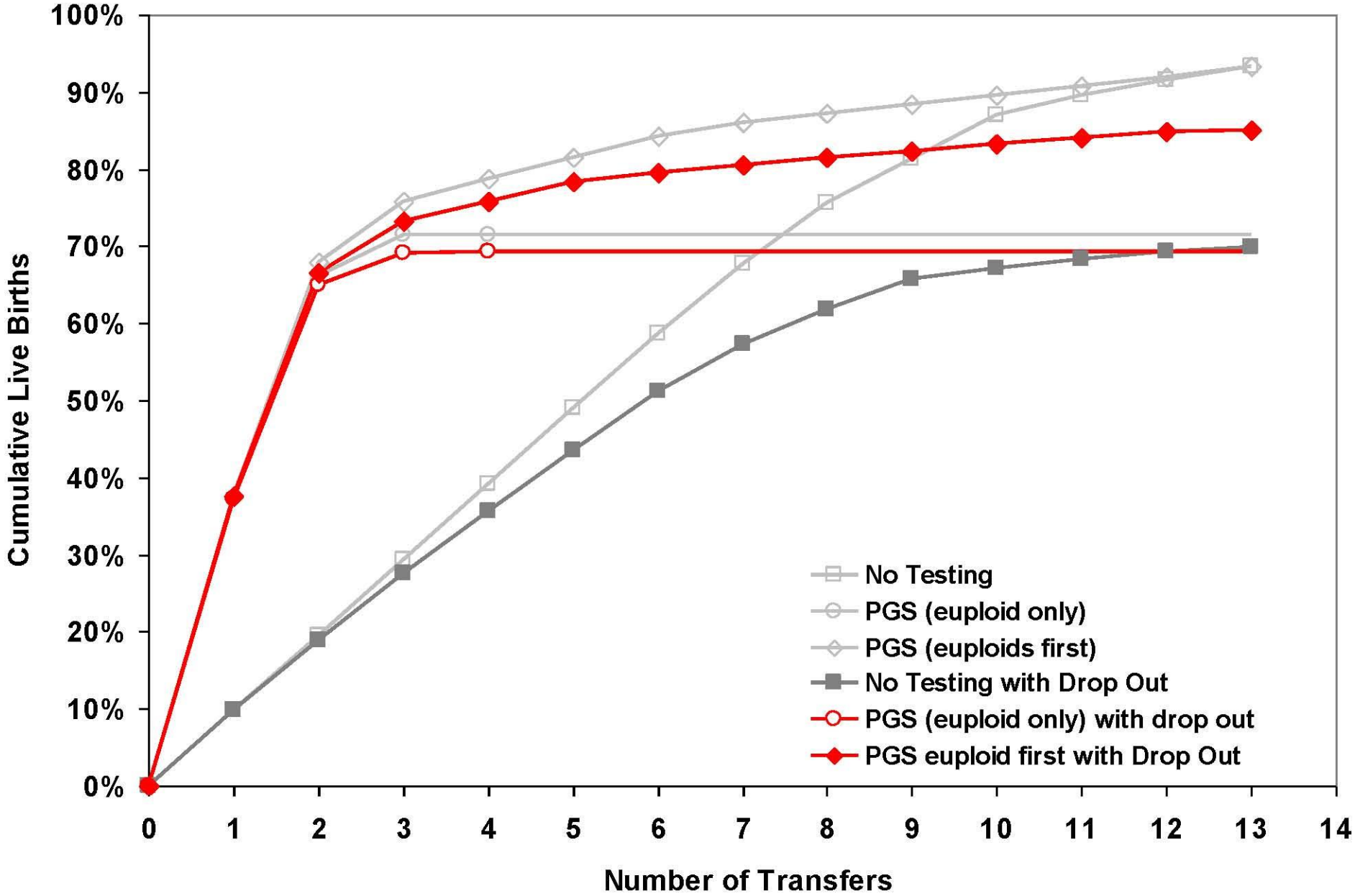
	PGS (qPCR)	No Testing
Cumulative Live Birth Rate (13 embryos, average of 2 euploid)	71.4%	93.2%
Number of Transfers (Mean / Maxiumum)	1.3 / 4	6 / 13

Don’t be convinced by this yet….


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Live Births
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Number of Transfers
No Testing
PGS (euploid only)


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Live Births
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Number of Transfers
3.4 transfers/retrieval
6.0 transfers/retrieval
1.3 transfers/retrieval
No Testing
PGS (euploid only)
PGS (euploids first)

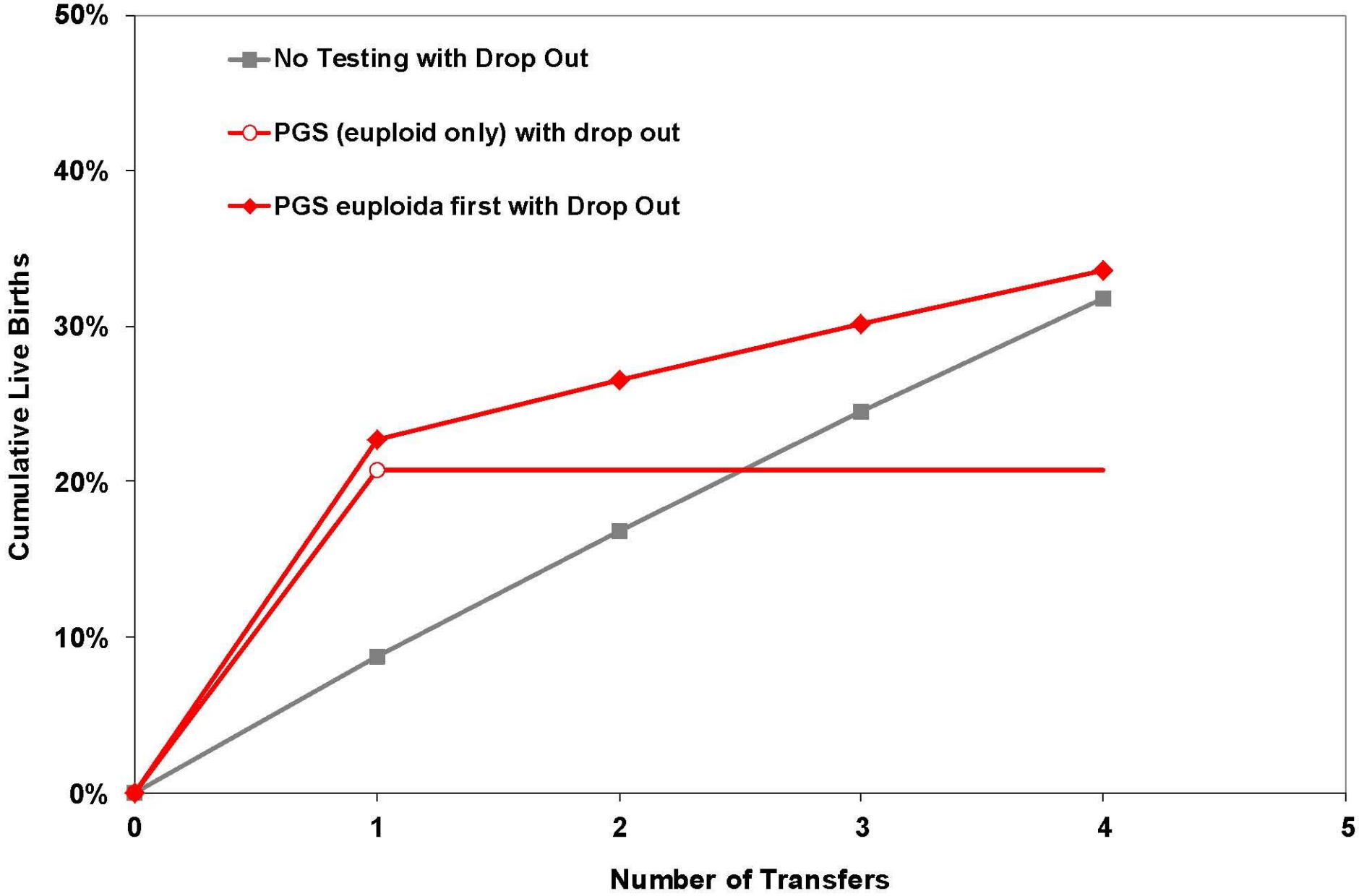
Effect of Patient Drop Out… (7.5%)



Cumulative Pregnancy Rates

- Patients with 4 embryos for transfer
  - Patients average 0.5 embryos with euploidy
    - 50% have NO embryos with euploidy
    - 50% have ONE embryo with euploidy
  - Live Birth Rates for Embryos with:
    - Euploid Biopsy = 0.414
    - Aneuploid Biopsy = 0.0404
    - Scott, Ferry, Su, Tao, Scott & Treff. *Fertil. Steril.* (2012)

Effect of Patient Drop Out… (7.5%)



- Effects of platform on euploidy rates
- qPCR
- aCGH
- NGS
- Mosaicism (the reality)
- Mosaicism (the diagnosis)

Summary

- PGS is a tool, a test, and how it is used depends on the practitioner
- We have been told that “No testing” can achieve higher results than “PGS.”
- This is not true if
  - Euploid transfers are followed by aneuploid transfers
    - Result: equivalence of cumulative live birth rates
  - Patients drop out of treatment
    - Result: “No Testing” NEVER catches up
- Our patients deserve a more thoughtful approach that results in live births sooner rather than later
- This can only be accomplished with PGS

Is Preimplantation Genetic Testing for Ploidy Cost Effective?

David H. McCulloh,
Brook Hodes-Wertz,
James A. Grifo

NYU Fertility Center
New York University Langone Medical Center
New York, New York USA

Problem

- Benefits of analysis and selection of embryos by the use of comprehensive chromosome analysis (preimplantation genetic testing for euploidy = PGS) are apparent
  - Higher implantation rates
  - Lower miscarriage rates
- The added cost of PGS has precluded its widespread/universal application as a adjunct to assisted reproductive technologies
- It remains unclear whether PGS is cost effective.

Purpose

- To examine whether the inclusion of PGS is a cost-effective addition to ART therapy at our facility in New York
- To consider whether the inclusion of PGS would be cost-effective at other facilities

Methods

Included in the analysis were:

- All patients presenting for IVF treatment at NYU Fertility Center between 2011 and 2013
  - IVF retrievals
  - Subsequent FETs
  - Either with or without the use of PGS

Methods

- The following costs were considered:
  - routine IVF cycle with and without embryo transfer
  - frozen embryo transfer of unscreened and euploid embryos
  - PGS, including
    - Biopsy
    - Shipping of specimen
    - Outside laboratory cost to perform array comparative genome hybridization (aCGH) testing for ploidy determination
    - Cryopreservation of embryos with and without transfer
  - Dilitation and curettage performed on early pregnancy failure,
  - Termination of pregnancy,
  - Laparoscopic salpingectomy performed for ectopic pregnancy,
  - Livebirth
    - Singleton
    - Twins
    - Triplets

Costs

- Costs of procedures at NYU Fertility Center were determined
  - Stimulation & Retrieval
  - Genetic Testing (biopsy, transport, testing)
  - Uterine Preparation & Frozen Embryo Transfer
- Costs of Prenatal and Postnatal care were obtained (Lemos, et al., 2013) for
  - Singleton
  - Twins
  - Triplets

Lemos EV, Zhang D, Van Voorhis BJ, Hu XH. Healthcare expenses associated with multiple vs singleton pregnancies in the United States. *Am J Obstet Gynecol.* 2013;209(6):586.e581-586.e511.

	IVFsuFET	IVFPGS
Number of patients	1410	440
IVF (no TE biopsy) with fresh ET (# cycles with ER)	1899	
IVF (no TE biopsy) without ET (# cycles with ER)	101	63
Subsequent unscreened FET (# FETs)	297	
IVF-TE biopsy- no FET (# cycles with ER (number of embryos biopsied))		223 (632 embryos)
IVF-TE biopsy-euploid FET (# cycles with ER and euploid FET (number of embryos biopsied))		291 (1852 embryos)
Subsequent euploid FET (# FETs)		44
D&C for SAB (# of procedures)	157	18
Termination of Pregnancy (# of procedures)	11	1
Ectopic salpingectomy (# of procedures)	5	1
Singleton livebirths	564	174
Twin livebirths	121	9
Triplet livebirth	2	0

Overview of Outcomes (not cost)

- Number of embryos transferred: IVF-PGS significantly less
    - 1.1 euploid embryos (PGS) vs.
    - 2.1 embryos (no PGS) IVFsuFET group, $p<0.01$
        - 2.1 in the fresh ETs and
        - 1.8 in the unscreened FETs
- Clinical pregnancy rate- IVF-PGS significantly higher
    - 64% (PGS) vs.
    - 42% (no PGS) ($p<0.001$)
- SAB rate: IVF-PGS significantly lower
    - 15% (PGS) vs.
    - 24%, (no PGS) $p<0.05$
- There were two triplet pregnancies in the IVFsuFET group and none in the IVFPGS group.

Consideration of Cost

	No. of IVF-suFET patients (deliveries)	No. of IVF-PGS patients (deliveries)	Multiple Gestation Rate IVF-suFET	Multiple Gestation Rate IVF- PGS	Cost per delivery with IVF-suFET	Cost per delivery with IVF-PGS
<35 yrs old	412 (272)	85 (47)	21%	4%	$65,356	$ 65,278
35-39 yrs old	473 (263)	150 (83)	17%	7%	$69,751	$ 66,841
40-42 yrs old	381 (123)	141 (47)	22%	2%	$102,131	$ 89,350
>42 yrs old	194 (28)	74 (6)	4%	0%	$182,463	$ 291,907

At NYU Fertility Center

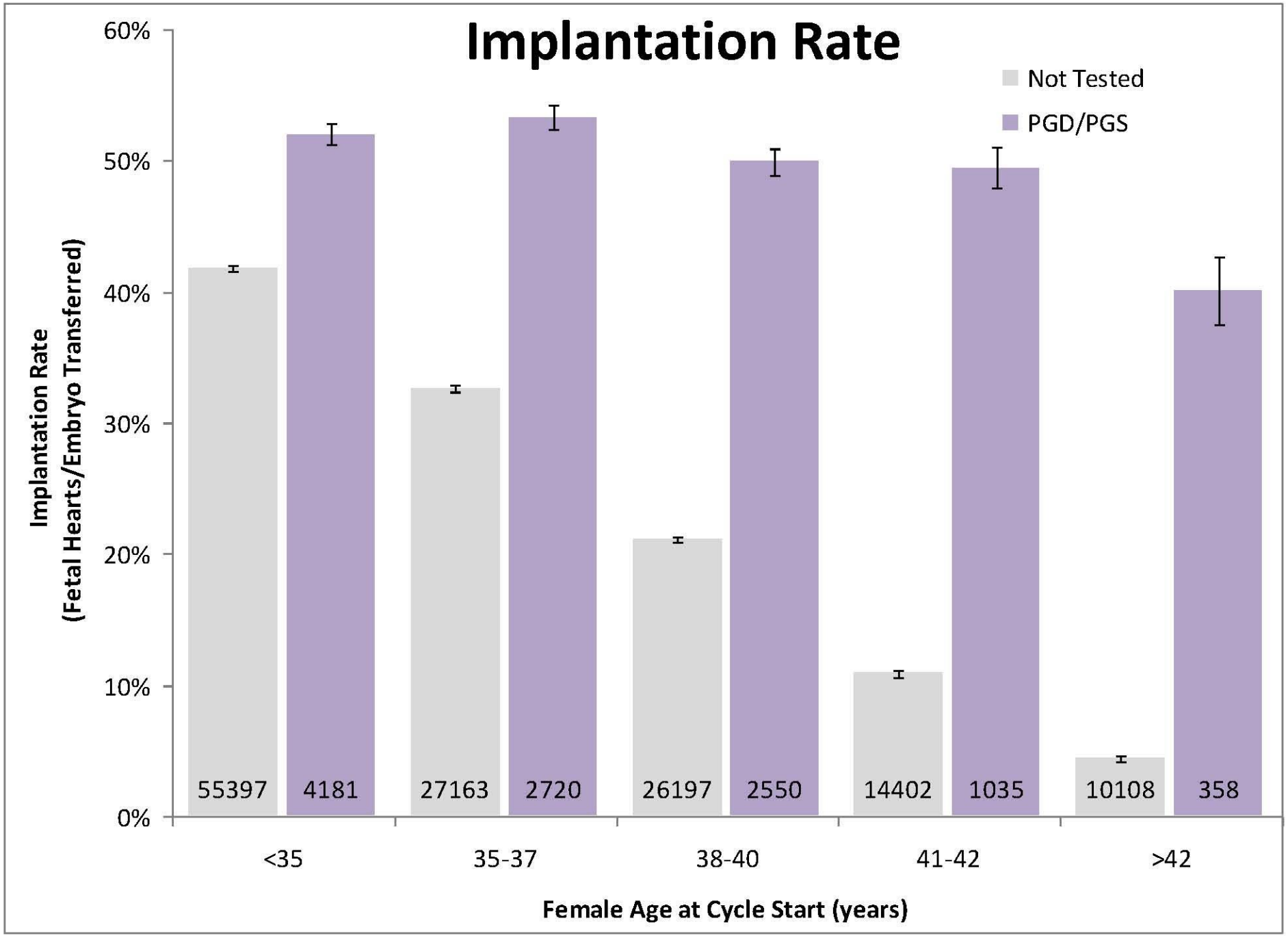
- For patients 42 years and under, the cost for use of aCGH for PGS was less than or equal to No PGS per delivery
- For patients 43 years and older, the cost per delivery was greater using PGS
  - Largely due to the high number of retrievals with no euploid embryos and no transfers
    - Despite the dramatic decrease in miscarriages

What about outside of New York City?

What Determines Cost Effectiveness?

- Cost of Stimulation & Retrieval
- Cost of Genetic Testing
- Cost of Uterine Prep & Frozen Embryo Transfer
- Cost of Prenatal Care
- Cost of Postnatal Care

- Cost of Stimulation & Retrieval
- Cost of Genetic Testing
- Cost of Uterine Preparation & Frozen Embryo Transfer
- Cost of Prenatal Care
- Cost of Postnatal Care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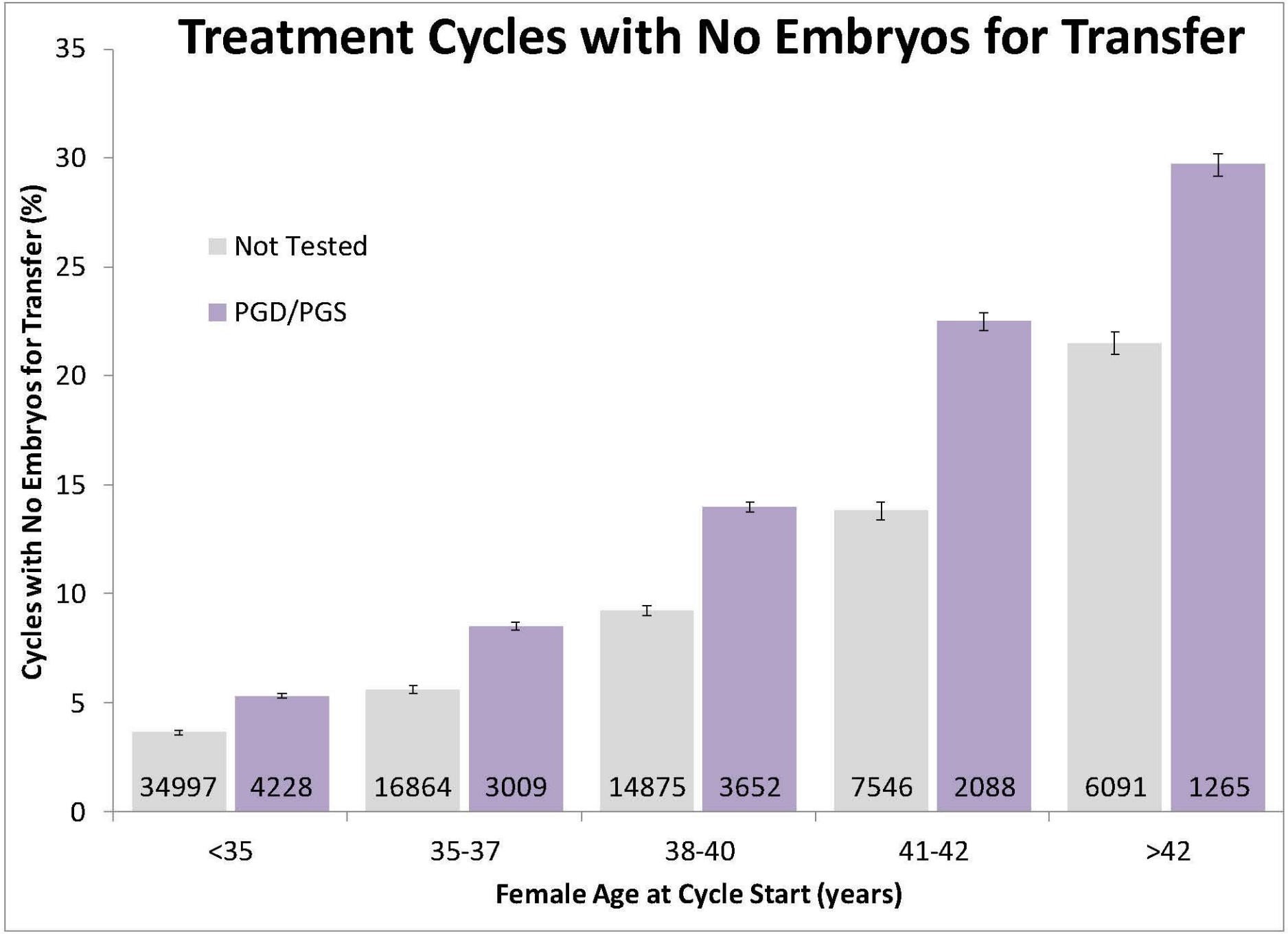
Female Age at Cycle Start (years)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Cycles with No Embryos for Transfer (%)
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25
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5
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2088
6091
1265
<35
35-37
38-40
41-42
>42
Female Age at Cycle Start (years)

For Single Embryo Transfer

Implantation Rate =

Implantations/Transfer of one embryo

#Transfers required for an implantation =

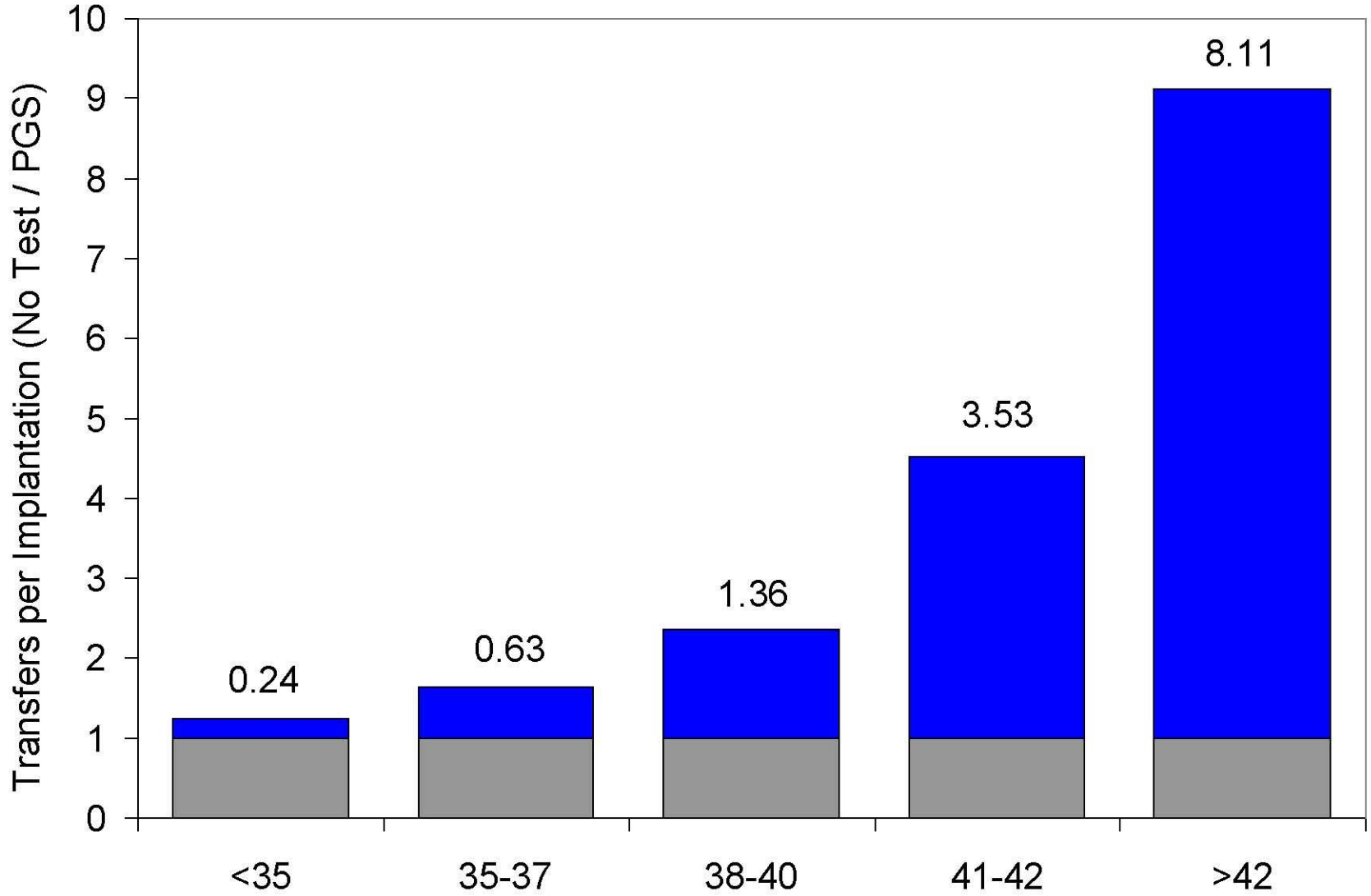
1/Implantation Rate

Additional Transfers needed without PGS =

$\#Transfers_{no\ PGS} - \#Transfers_{PGS}$

$\sim (\#Transfers_{no\ PGS} / \#Transfers_{PGS}) - 1$

Additional FETs for Implantation



For Obtaining a Transferable Embryo

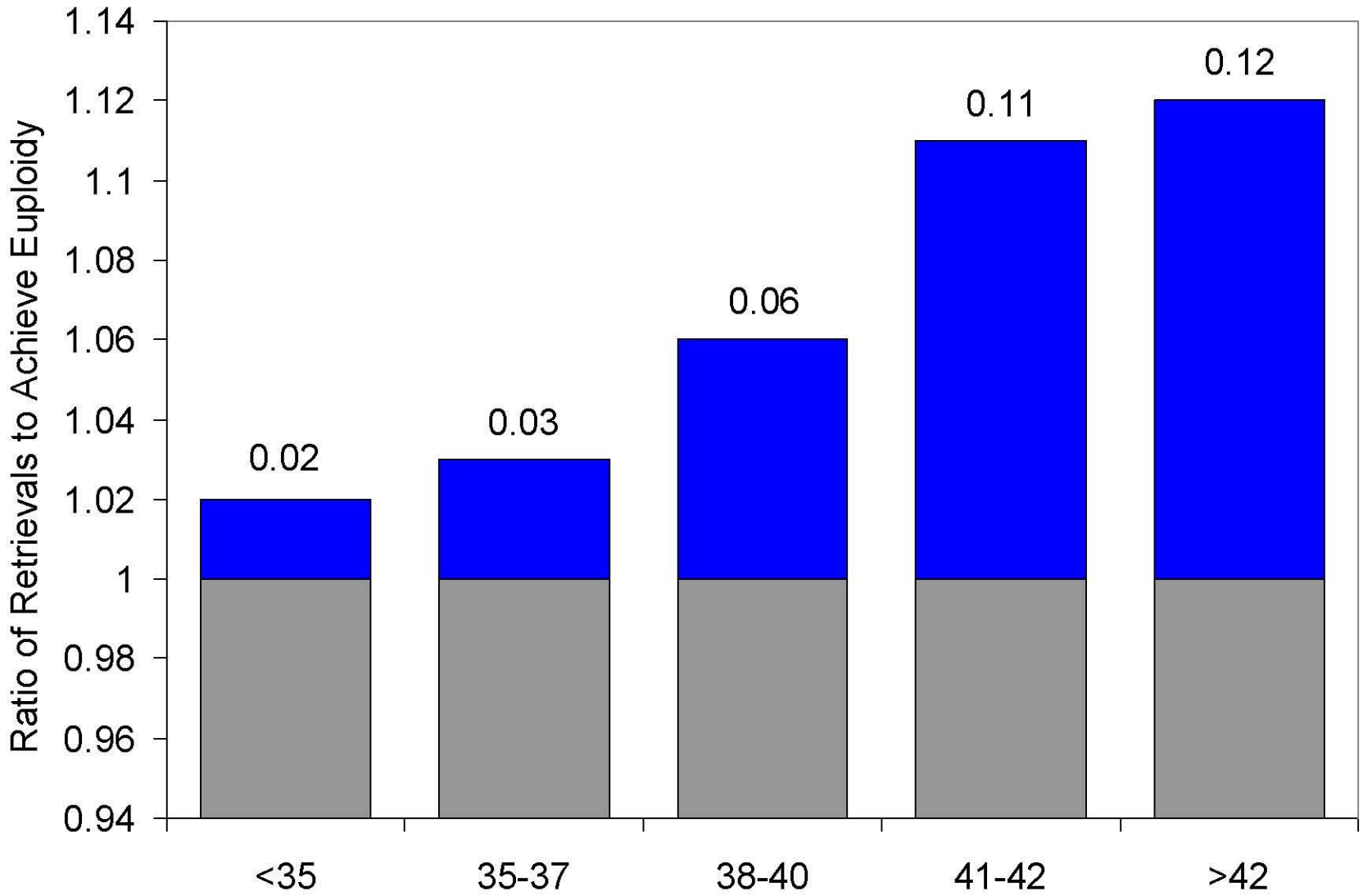
$\%Ret_{ET}$ =

%Retrievals w/ $\geq$ 1 Embryo to Transfer either with PGS (euploid) or w/o PGS

Additional Retrievals with PGS =

$(\%Ret_{ET\text{ - No PGS}} / \%Ret_{ET\text{ - PGS}}) - 1$

Additional Retrievals for an Embryo to Transfer



Marginal Procedure Costs for No PGS

Additional Costs =

Additional FETs X Cost of FET +

Additional Retrievals X Cost of Retrieval

Compare to Costs of PGS (aCGH)

Cost of Procedures vs. PGS

- Procedure Costs vary in different locations around the world
- PGS Costs are quite similar around the world (using Comprehensive Chromosome Screening [aCGH, NGS])

  ~ $3500 per cycle

Do Additional Procedures Cost more than PGS ($3500)?

Female Patient Age (years)	USA[1]	Australia[2]	Sweden[3]	Outside USA[4]
<35	$760	$604	$191	$280
35 - 37	$1781	$1429	$430	$656
38 - 40	$3800	$3051	$913	$1400
41 – 42	$9429	$7601	$2227	$3474
>42	$20401	$16542	$2499	$7516

1. Nachtigal, R, (2006) Fertil. Steril. 85(4):871-875
2. Chambers et al., (2006) Med. J. Aust. 184(4):155-158
3. Kjellberg et al., (2005) Hum. Reprod. 21(1): 210-216
4. Collins (2002) Hum. Reprod. Update 8(3):265-277

Conclusion

- PGS with aCGH is cost effective for patients at NYU Fertility Center if they are 42 years or younger
- Cost effectiveness of PGS varies in different locations since
  - the cost of IVF/FET procedures varies widely
  - the cost of PGS (aCGH) does not vary much
- For PGS to be cost effective for everyone, the cost of PGS biopsy and testing must decrease relative to IVF & FET
  - Or be covered by insurance

Strategies

1. **Every Embryo is sacred (Paulsen, 2016)**

2. **Let's be as efficient as possible (time, #procedures, cost)**

- SART/NASS have made our efficiency the highlight of their comparisons
  - (and we are not supposed to compare)

- Gleicher has called to question the ethics/morality of using selection methods to improve efficiency

- In the end, it should be the patients' decision

Conclusions

- Discuss PGS with all patients
- Decide which approach best fits the patient's needs
  - Can they tolerate more attempts with
    - No pregnancy?
    - Clinical pregnancy loss?
    - Risk of premature delivery/twin pregnancy?
  - Would they prefer to achieve live birth with fewer cycles failed?
  - Acknowledge that PGS is a test that is not perfect
    - Are patients averse to use/disposal of embryos with low chances of success?
  - Is PGS cost effective in your facility?
- Proceed with the patient's desires