The Shanghai Birth Cohort Study: Current status and results

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To study the effects of genetic, environmental and behavioral factors on reproductive health, pregnancy outcomes, child growth, development and risks of diseases.
Eligibility Criteria

Inclusion criteria:
- Women who are 20 years of age or older and married
- Plan to be pregnant or pregnant women in the first trimester (≤ 16 weeks of gestation)
- Registered residents of Shanghai municipality
- Intend to receive prenatal care and give birth in the participating hospital
- Not plan to move out of the catchment area of any one of the participating hospitals in the next 2 years

Exclusion criteria:
- Women who have tried to conceive spontaneously for more than 12 months
Visit Schedule

• Women and husband
  – Women: Preconception, 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} trimester, birth
  – or 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd} trimester, birth
  – Husband: during pregnancy

• Children
  – Newborn and 42 days postpartum
  – Hospital visit at 6\textsuperscript{th}, 12\textsuperscript{th} and 24\textsuperscript{th} months
Contents – 1. Questionnaire

- Questionnaire
  - Socio-economic status
  - Social support
  - Health behavior: physical activity, sleeping, smoking, alcohol, tea, drugs
  - Reproductive history
  - Medical history
  - Medication and supplements
  - Family history

- Environment, occupation
- Psychology: stress, anxiety and depression
- Diet and nutrition
- Infant feeding and habit
- Family and community environment
- Child developmental tests
- Child ASQ, M-CHAT
- Child psychological behavior
- Child diseases
Contents – 2. Biological Specimens

– Women’s blood, urine, hair and nail
– Partners’ blood, urine, buccal swab
– Cord blood
– Placental tissue
– Child blood spots
– Child urine and blood
Contents – 3. Medical record review

- **Record review**
  - Preconceptional care
  - Prenatal history and complications
  - Labor & delivery record
  - Newborn (NICU) record
  - 42-day infant physical exam
  - Well-baby physical exams

- **Disease confirmation**
  - Child illness journal by mother
  - Standard questionnaire
  - Electronic medical record
  - Hospital chart review
  - Expert review
  - Confirmation diagnosis
Coverage Area

Phase I:
5,000 couples,
3,500 children,
oldest 2 years
Environmental Triclosan Exposure and Female Reproductive Health

Wenting Zhu, Jun Zhang
Background

- Triclosan (2,4,4-trichloro-2-hydroxy-diphenyl ether, TCS), a broad spectrum antimicrobial agent.

- It is widely used in personal care, household as well as health care products, including toothpastes, antibacterial soaps, shampoos, deodorants, cosmetics, kitchen utensils, toys, bedding and clothes.
Background

- TCS is absorbed mainly through the digestive tract and skin.

- Detected in various human body fluids and tissues
  
  **Blood**: 0.01–38 ng/ml
  
  **Breast milk**: 20–300 ng/g
  
  **Urine**: 2.4–3,790 μg/L
Background

Triclosan

Estradiol

Diethylstilbestrol

BPA

Thyroxine
Background


Estrogen sulfotransferase (EST)
E2
E2-S

Study design

1. To examine the effect of TCS on menstrual irregularity and female fecundity
   • A prospective cohort study

2. To assess the association between TCS and female reproductive disorders in infertile couples
   • A multicenter case-control study
1 The effect of TCS on menstrual irregularity and fecundity

- Shanghai Birth Cohort Study: the preconceptional cohort

**Inclusion criteria**
- Married couple, age ≥ 20y;
- Plan to be pregnant;
- Registered resident of Shanghai;
- No plan to move out of Shanghai in the next 2 years;
- Plan to give birth in collaborating hospitals

**Exclusion criteria**
- Have tried to conceive for > 12 months
The preconceptional cohort

- Recruited through 2 preconceptional care clinics;
- Standardized questionnaire: demographic characteristics, living and working environment, health-related behaviors, menstrual history, medical history;
- Biological samples: blood and urine samples from men and women;
- Women were followed via telephone every 2 months for up to 12 months. Information on pregnancy, miscarriage, etc. was collected.
1 The effect of TCS on menstrual irregularity and fecundity

Criteria of menstrual irregularity

- Cycle Length: 21-35 days;
- Length of menstruation: 3-7 days;
- Menstrual bleeding: minimal, normal and heavy (self-report);
- **Menstrual regularity**: menstrual cycle length, length of menstruation and menstrual bleeding volume are within the normal range;
- **Menstrual irregularity**: any of the above criterion is beyond the normal range;
The effect of TCS on menstrual irregularity and fecundity

Inclusion and exclusion of volunteers (TCS and menstrual irregularity)

1. Volunteers recruited N=1183
2. Volunteers with TCS levels in urine N=716
3. No urine N=57
   Low urine volume < 24 ml N=410
4. No menstrual information N=6
5. Volunteers in the final analysis N=710
# TCS measurements

<table>
<thead>
<tr>
<th></th>
<th>Detection rate</th>
<th>LOD</th>
<th>10th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
<th>95th</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCS (ng·mL⁻¹)</td>
<td>98.3</td>
<td>0.1</td>
<td>0.41</td>
<td>0.86</td>
<td>2.13</td>
<td>7.29</td>
<td>30.74</td>
<td>53.16</td>
<td>122.19</td>
</tr>
<tr>
<td>TCS_Cre (ng·mg⁻¹)</td>
<td>98.3</td>
<td></td>
<td>0.57</td>
<td>1.16</td>
<td>2.67</td>
<td>8.75</td>
<td>34.58</td>
<td>66.04</td>
<td>293.42</td>
</tr>
</tbody>
</table>

The values less than LOD were imputed as \((\text{LOD} \times 2)^{0.5}\)
Inclusion and exclusion of volunteers (TCS and fecundity)

Volunteers recruited N=1183

Follow-up N=1138
(follow-up rate=96.2%)

With TCS concentration N=706

contraception use or
TTP<12m N=117

With outcomes (pregnancy,
infertility or miscarriage) N=554

No urine or low volume N=432

ART N=2
Drugs assisted conception N=29
Age>40y N=4

No inclusion or exclusion.
Pre-pregnancy TCS exposure and pregnancy rate

% of women still not pregnant

Duration of trying to conceive

> 0.66 ng/g cre
≤ 0.66 ng/g cre
TCS and female reproductive health

• TCS exposure may increase the risk of menstrual irregularity;

• Pre-pregnancy TCS exposure may increase the risk of infertility;
To assess the association between TCS and female reproductive disorders in infertile couples

• A multicenter case-control study
Multicenter case-control study on environmental endocrine disruptors and female reproductive disorders

Cases:
• Polycystic ovarian syndrome (PCOS) \( N = 276 \)
• Endometriosis \( N = 138 \)
• Endometrial polyps or uterine fibroids \( N = 72 \)
• Repeated failure of artificial insemination by donor (AID) \( N = 72 \)
• Premature ovarian failure (POF) \( N = 47 \)

Controls:
• Male factors \( N = 305 \)
• Tubal obstruction/intrauterine adhesion \( N = 220 \)
  – Regular menstruation \( N = 316 \)
Multicenter case-control study on environmental endocrine disruptors and female reproductive disorders

- Fertility Centers: Shandong, Zhejiang, Shanghai
- Standardized questionnaire: demographic characteristics, living and working environment, health-related behaviors, menstrual history, medical history;
- Medical records abstraction: diagnosis and all test results;
- Biosamples of the women: blood and urine;
### TCS and endometriosis, endometrial polyps/uterine fibroids

<table>
<thead>
<tr>
<th>Sample size</th>
<th>TCS-Crea</th>
<th>Unadjusted-OR (95% CI)</th>
<th>P value</th>
<th>Adjusted-ORb (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>316</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>100</td>
<td>0.80 (0.63, 1.02)</td>
<td>0.661</td>
<td>1.42 (1.04, 1.96)</td>
<td>0.029</td>
</tr>
<tr>
<td>Polyps/fibroids</td>
<td>72</td>
<td>0.94 (0.72, 1.23)</td>
<td>0.662</td>
<td>1.45 (1.04, 2.02)</td>
<td>0.030</td>
</tr>
<tr>
<td>EM + EP/fib</td>
<td>38</td>
<td>1.08 (0.77, 1.51)</td>
<td>0.637</td>
<td>1.99 (1.31, 3.04)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*aLn/SD; bAdjusted for age, BMI, education, income, center and batch;*

<table>
<thead>
<tr>
<th>Center, n (%)</th>
<th>Control N=316</th>
<th>EM N=100</th>
<th>EP/UF N=72</th>
<th>EM + EP/UF N=38</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhejiang</td>
<td>62 (19.6)</td>
<td>87 (87.0)</td>
<td>60 (83.3)</td>
<td>38 (100.0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Shanghai</td>
<td>81 (25.6)</td>
<td>8 (8.0)</td>
<td>4 (5.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Shandong</td>
<td>173 (54.8)</td>
<td>5 (5.0)</td>
<td>8 (11.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample size</td>
<td>Unadjusted-OR (95% CI)</td>
<td>P value</td>
<td>Adjusted-OR (95% CI)</td>
<td>P value</td>
</tr>
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<td>------------------</td>
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</tr>
<tr>
<td>Control</td>
<td>62</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>86</td>
<td>1.17 (0.82, 1.66)</td>
<td>0.389</td>
<td>1.31 (0.88, 1.93)</td>
<td>0.189</td>
</tr>
<tr>
<td>Polyps/fibroids</td>
<td>59</td>
<td>1.24 (0.85, 1.82)</td>
<td>0.263</td>
<td>1.28 (0.84, 1.94)</td>
<td>0.253</td>
</tr>
<tr>
<td>EM + EP/fib</td>
<td>38</td>
<td>1.73 (1.15, 2.62)</td>
<td>0.009</td>
<td>1.86 (1.19, 2.92)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

aLn/SD; bAdjusted for age, BMI, education, income, center and batch; c Sensitive Analysis (SA): only included Zhejiang center;
TCS and PCOS, POF, Repeated AID failure

<table>
<thead>
<tr>
<th>Sample size</th>
<th>PCOS(^b)</th>
<th>276</th>
<th>1.10 (0.93, 1.29)</th>
<th>0.279</th>
<th>1.06 (0.87, 1.29)</th>
<th>0.582</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted-OR (95% CI)</td>
<td>P value</td>
<td>Adjusted-OR(^b) (95% CI)</td>
<td>P value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POF(^c)</td>
<td>47</td>
<td>1.12 (0.82, 1.52)</td>
<td>0.480</td>
<td>1.21 (0.88, 1.67)</td>
<td>0.247</td>
<td></td>
</tr>
<tr>
<td>Repeated AID failure(^d)</td>
<td>70</td>
<td>0.71 (0.38, 1.35)</td>
<td>0.294</td>
<td>0.82 (0.43, 1.58)</td>
<td>0.548</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Ln/SD;
\(^b\)Adjusted for BMI, income, center and batch;
\(^c\)Adjusted for age, education, sleep and center;
\(^d\)Adjusted for BMI;
In women seeking fertility treatment

• TCS exposure may increase the risks of endometriosis, endometrial polyps/uterine fibroids;
• No association was found between TCS exposure and polycystic ovarian syndrome, premature ovarian failure, or repeated failure of artificial insemination by donor.
Acknowledgment

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