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Opportunities and challenges for subfecundity research in ECHO

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No conflicts to declare

Background

July 25, 1978--the dawn of a brave new world in reproductive health!

FINAL

DAILY NEWS

News, news
and news
this afternoon
Details page 111.

Vol. 88, No. 38

New York, Thursday, July 27, 1978

Price: 20 cents

Test Tube Baby

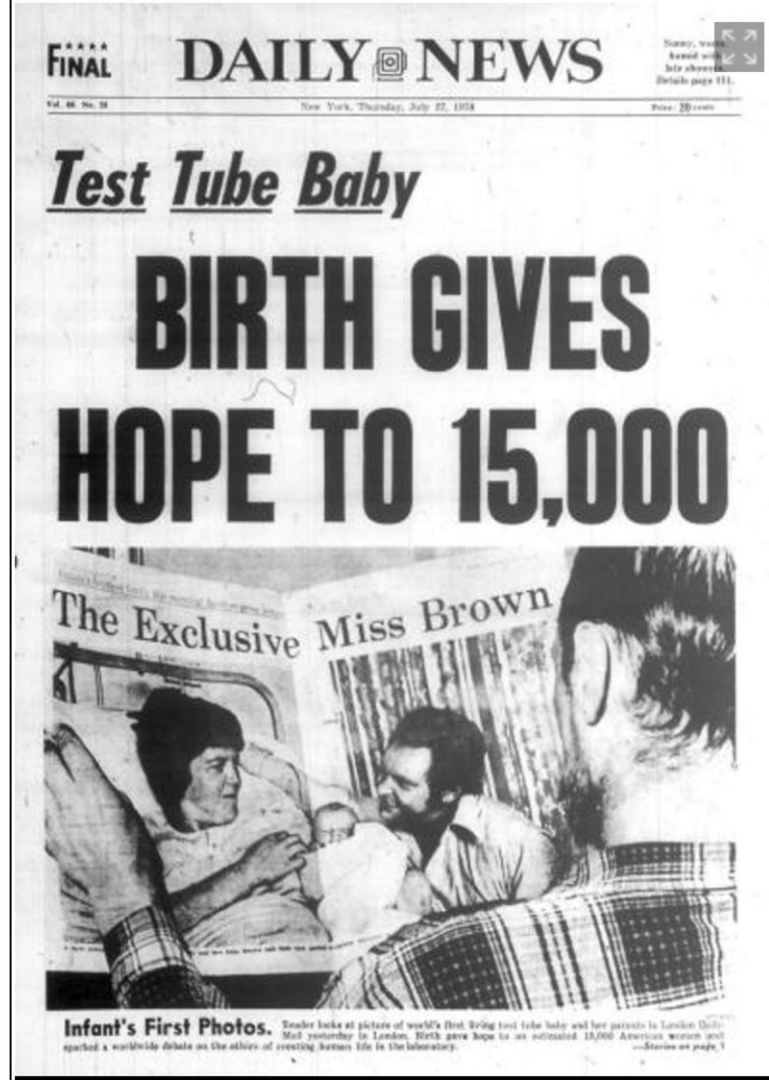
BIRTH GIVES HOPE TO 15,000



Infant's First Photos. Tender looks at picture of world's first living test tube baby and her parents in London Daily Mail newspaper in London. Birth gave hope to an estimated 15,000 American women and sparked a worldwide debate on the ethics of creating human life in the laboratory. —Photos on page 1

July 25, 1978--the dawn of a brave new world in reproductive health!

- Louise Brown delivered by Patrick Steptoe who, in collaboration with Robert Edwards, pioneered *in vitro* fertilization (IVF)
- December 28, 1981: first IVF baby, Elizabeth Carr, born in the United States; IVF conducted by Howard and Georgeanna Jones
- Prior treatment for infertility limited to ovarian stimulation, introduced in the early 1960s



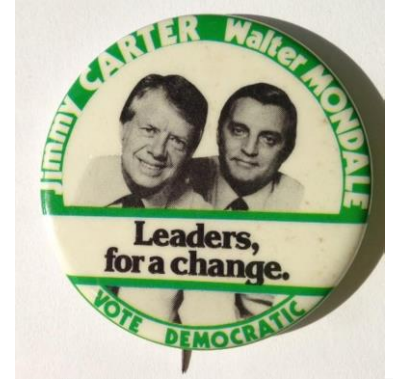
What was the government's response?

- 1978: Ethics Advisory Board of the Department of Health, Education, and Welfare established to provide guidance on federal oversight and regulation of IVF; report issued in May 1979 concluded that research on IVF was ethical within certain parameters but would have to receive prior approval by the Ethics Advisory Board



What was the government's response?

- 1978: Ethics Advisory Board of the Department of Health, Education, and Welfare established to provide guidance on federal oversight and regulation of IVF; report issued in May 1979 concluded that research on IVF was ethical within certain parameters but would have to receive prior approval by the Ethics Advisory Board
- With the election of Ronald Reagan, the Ethics Advisory Board was dissolved
 - New Ethics Advisory Board never convened
 - Medical doctors were not eager for interference in clinical practice
 - To date the federal government has never funded IVF research



IVF is virtually unregulated in the United States

- IVF never required FDA approval because it involved no new drugs or medical devices, therefore no safety trials were ever conducted
- The only existing regulation in the entire assisted reproduction space is mandatory testing of donors for communicable diseases
 - No genetic testing is required
 - No systematic follow-up of women's or children's health
- CDC maintains data collected by the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) on cycle-specific outcomes, required by the Fertility Clinic Success Rate and Certification Act of 1992
- Clinic-specific outcomes available to the public at cdc.gov/art/success-rates/index.html

Are there adverse health outcomes for women and children?



Three major challenges to studying health (vs. pregnancy) outcomes related to IVF and subfecundity

1. Follow-up

- Motivational limitations
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- Recruitment concerns

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- Studies have mostly focused on heterogeneity of outcome (e.g., cancer type) but not heterogeneity of exposure beyond non-IVF treatment vs. IVF, and fresh vs. frozen embryo transfer
- IVF protocols vary by time period and geography
- IVF protocols vary by individual

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3. Confounding by indication

- Are health outcomes the result of the IVF procedure or the intended parents' underlying subfecundity?

Administrative health database research

Pros:

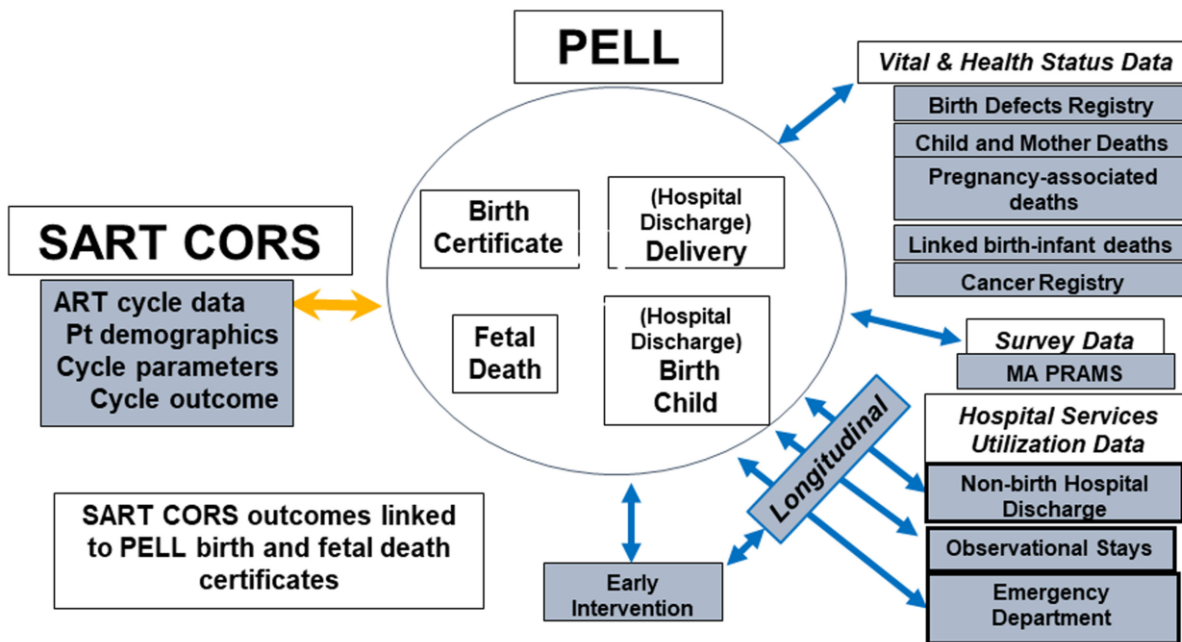
- Large numbers
- Representative
- Linkage available across validated datasets
- Minimal loss to follow-up, especially for nationwide databases
- Potential for linkage to other pregnancies within the same family or other family members
- Equal access to treatment (not in US!)

Cons:

- Outcomes generally limited to clinical diagnoses
- Often do not include reason for infertility diagnosis or IVF use (e.g., male vs. female factor; heterosexual vs. same-sex vs. single parents by choice)
- Often missing sociodemographic information
- Variable information on treatment specifics
- Often not generalizable to the US

MOSART (Massachusetts Outcomes Study of Assisted Reproductive Technology)

Covers >1 million deliveries from 2004-2017



Stern et al, 2022

MOSART definitions

- Infertile: IVF use for index pregnancy (known from SART CORS)
- Subfertile: no IVF use for index pregnancy plus either:
 - Fertility treatment indicated on the birth or fetal death record of a prior delivery
 - ICD-9 code for infertility in the past 5 years
 - Prior IVF recorded in SART CORS
- Subfertile group divided into non-IVF treatment vs. fertile (natural conception)

MOSART findings

- Both subfertile and IVF groups had elevated risk of gestational hypertension, uterine bleeding, placental complications, cesarean section, and prenatal and postpartum maternal hospitalizations (up to 8 years postpartum) vs. fertile group
- For singleton births, both subfertile and IVF groups had elevated risk of preterm birth and low birth weight vs. fertile group
- Singleton infants from subfertile and IVF groups had elevated risk of infectious disease, respiratory conditions, and gastrointestinal conditions during delivery hospitalization vs. infants from fertile group
- Both subfertility and IVF were associated with increased likelihood of Early Intervention (EI) at age 0-3 years, controlling for preterm birth; no associations with autism diagnosis in children age 0-3 years

Infertility/subfecundity variables in ECHO

Data harmonization

Collaborators: Noya Galai, Haozuo Zhao, Joseph Stanford

- 94 key words were used to search all surveys in the ECHO database, including:
 - Descriptors of efforts to become pregnant
 - Infertility-related terms, procedures, and medications
 - Medical conditions related to infertility
- Yielded 4,704 items that were identified on 265 different instruments from 52 cohorts in Cycle 1

Final cleaned variable list (n's as of 10/1/2024)

- IVF use (index pregnancy, n=25,671)
- Artificial insemination (index pregnancy, n=24,538)
- Ovarian stimulation (index pregnancy, n=18,568)
- Other treatment (index pregnancy, n=11,491)
- Unspecified treatment (index pregnancy, n=18,726)
- Prior infertility evaluation, diagnosis, or treatment for either partner (n=14,764)
- Which partner diagnosed with infertility (n=1,291)
- Fibroid diagnosis (ever, n=9,243)
- PCOS diagnosis (ever, n=8,380)
- Endometriosis diagnosis (ever, 7,647)
- Any benign gynecological condition (n=13,621)
- Miscarriage (ever, n=21,198)
- Number of prior miscarriages
- Recurrent miscarriage (≥ 2 prior to index pregnancy)
- Time to pregnancy (TTP, months or cycles, index pregnancy, n=6,831)
- TTP ≥ 12 months (index pregnancy)
- Ever ≥ 12 months of unprotected intercourse without pregnancy (n=11,981)
- Birth control type used at time of conception (index pregnancy, n=12,359)
- Intendedness (index pregnancy, n=10,944)

Combined infertility treatment and subfecundity variables

Infertility treatment (n=31,223):

- IVF OR
- Ovarian stimulation (OS) OR
- Artificial insemination (AI) OR
- Other or unspecified fertility treatment

...for the index pregnancy

Subfecundity (n=27,777):

- TTP ≥ 12 months for the index pregnancy OR
- Ever ≥ 12 months of unprotected intercourse without pregnancy OR
- ≥ 2 miscarriages prior to the index pregnancy OR
- Prior infertility evaluation, diagnosis, or treatment for either partner

EC0697: Subfecundity as a risk factor for adverse child neurodevelopmental outcomes

Results of prior studies have had significant limitations

- Most have been small (N<400) and compared IVF and/or OS/AI pregnancies to natural conceptions without accounting for subfertile group within the natural conceptions, which would result in bias toward the null if subfecundity is associated with outcomes.
- MOSART study reporting higher EI enrollment among both subfertile and IVF groups did not stratify by reason for EI enrollment, so findings cannot be attributed to neurodevelopmental outcomes (Diop et al, 2016)
- Record-linkage studies from Ontario, Canada (Fine et al, 2022; Velez et al, 2023) reporting higher rates of ADHD and ASD among subfertile, OS/AI, and IVF groups could not investigate subclinical neurodevelopmental outcomes

Analytic sample—Cycle 1 data through 10/31/2023

Inclusion criteria:

- Fertility exposure and neurodevelopmental outcomes data

Exclusion criteria:

- Adoption cohorts, pregnancies conceived with donor gametes, and those from cohorts with <5 pregnancies

Final n=15,384 pregnancies from 44 cohorts

Exposures

Variable	Approximate prevalence within total analytic sample
IVF	9%
Non-IVF fertility treatment (OS/AI)	11%
Natural conception	80%
TTP ≤ 12 months	75% (94% of natural conceptions)
TTP > 12 months	5% (6% of natural conceptions)
Any subfecundity	23.5%

Covariates included in our models

Maternal characteristics	
Maternal age, mean (SD)	30.9 (5.3)
Race: White	9,891 (74.2%)
Asian	1,089 (8.2%)
Black	1,488 (11.2%)
Multiple	739 (5.5%)
Other	1,115 (8.4%)
Hispanic	3,591 (23.7%)
PP BMI: Normal/under	6,737 (43.8%)
Overweight	3,686 (24.0%)
Obese	3,655 (23.8%)
Parous	8,780 (61.0%)

Maternal characteristics	
Tobacco use (Y)	961 (6.8%)
Alcohol use (Y)	2,113 (16.2%)
Psychiatric disorder (Y)	5,247 (37.6%)
Education: ≥High school	14,081 (94.5%)
Income: <\$30,000	2,077 (17.5%)
\$30,000-<\$50,000	1,201 (10.1%)
\$50,000-<\$75,000	1,542 (13.0%)
>\$75,000	7,056 (59.4%)
Child sex: Male	7,248 (47.1%)
Female	8,136 (52.9%)

Birth and neurodevelopmental outcomes

Birth/child characteristics	
Birth weight, g	3,230 (736)
Gestational age, weeks	38.2 (3.1)
Birthweight: Low (<2,500g)	1,578 (10.6)
Normal	11,905 (80.3%)
High (≥4,000g)	1,345 (9.1%)
Cesarean delivery	5,180 (35.0%)
Multiples	349 (2.3%)
ADHD diagnosis	876 (7.6%)
ASD diagnosis	819 (7.1%)

Four continuous outcomes (raw scores):

- Externalizing behavior (harmonized SDQ and CBCL)
- Internalizing behavior (harmonized SDQ and CBCL)
- Total Problems (harmonized SDQ and CBCL)
- Social communication problems (SRS)

If assessed more than once (at age 2-5 and 6-10), earlier time point selected (closer to exposure)

Models for these outcomes additionally included child age at assessment

Methods

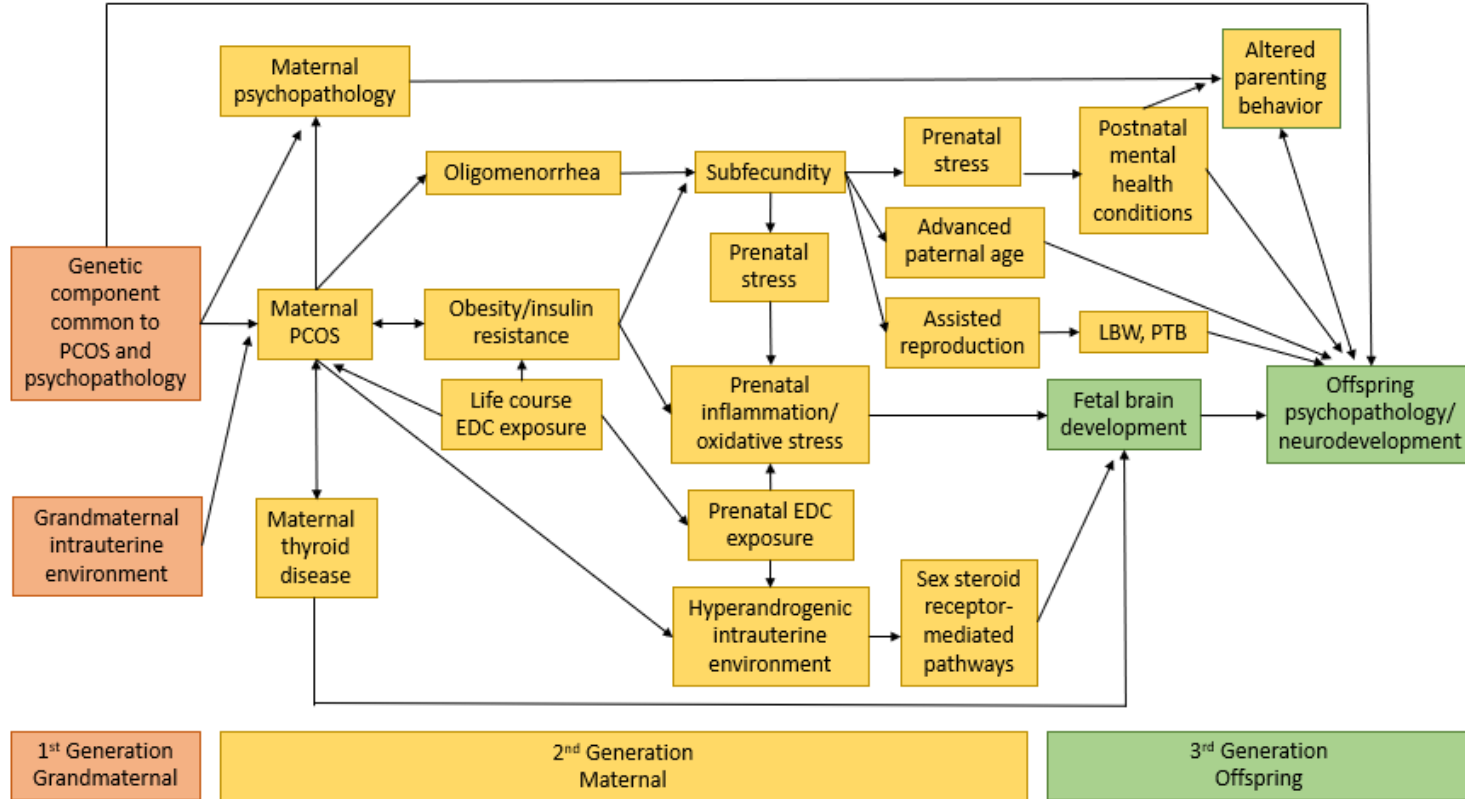
- For internalizing and externalizing behavior (modeled simultaneously to account for correlation): multivariate linear models with random effects for cohort
- For social communication problems and total problems (modeled separately): mixed effects linear models with random effects for cohort
- For binary outcomes (ADHD or ASD diagnosis): mixed effects logistic models with random effects for cohort
- Multiple imputation for missing covariate data
- For multiple gestations, one twin selected at random
- Sensitivity analysis conducted among “general population” (unselected) cohorts

Results

	Among all conceptions, subfecundity (i.e., with or without treatment) vs. natural conception and no subfecundity	Among natural conceptions, subfecundity vs. no subfecundity
Outcome	beta or OR (95% CI)	beta or OR (95% CI)
Externalizing behavior	0.47 (0.14, 0.81)	0.45 (0.07, 0.83)
Internalizing behavior	0.23 (-0.10, 0.57)	0.14 (-0.23, 0.520)
Total problems	1.36 (0.40, 2.32)	1.26 (0.17, 2.35)
Social communication problems	1.08 (0.01, 2.14)	1.12 (-0.09, 2.34)
ADHD diagnosis	1.02 (0.84, 1.23)	0.91 (0.73, 1.12)
ASD diagnosis	1.27 (1.03, 1.57)	1.31 (1.04, 1.64)

	TTP > 12 months vs. TTP ≤ 12 months	IVF vs. TTP ≤ 12 months	Non-IVF treatment vs. TTP ≤ 12 months	IVF vs. TTP > 12 months	Non-IVF treatment vs. TTP > 12 months
Outcome	beta or OR (95% CI)	beta or OR (95% CI)	beta or OR (95% CI)	beta or OR (95% CI)	beta or OR (95% CI)
Externalizing behavior	0.21 (-0.73, 1.15)	1.03 (0.18, 1.88)	0.75 (-0.01, 1.51)	0.83 (-0.38, 2.03)	0.55 (-0.61, 1.70)
Internalizing behavior	-0.36 (-1.30, 0.58)	0.64 (-0.21, 1.49)	0.64 (-0.11, 1.41)	1.00 (-0.20, 2.21)	1.02 (-0.13, 2.17)
Total problems	-0.55 (-3.15, 2.06)	2.61 (0.22, 4.99)	2.24 (0.09, 4.38)	3.15 (-0.22, 6.52)	2.79 (-0.44, 6.01)
Social communication problems	1.53 (-1.77, 4.82)	2.57 (-0.30, 5.44)	3.42 (1.00, 5.85)	1.04 (-3.12, 5.20)	1.90 (-1.97, 5.77)
ADHD diagnosis	1.03 (0.53, 2.00)	1.86 (0.97, 3.56)	2.29 (1.47, 3.56)	1.80 (0.74, 4.40)	2.22 (1.05, 4.73)
ASD diagnosis	1.16 (0.43, 3.08)	1.51 (0.57, 3.96)	1.38 (0.67, 2.86)	1.30 (0.35, 4.79)	1.20 (0.38, 3.73)

Could PCOS be the problem?



Sneak preview of EC0697a!

	PCOS vs. no PCOS
Outcome	beta or OR (95% CI)
Externalizing behavior	1.03 (0.24, 1.82)
Internalizing behavior	0.48 (-0.31, 1.27)
Total problems	2.54 (0.29, 4.79)
Social communication problems	1.44 (-0.85, 3.73)
ADHD diagnosis	2.12 (1.53, 2.94)
ASD diagnosis	1.31 (0.76, 2.24)

	No PCOS	PCOS
TTP ≤12 months	1,744 (83.7%)	91 (33.1%)
TTP >12 months	109 (5.2%)	16 (5.8%)
IVF	106 (5.1%)	47 (17.1%)
Non-IVF treatment	125 (6.0%)	121 (44.0%)

Models not adjusted for maternal psychiatric condition

Strengths and Limitations

Strengths

- Large n
- Diverse population
- Creation of a more inclusive subfecundity variable
- Ability to examine subfecundity among those who naturally conceive
- Ability to control for many covariates known to be associated with access to infertility treatment

Limitations

- Not all participants had data on all exposure and outcome variables, resulting in slightly different subsets of the cohort in each analysis
- For some contrasts, exposed group <10% of sample, resulting in wide confidence intervals
- Limited information on reasons for treatment
- Limited information on underlying medical conditions

Conclusions

- Subfecundity is associated with higher total problems score, driven by externalizing problems, and higher social communication problems and odds of ASD even among those who conceive naturally
- Both IVF and non-IVF fertility treatment are generally associated with higher total problems score, social communication problems, and odds of ADHD compared with those who conceive naturally either \leq or $>$ 12 months
- More work to be done to tease out whether particular indications for treatment (e.g., PCOS) are driving these associations

Thank you



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