What’s New in REI?

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Disclosures

I do not have any disclosures
Outline

• Does Vaping Harm Fertility?

• Does Pre-implantation Genetic Testing Improve Pregnancy Rates?
E-Cigarette Exposure Delays Implantation and Causes Reduced Weight Gain in Female Offspring Exposed In Utero


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Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial

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Outline

• Does Vaping Harm Fertility?

• Does Pre-implantation Genetic Testing Improve Pregnancy Rates?
Does Vaping Harm Fertility?

• What do we know about smoking and fertility?
  
  • 21% of reproductive age women smoke
  
  • Smoking increases risk of: preterm labor, IUGR, abruption, previa, PPROM
Does Vaping Harm Fertility?

• What do we know about smoking and fertility?
  • Smokers are 50% more likely to take >12 months to conceive
  • Dose-dependent adverse effect of smoking on fertility
  • More cigarettes smoked per day -> longer time to conception
  • Smokers require twice as many IVF cycles to conceive
Does Vaping Harm Fertility?

• What do we know about smoking and fertility?

  • Mechanisms:
    - Smoking impairs fallopian tube ciliary function
    - Smoking more rapidly depletes oocyte pool
    - Smoking increases rates of aneuploidy
Does Vaping Harm Fertility?

<table>
<thead>
<tr>
<th>Smoking risk</th>
<th>Knowledge of risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>99</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>99</td>
</tr>
<tr>
<td>Heart disease</td>
<td>96</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>39</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>30</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>27</td>
</tr>
<tr>
<td>Infertility</td>
<td>22</td>
</tr>
<tr>
<td>Early menopause</td>
<td>17</td>
</tr>
</tbody>
</table>
Does Vaping Harm Fertility?

• What do we know about smoking and fertility?

  • Patient education re: risks increases chances of quitting

  • Smoking cessation rates generally are better for infertile women than for pregnant women
Does Vaping Harm Fertility?

E-cigarette use is increasing in popularity

• A “lesser of two evils” vs smoking?

• Use is growing rapidly among young adults
  • Discrete
  • Flavored
  • Can be used in areas that restrict tobacco smoke
  • Susceptible to abuse
Does Vaping Harm Fertility?

• **What is vaping?**
  
  • E-cigarettes entered the market in 2003 (China) and 2006 (EU and USA)
  
  • **Contain electronic nicotine delivery system**
    • Cartridge containing a liquid
    • An atomizer (vaporization chamber with a heating element)
    • A battery Activated by pressing a button and inhaling
  
  • Atomized heats and aerosolizes liquid, creating vapor (not smoke)

https://www.uptodate.com/contents/vaping-and-e-cigarettes?search=vaping&source=search_result&selectedTitle=1~65&usage_type=default&display_rank=1
Does Vaping Harm Fertility?

• What is in an e–cigarette?
  • Nicotine – range from nicotine-free up to 36 mg/mL,
  • Other compounds – tin, lead, nickel, chromium, manganese, and arsenic
  • Flavorings – 7000 flavors are available
    • Candy
    • Fruit
    • Soda
  • Can be abused (“dripping”)

https://www.uptodate.com/contents/vaping-and-e-cigarettes?search=vaping&source=search_result&selectedTitle=1~65&usage_type=default&display_rank=1
Does Vaping Harm Fertility?

• **Who is Vaping?**
  - Vaping increasing among current and former smokers (2014->2016)
    - Increased among current smokers (48 to 52%)
      - Smokers prefer them for their perceive value as quitting agents
    - Increased among former smokers (12 to 16%)
    - Increased among never smokers (3 to 6%)
      - Non-smokers typically try for novelty
Does Vaping Harm Fertility?

• E-cigarette, or vaping, product use associated lung injury (EVALI)

  • Vaping-Induced Lung Injury has recently been recognized

• There have been few studies known about the effects on fertility and pregnancy outcomes
Does Vaping Harm Fertility?

• Who is Vaping?

More High School Students Are Current E-cigarette Users

$ 125 million / year advertising

https://e-cigarettes.surgeongeneral.gov/getthefacts.html

$ 2.5 billion / Year Industry in USA
Does Vaping Harm Fertility?

• Who is Vaping?

True or False?

More than 6 of 10 youth believe that occasional use of e-cigarettes causes only little or some harm.

True!

More than 60 percent of teens believe that occasional use of e-cigarettes causes only little or some harm.
Does Vaping Harm Fertility?

• Do patients consider it safer than smoking?

• Smokers often see vaping as a safe alternative to smoking

• Patients refer to practitioners as a source of e-cigarette guidance

• Few practitioners feel confident advising

• Little evidence-based guidance -> inconsistencies in practitioner advice


Does Vaping Harm Fertility?

E-Cigarette Exposure Delays Implantation and Causes Reduced Weight Gain in Female Offspring Exposed In Utero

Margeaux Wetendorf,1 Lewis T. Randall,2 Mahlet T. Lemma,2 Sophia H. Hurr,1 John B. Pawlak,1 Robert Tarren,1 Claire M. Doerschuk,2 and Kathleen M. Caron1

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Does Vaping Harm Fertility?

• Methods
  
  • Mouse model, exposure to e-cigarette vapor

• Compared:
  
  • Embryo implantation
  • Time to pregnancy
  • Epigenetic modifications in offspring exposed to vaping
  • Adult weight in offspring exposed to vaping
Does Vaping Harm Fertility?

• Methods

• Mouse model, exposure to e-cigarette vapor

• Compared:

  • Embryo implantation
  • Time to pregnancy
  • Epigenetic modifications in offspring exposed to vaping
  • Adult weight in offspring exposed to vaping
Does Vaping Harm Fertility?

**Onset of First Litter**

*p-value=0.002*

![Graph showing onset of first litter](image)

**Figure 2.**

![Images comparing SHAM and ECIG groups](images)
Does Vaping Harm Fertility?
Does Vaping Harm Fertility?

![Graph showing body weight comparison between SHAM Dam, ECIG Dam, SHAM Sire, and ECIG Sire. The p-values for the comparisons are marked: *p-value=0.006 and p-value=0.08.](image)
Does Vaping Harm Fertility?

• In mice, vaping appears to:
  • Reduce # of implanted embryos
  • Delay time to pregnancy
  • Affect health of offspring born to mothers who vape

• More research needed

• Reason to caution patients not to vape when trying to become pregnant
Outline

• Vaping Harms Fertility

• Pre-implantation Genetic Screening Should Not be Widely Used
Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial

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Background Information

- High incidence of chromosome aneuploidy is a major cause of IVF failure and miscarriage
- 2016 SART data: cumulative LBR 54.5% in young patients to 13.4% in women aged 41-42
- 80% aneuploidy in women aged 42 and older
- Transfer of euploid embryo results in similar implantation rates regardless of maternal age
**PGT-A History**

- Morphologic assessment previously standard method of prioritizing embryos to transfer
- Initial PGT-A studies performed on cleavage state (Day 3) embryos using fluorescence in situ hybridization (FISH)
  - Demonstrated an improvement in pregnancy outcomes but without RCT data
- RCTs of day 5 blastocyst biopsies have shown significant improvement in ongoing pregnancy rate PER embryo transfer
Next Generation Sequencing

- Each letter represents a nucleotide that is strung together in a particular order
- Segments of such letters form gene
- NGS is able to identify each specific “letter” from a bulk DNA sample collection, yielding gene information at single-nucleotide resolution as compared to a control reference genome

https://medium.com/@mohammedharris/hybrid-fusion-fish-vs-4ce5fae6b21e
Study Design

• Evaluate next generation sequencing (Trophectoderm biopsy) of blastocyst stage embryos in a frozen embryo cycle

• RCT from 34 clinics/9 laboratories
  • US, UK, Canada, Australia

• Ovarian stimulation/FET protocols per clinic preference
• **Inclusion Criteria:**
  • Women ages 25-40 undergoing IVF with at least 2 embryos to biopsy

• **Exclusion Criteria:**
  • DOR, two prior failed IVF-ETs, >1 miscarriage, azoospermia, severe oligozoospermia

• **Control group:** embryo with most favorable morphologic assessment was transferred, remaining were biopsied for PGT-A

• **PGT-A Group:** embryo selected based on euploid result and most favorable morphologic assessment

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*Study Design Continued*
Materials and Methods

- Pregnancy outcomes per ITT randomization and per transfer were recorded

- *Primary study outcome: ongoing pregnancy at 20 weeks*
**Intention to Treat Analysis**

“Once randomized, always analyze”

- More conservative analysis (compared to per protocol analysis)
- ITT preserves randomization and equalizes prognostic factors in both groups
- **Limitations**: poor treatment adherence may result in lower estimates of treatment efficacy and loss of study power
- **Benefits**: estimates from ITT protocol are more clinically relevant because real world effectiveness is limited by patient/clinician ability to adhere to a treatment
Results

• STAR trial (Single Embryo Transfer of Euploid Embryo)
Enrollment, assignment, treatment, and analysis of patients. PGT-A = preimplantation genetic testing for aneuploidy.

TABLE 1

Characteristics of the intention-to-treat study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PGT-A (n = 330)</th>
<th>Control (n = 331)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>33.7 ± 3.59</td>
<td>33.8 ± 3.58</td>
</tr>
<tr>
<td>Median</td>
<td>34.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Range</td>
<td>25–40</td>
<td>25–40</td>
</tr>
<tr>
<td>&lt;35 y</td>
<td>179 (54.2%)</td>
<td>177 (53.5%)</td>
</tr>
<tr>
<td>35–37 y</td>
<td>95 (28.8%)</td>
<td>96 (28.9%)</td>
</tr>
<tr>
<td>38–40 y</td>
<td>56 (17.0%)</td>
<td>58 (17.5%)</td>
</tr>
<tr>
<td>BMI, a kg/m²</td>
<td>25.24 ± 5.285</td>
<td>25.10 ± 5.204</td>
</tr>
<tr>
<td>Nulliparous, n (%)</td>
<td>219 (66.4%)</td>
<td>211 (63.7%)</td>
</tr>
<tr>
<td>Clinical infertility diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low ovarian reserve</td>
<td>8 (2.4%)</td>
<td>5 (1.5%)</td>
</tr>
<tr>
<td>Ovulatory dysfunction</td>
<td>77 (23.3%)</td>
<td>80 (24.2%)</td>
</tr>
<tr>
<td>Tubal factor</td>
<td>29 (8.8%)</td>
<td>29 (8.8%)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>17 (5.2%)</td>
<td>17 (5.1%)</td>
</tr>
<tr>
<td>Uterine abnormality</td>
<td>7 (2.1%)</td>
<td>11 (3.3%)</td>
</tr>
<tr>
<td>Other female factor</td>
<td>68 (20.6%)</td>
<td>72 (21.8%)</td>
</tr>
<tr>
<td>Combination factor</td>
<td>19 (5.8%)</td>
<td>21 (6.3%)</td>
</tr>
<tr>
<td>Male factor</td>
<td>117 (35.5%)</td>
<td>121 (36.6%)</td>
</tr>
</tbody>
</table>
### TABLE 2

In vitro fertilization laboratory and genetic testing results for the intention-to-treat population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PGT-A (n = 330)</th>
<th>Control (n = 331)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes retrieved, mean ± SD per retrieval</td>
<td>18.6 ± 9.2</td>
<td>18.9 ± 10.0</td>
</tr>
<tr>
<td>Mature oocytes, mean ± SD per retrieval</td>
<td>14.6 ± 7.6</td>
<td>15.0 ± 8.1</td>
</tr>
<tr>
<td>Fertilization method, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional insemination</td>
<td>37 (11.2%)</td>
<td>42 (12.7%)</td>
</tr>
<tr>
<td>Intracytoplasmic sperm injection</td>
<td>293 (88.8%)</td>
<td>288 (87.0%)</td>
</tr>
<tr>
<td>Fertilized oocytes, mean ± SD per retrieval</td>
<td>11.8 ± 6.5</td>
<td>12.1 ± 6.9</td>
</tr>
<tr>
<td>Day 5/6 blastocysts, mean ± SD per retrieval</td>
<td>7.4 ± 4.5</td>
<td>7.4 ± 5.4</td>
</tr>
<tr>
<td>Biopsied embryos, mean ± SD per retrieval</td>
<td>2,178 (6.6 ± 4.1)(^a)</td>
<td>1,758 (5.5 ± 4.1)</td>
</tr>
</tbody>
</table>

Embryo classification by preimplantation genetic screening, n (% of embryos biopsied)

<table>
<thead>
<tr>
<th>Classification</th>
<th>PGT-A (n = 330)</th>
<th>Control (n = 331)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetermined(^b)</td>
<td>61 (2.8)</td>
<td>59 (3.4)</td>
</tr>
<tr>
<td>Normal/Euploid</td>
<td>939 (43.1)</td>
<td>719 (40.9)</td>
</tr>
<tr>
<td>Aneuploid</td>
<td>1,181 (54.2)</td>
<td>987 (56.1)</td>
</tr>
<tr>
<td>Monosomy</td>
<td>196 (9.0)</td>
<td>181 (10.3)</td>
</tr>
<tr>
<td>Trisomy</td>
<td>163 (7.5)</td>
<td>137 (7.8)</td>
</tr>
<tr>
<td>Mosaic(^c)</td>
<td>366 (16.8)</td>
<td>285 (16.2)</td>
</tr>
<tr>
<td>Subsegmental</td>
<td>105 (4.8)</td>
<td>86 (4.9)</td>
</tr>
<tr>
<td>Other(^d)</td>
<td>10 (0.5)</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Complex(^e)</td>
<td>341 (15.7)</td>
<td>287 (16.3)</td>
</tr>
</tbody>
</table>
Ongoing pregnancy rate in ITT population

<table>
<thead>
<tr>
<th>Group</th>
<th>Rate</th>
<th>(Numerator/Denominator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGT-A arm</td>
<td>41.8%</td>
<td>(138/330)</td>
</tr>
<tr>
<td>Control arm</td>
<td>43.5%</td>
<td>(144/331)</td>
</tr>
</tbody>
</table>

P = 0.65
# Outcomes per Embryo Transfer

**TABLE 3**

Outcomes in patients undergoing an embryo transfer with embryo selection by means of preimplantation genetic testing for aneuploidy (PGT-A) versus morphology (Control), n (%).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PGT-A (n = 152)</th>
<th>Control (n = 168)</th>
<th>PGT-A (n = 122)</th>
<th>Control (n = 145)</th>
<th>PGT-A (n = 274)</th>
<th>Control (n = 313)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative $\beta$-hCG</td>
<td>46 (30.3)</td>
<td>53 (31.5)</td>
<td>34 (27.9)</td>
<td>59 (40.7)</td>
<td>80 (29.2)</td>
<td>112 (35.8)</td>
<td>.0934</td>
</tr>
<tr>
<td>Positive $\beta$-hCG</td>
<td>106 (69.7)</td>
<td>115 (68.5)</td>
<td>88 (72.1)</td>
<td>86 (59.3)</td>
<td>194 (70.8)</td>
<td>201 (64.2)</td>
<td>ND</td>
</tr>
<tr>
<td>Biochemical pregnancy</td>
<td>14 (9.2)</td>
<td>10 (6.0)</td>
<td>15 (12.3)</td>
<td>16 (11.0)</td>
<td>29 (10.6)</td>
<td>26 (8.3)</td>
<td>.3315</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>17 (11.2)</td>
<td>14 (8.3)</td>
<td>10 (8.2)</td>
<td>16 (11.0)</td>
<td>27 (9.9)</td>
<td>30 (9.6)</td>
<td>.8979</td>
</tr>
<tr>
<td>Elective termination</td>
<td>0</td>
<td>2 (1.2)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>1 (0.4)</td>
<td>2 (0.6)</td>
<td>6.603</td>
</tr>
<tr>
<td>Ongoing pregnancy at 20 weeks' gestation</td>
<td>75 (49.3)</td>
<td>89 (53.0)</td>
<td>62 (50.8)</td>
<td>54 (37.2)</td>
<td>137 (50.0)</td>
<td>143 (45.7)</td>
<td>.3177</td>
</tr>
</tbody>
</table>

*P value for age subgroups P = .5757, P = .0349*
## ITT analysis of Ongoing Pregnancy Rate by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>PGT-A</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-34 years</td>
<td>42.5%</td>
<td>50.3%</td>
<td>0.17</td>
</tr>
<tr>
<td>35-40 years</td>
<td>41.1%</td>
<td>35.7%</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Conclusion

• No overall improvement in ongoing pregnancy rate in women 25-40 years of age.

• PGT-A for women 35–40 years associated with higher ongoing pregnancy rate per frozen-thawed embryo transfer, but not per patient.
Review: What We Discussed

• Vaping Likely Harms Fertility

• Pre-implantation Genetic Screening Should Not be Widely Used
THANK YOU
QUESTIONS?