Social Origins of Adverse Reproductive Health Outcomes: Human Fertility

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Objectives

• What are the data supporting or refuting disparities in diagnosis and in outcomes following fertility treatments?
• What is (are) the potential reason (s) for these differences?
• What are the controversies surrounding such disparities?
What is a Health Disparity?

*Differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States*  

*National Institutes of Health*
Differences in Racially Diverse Populations

- true biologic differences because of genetic background
- variations in environmental exposures, lifestyle factors, cultural factors
- access to care, and specifics of treatments once care has been accessed
- cost

Discussion

• White vs. Black
• (Hispanic and Asian)

➢ race and ethnicity
➢ self reporting
Disparities in Infertility Prevalence

• National Survey of Family Growth (1982-2002)
  • 1.7 fold higher odds of infertility in non-Hispanic Blacks*
    – “Rise” in prevalence in non-Hispanic Blacks
      – 7.8% (Blacks) vs 11.6% (Whites) in 1982
      – 11.6% (Blacks) vs 7.1% (Whites) in 2002
  • 1.3 fold higher odds of infertility in Hispanics*
    – Stable prevalence
  • Increased odds of infertility with diminished educational attainment

*Adjusted for education, income and self-reported history of PID

Disparities in Infertility Prevalence

- Cross Sectional Study of Coronary Artery Risk Development in Young Adults (CARDIA)
  - Correlates of PCOS with development of coronary artery calcium
  - Women were 33-44 years old (n=764) from 4 US communities
  - Two fold higher adjusted odds of ever infertility in African Americans regardless of marital status*
  - African Americans were more likely to have fibroids but the increased odds of ever-infertility was similar in black and white women with fibroids

- Can we adequately address disparities in infertility with treatments, especially highly effective ones?

*adjusted for SES, correlates of pregnancy intent, age, smoking, fibroids, ovarian volume and testosterone
## ART Costs and Infertility Insurance Mandates

<table>
<thead>
<tr>
<th>Costs of ART cycles</th>
<th>States with Infertility Coverage Mandate</th>
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</thead>
<tbody>
<tr>
<td>• &gt;$12,000 per completed cycle</td>
<td>• Arkansas</td>
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<tr>
<td>• Up to $85,000 for cumulative cost of failed cycles and medications</td>
<td>• Illinois</td>
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<tr>
<td>• $41,132 per live birth</td>
<td>• Montana</td>
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<td></td>
<td>• Rhode Island</td>
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<td>• Massachusetts</td>
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<td>• Ohio</td>
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</tbody>
</table>

*Ryan et al. Fertil Steril 2008;89:66–73*


*Neumann PJ et al. NEJM 1994;331:239-43*
Different Degrees of Coverage Summary

- **IVF Coverage (Comprehensive)**
  - Massachusetts, Rhode Island, Connecticut, Illinois, New Jersey, Maryland
  - Multiple cycles of IVF coverage
    - Sometimes preceded by multiple IUI cycles
    - Some restrictions for initiating IVF based on patient age and FSH level may exist
    - Donor Egg coverage in some situations

- **IVF Coverage (Limited)**
  - Arkansas, Hawaii

- **Mandate to Offer**
  - Texas
  - New York
  - Louisiana
  - California
  - New York
  - Ohio
  - West Virginia
Insurance Mandates for IVF Improve Access to Care

• Mandates increase utilization of ART services
  – Jain et al., 2002
    • Complete IVF coverage (3 states)
      – 3.35 fresh transfers/1000 reproductive age women
      – 0.43 frozen transfers/1000 women
    • Partial/Limited IVF coverage (5 states)
      – 1.46 fresh transfers/1000 women
      – 0.3 frozen transfers/1000 women
    • No IVF coverage (37 states + Washington DC and Puerto Rico)
      – 1.21 fresh transfers/1000 women
      – 0.2 frozen transfers/1000 women

Jain et al. NEJM 2002; 347:661-6
“Since infertility is more common in AAs, Latinas and low SES women, they should be appropriately (proportionately?) represented in infertility subspecialty clinics in MANDATED STATES”
Access to Infertility Treatments – Disparities?

– Bitler and co-workers
  • National Survey of Family Growth (NSFG) data
  • Black women were 29% less likely to report ever having had infertility treatment
  • Hispanic women were 19% less likely to report infertility treatment
  • In general state-level characteristics did not affect access to infertility treatments
    – Women in states with higher median income were significantly more likely to report having seen a doctor for treatment
• The mandates significantly increased access for educated White women over age 30

Access to Infertility Treatments – Disparities?

– Jain et al., 2006

• Cross sectional survey of 1500 consecutive women presenting for care in a mandated state with comprehensive IVF coverage

• African Americans tended to experience a longer duration of infertility before getting to subspecialist (4.3 vs 3.3 years)

• Majority of women who accessed care were highly educated, wealthy and non-Hispanic White

– No evidence that racial, ethnic or SES disparities are ameliorated by health insurance mandates
ART Outcome Disparities – Individual Clinic Data

• Sharara et al., 2000
  – Mandated State (Maryland)
    • 28% of treated patients were Black
  – University practice
  – 158 Fresh non-donor cycles – multiple cycles per woman
  – Exclusion Criteria
    • Hydrosalpinges
    • Intracavitary fibroids
    • FSH of 11 IU/L or greater

ART Disparities – Individual Clinic Data

Demographics/Predictors

- No differences in age, D3 FSH, cancellation rates
- Black women were more likely to need more aggressive stimulation protocols
- Black women had higher mean BMI
- Black women had 1.3 more years of infertility prior to treatment

Outcomes

- No differences in embryologic outcomes (oocytes retrieved, embryos transferred)
- Black women experienced worse treatment outcomes in univariate analysis
  - Implantation rate 9.8% vs 23.4% (p=0.0005)
  - Clinical pregnancy 19.2% vs 42.2% (p=0.009)
  - Ongoing pregnancy (beyond 20 weeks) 14.9% vs 38.8% (p=0.005)

## Summary of Literature – Individual Clinic Data

<table>
<thead>
<tr>
<th></th>
<th>Disparity</th>
<th>Cycles</th>
<th>Account for SES</th>
<th>Account for Anatomic Factors</th>
<th>Multiple Cycles Per Woman</th>
<th>Account for BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharara et al.</td>
<td>+</td>
<td>158</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>--</td>
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<tr>
<td>Feinberg et al.</td>
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<td>1457</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Dayal et al.</td>
<td>--</td>
<td>251</td>
<td>+</td>
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<tr>
<td>Purcell et al.</td>
<td>+</td>
<td>567</td>
<td>--</td>
<td>+</td>
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</tbody>
</table>

*Dayal M et al. Fertil Steril 2009;91:2414–8*
*Feinberg E et al. Fertil Steril 2006;85:888–94*
Society of Assisted Reproductive Technologies/CDC
National Registry of ART Cycles

• Mandated by Fertility Clinic Success Rate and Certification Act of 1992
• Contains data collected primarily by SART maintained by CDC
  – Clinics submit information about ART treatment cycles and outcomes
  – Greater than 90% clinic compliance
Reporting on Race and Ethnicity

- Reporting on race and ethnicity to SART became mandatory in 2005
  - Clinics submit data to SART according to a standardized protocol that includes prompts for ethnicity (Hispanic or not) and race (White, Asian, Black or other)
  - Limited guidance on reporting
  - Reporting biases that vary by clinic and patient
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Cycles</th>
<th>Racial/Ethnic Breakdown</th>
<th>Adjusted Live Birth Estimates (OR and 95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purcell et al. (2007)</td>
<td>27,272 first fresh non donor cycles (1999-2000)</td>
<td>Asians 5.2% (1429) Whites 94.8% (25,843)</td>
<td>$1^{st}$ Cycle: 0.76 (0.66-0.88)</td>
</tr>
</tbody>
</table>
| Seifer et al. (2008)   | 80,390 non donor cycles (1999-2000) | Blacks 4.6% (3,666) Whites 85.4% (68,607) | • $1^{st}$ Fresh Cycle: 1.24 (1.12-1.36)  
• Repeat Fresh Cycles: 1.38 (1.20-1.57) |
| Seifer et al. (2010)   | 158,693 non donor cycles (2004-2006) | Black 7.7% (12,287) White 92.3% (146,406) | $1^{st}$ Fresh Cycle: 1.31 (1.26-1.37)  
 Repeat Fresh Cycles: 1.33 (1.24-1.42)  
 Cryo Cycles 1.10 (1.0-1.21) |
| Fujimoto et al. (2010) | 139,027 fresh non donor cycles (2004-2006) | Blacks 6.5% (8903) Asians 9.8% (13,671) Hispanics 6.5% (8969) Whites 77.2% (107,484) | Blacks 0.62 (0.56-0.68)  
 Asians 0.9 (0.82-0.97)  
 Hispanics 0.87 (0.79-0.96) |
ART Outcomes

• Seifer 2008:
  – Black women had a longer duration of infertility before initiating ART (40 months versus 34 months for first cycle of ART, p<0.001)
  – Lower clinical pregnancy rates per cycle in Black women*
    • No prior ART: 27.7% vs 33.6%
    • Prior ART: 22.1% vs 28.9%
  – Higher miscarriage rates*
    • No Prior ART: 20.45 vs 13.2%
    • Prior ART: 22.1% vs 28.9%

* p values <0.001

### Secular Trends in ART Outcomes for Black Women

<table>
<thead>
<tr>
<th></th>
<th>Proportion Older than 35 at First Cycle</th>
<th>Proportion with DOR at First Cycle</th>
<th>Live Birth Rate per Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seifer 2008</strong></td>
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<tr>
<td>(Cycles 1999-2000)</td>
<td>49.9%</td>
<td>7.5%</td>
<td>1st Fresh Cycle: 20.7%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Repeat Fresh Cycles: 15.7%</td>
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<tr>
<td><strong>Seifer 2010</strong></td>
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</tr>
<tr>
<td>(Cycles 2004-2006)</td>
<td>57.9%*</td>
<td>14.4%*</td>
<td>1st Fresh Cycle: 22.2%**</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Repeat Fresh Cycles: 17.5%***</td>
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</tbody>
</table>

*\( p < 0.001 \) for comparison of proportions across time
**\( p = 0.19 \) for comparison of proportions across time
***\( p = 0.16 \) for comparison of proportions across time

## Perinatal Morbidity Disparities

<table>
<thead>
<tr>
<th></th>
<th>Singleton Pregnancies**</th>
<th>Twin Pregnancies**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Early Preterm Birth</strong></td>
<td></td>
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<tr>
<td>(&lt;29 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Asian</td>
<td>0.77</td>
<td>0.48-1.25</td>
</tr>
<tr>
<td>Black</td>
<td>4.25</td>
<td>3.14-5.76</td>
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<tr>
<td>Hispanic</td>
<td>1.38</td>
<td>0.91-2.09</td>
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<tr>
<td><strong>Early Preterm Birth</strong></td>
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<tr>
<td>(&lt;32 weeks)</td>
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<td></td>
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<tr>
<td>White</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Asian</td>
<td>1.01</td>
<td>0.78-1.31</td>
</tr>
<tr>
<td>Black</td>
<td>2.72</td>
<td>2.19-3.38</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.19</td>
<td>0.91-1.56</td>
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<tr>
<td><strong>Preterm Birth</strong></td>
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<tr>
<td>(&lt;37 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Asian</td>
<td>0.95</td>
<td>0.85-1.06</td>
</tr>
<tr>
<td>Black</td>
<td>1.79</td>
<td>1.59-2.03</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.22</td>
<td>1.08-1.37</td>
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<tr>
<td><strong>Term Birth</strong></td>
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<tr>
<td>(≥ 37 weeks)</td>
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<tr>
<td>White</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Asian</td>
<td>1.06</td>
<td>0.94-1.18</td>
</tr>
<tr>
<td>Black</td>
<td>0.56</td>
<td>0.49-0.63</td>
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<tr>
<td>Hispanic</td>
<td>0.82</td>
<td>0.73-0.93</td>
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<tr>
<td><strong>Birth Weight</strong></td>
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<tr>
<td>Z-Score &lt; -1</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Asian</td>
<td>1.78</td>
<td>1.58-2.01</td>
</tr>
<tr>
<td>Black</td>
<td>1.81</td>
<td>1.56-2.11</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.36</td>
<td>1.17-1.58</td>
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<tr>
<td>Z-Score &lt; -2</td>
<td>1.00</td>
<td>Reference</td>
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<tr>
<td>Asian</td>
<td>2.05</td>
<td>1.50-2.80</td>
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<tr>
<td>Black</td>
<td>2.17</td>
<td>1.47-3.19</td>
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<tr>
<td>Hispanic</td>
<td>1.64</td>
<td>1.11-2.42</td>
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</tbody>
</table>

*Models adjusted for maternal age; number of embryos transferred; and diagnoses of male factor, endometriosis, polycystic ovarian syndrome, diminished ovarian reserve, tubal factors, uterine factors, and other factors.

**Pregnancy outcomes limited to gestations ≥ 154 days (22 weeks) and birth weights > 300 grams.

Fujimoto et.al., 2010

- **Singletons**
  - moderate and severe growth restriction increased for all minority children
  - preterm birth increased among Black and Hispanic

- **Twins**
  - odds of moderate growth restriction increased in Asian and Black infants
  - odds of severe growth restriction increased among Black infants
  - odds of preterm birth increased for Blacks but decreased for Asians
Donor Egg Disparities

• Bodri et al., 2010
  – Multiethnic matched cohort study of ongoing pregnancy rates among Black and Asian donor oocyte recipients compared with White controls (self reported)
    • All donors were 18-35
    • Donor matching was performed with the phenotypically closest recipient
    • 1st fresh oocyte donation cycle
    • Black (n=280) and Asian (n=43) recipients were age-matched to White recipients
    • Submucous myomas were resected and patients were counseled to have hydrosalpinges removed

## Donor Egg Disparities

### Demographics
- Asian and White recipients were demographically comparable except for lower BMI in Asian recipients.
- Black recipients were more likely to have tubal factor, fibroids present, higher BMI, previous pregnancy and live birth, and younger donors with higher parity.

### Outcomes
- Adjusted OR (95% CI) for ongoing pregnancy:
  - Black recipients 0.62 (0.43-0.89), p=0.009
  - Asian recipients 1.0 (0.49-2.04), p=1.0
- Cycle data Blacks and Asians:
  - Favorable number of mature oocytes retrieved
  - Favorable fertilization rate

Adjusted for tubal factor, donor previous LB, duration of endometrial preparation, # of embryos transferred, day of ET
Conclusions (ART)

• Variety of studies with some conflicting results about ART disparities
  – Data from registries supports a disparity while some single clinic data does not
  – Disparity in donor egg IVF
  – Important to look at single cycles
  – ART does not improve perinatal morbidity

• Access to treatments is suboptimal in certain populations despite insurance coverage
Summary

- Race and ethnicity are important correlates of infertility risk and access to infertility treatments.
- Studies utilizing large data sets largely support a disparity in ART outcomes for non-White and Hispanic women.
- Aim of disparities research is to isolate basic determinants and formulate strategies to improve outcomes for women at risk.
Going Forward

• How can some of these disparities be addressed?
  – More research is needed to unravel the elements of access disparities
  – Patient and provider education that disparities exist
  – Reproductive clinical research that is broadly inclusive of study participants
  – Basic research (biologic underpinnings)
What is Race and Ethnicity?

- US Census and Office of Management and Budget
  - Self identification data
  - Residents choose the race or races with which they most closely identify
    - Social political construct
    - Not scientific or anthropological
    - Not primarily biological or genetic in reference
  - Residents identify ethnicity separately as Hispanic/Latino or not
Census Racial Categories

• **White** -- A person having origins in any of the original peoples of Europe, the Middle East or North Africa. It includes people who indicate their race as "White" or report entries such as Irish, German, Italian, Lebanese, Near Easterner, Arab, or Polish.

• **Black or African American** -- A person having origins in any of the Black racial groups of Africa. It includes people who indicate their race as 'Black, African Am., or Negro,' or provide written entries such as African American, Afro American, Kenyan, Nigerian, or Haitian.

• **American Indian and Alaska Native** -- A person having origins in any of the original peoples of North and South America (including Central America) and who maintain tribal affiliation or community attachment.

• **Asian** -- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example Bangladesh, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. It includes "Asian Indian," "Chinese," "Filipino," "Korean," "Japanese," "Vietnamese," and "Other Asian.

• **Native Hawaiian and Other Pacific Islander** -- A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. It includes people who indicate their race as "Native Hawaiian," "Guamanian or Chamorro," "Samoan," and "Other Pacific Islander."
Controversies in Disparities Research

• Aiming to capture
  – Genetic differences
  – Cultural differences/behaviors
  – Environmental exposure differences
  – Some combination

• Risks of identifying health disparities