Propensity Score Matching to Assess the Effect of Single versus Double Embryo Transfer for In Vitro Fertilization

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Joint work with Donald B. Rubin and the Division of Reproductive Health at the Centers for Disease Control and Prevention
Multiple Birth Rates
United States, 1973-2008

**Twin Birth**
(per $10^3$ Live Infants Born)

**High Order Birth**
(per $10^5$ Live Infants Born)
The Mastera twins, in a family photo at 2 months old, each weighed only about 3 pounds at birth. They are doing well now, but the path was difficult.

By STEPHANIE SAUL

Published: October 10, 2009
What is Assisted Reproductive Technology?

Treatments or procedures that include the handling of human eggs and sperm or embryos for the purpose of establishing a pregnancy.
Specific ART Treatments

- ART includes
  - In vitro fertilization with trans-cervical embryo transfer (IVF)
  - Intracytoplasmic sperm injection (ICSI)
  - Gamete and zygote intrafallopian transfer (GIFT, ZIFT)

- ART does NOT include
  - Assisted (artificial) insemination only
  - Use of ovarian stimulation medications without egg retrieval
What are the steps in a typical ART procedure?
ART data collection in the U.S.A.

1986: Society for Assisted Reproductive Technology (SART) established a data collection and reporting program available to ART clinics

1990's: Federal Trade Commission issued cease-and-desist orders based on inaccurate advertising by an ART program

1992: Congress enacts the Fertility Clinic Success Rate and Certification Act (FCSRCA)

1997: CDC publishes the 1995 ART Success Rates Report, the first published under FCSRCA
Use of ART in the USA over time

Number (thousands)

Year


ART procedures
Live infants
Multiple Births Attributed to ART, US 1997–2007


Percentage:
- 11.2
- 12.9
- 13.5
- 13.6
- 15.5
- 17.1
- 17.9
- 18
- 17.3
- 17.9
- 17.8

Graph showing the increase in multiple births attributed to ART from 11.2% in 1997 to 17.8% in 2007.
Percentage of ART cycles using fresh own embryos, by numbers of embryo transferred, USA, 1996-2009
Percentage of live-birth deliveries from ART cycles using fresh own embryos, by plurality, USA, 1996-2009
e-SET eligible ART cycles
USA, 2005-2006 (N=23,010)

Cycles by no. of embryos transferred

- 2: 78%
- 3: 14%
- 4+: 1.5%
- 1: 6.4%

Cycles by no. of embryos transferred and no. of live-born infants
e-SET eligible ART cycles
Actual outcomes, USA, 2005-2006 (N=23,010)

Cycles by no. of live-born infants
- None: 47%
- 1: 33%
- 2: 19%
- 3+: 1%

Infants (N=17,220) by delivery outcome
- 37wk+, 2.5Kg+: 50%
- 37wk+, 1.5-2.4Kg: 6%
- 37wk+, <1.5Kg: 11%
- <37wk, 2.5Kg+: 6%
- <37wk, 1.5-2.4Kg: 7%
- <37wk, <1.5Kg: 26%
## Cost estimates

<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>If repeated e-SET policy adopted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charges to patients, ART</td>
<td>358 (260-515)</td>
<td>470 (351-659)</td>
</tr>
<tr>
<td>Charges to patients, infant outcomes</td>
<td>383 (248-445)</td>
<td>136 (86-167)</td>
</tr>
<tr>
<td>Charges to third-party payers</td>
<td>1,531 (993-1,781)</td>
<td>546 (344-667)</td>
</tr>
<tr>
<td>Total charges</td>
<td>2,271 (1,501-2,741)</td>
<td>1,153 (781-1,493)</td>
</tr>
</tbody>
</table>
Does the decision to transfer one versus two embryos affect pregnancy rates?

Multiple birth rates?

Rates of prematurity and other complications?
Our Study Criteria

Fresh cycles, with patients’ own eggs
First-time IVF cycles
At least three embryos available for transfer
Either one or two embryos transferred
At least one embryo cryopreserved for possible later use
Goal:
Select a control group from the set of two-embryo cycles that is very similar, on background covariates, to the active treatment group of one-embryo cycles

No outcomes!
US Assisted Reproductive Technology Database

2004-2005:
22,735 patients in 420 clinics
US Assisted Reproductive Technology Database

1,025: single embryo transfer to uterus (SET) – low risk of twins
21,710: double embryo transfer to uterus (DET) – higher chance of success
US Assisted Reproductive Technology Database

1,025: single embryo transfer to uterus (SET) – low risk of twins
21,710: double embryo transfer to uterus (DET) – higher chance of success
Identifying Covariates

- Baseline patient data
- Clinic-level data
- Medical treatment data
- Complications prior to embryo transfer

Which are important for the decision to transfer one embryo v. two?

Which are related to outcomes?
61 important covariates identified:

- 3 for exact matching
- 21 “primary” binary
- 16 “secondary” binary
- 6 continuous
- 5 transformations of continuous covariates
- 10 pairwise interactions
Summarize multiple covariates with estimated propensity score:

– Fit logistic regression model to predict treatment status given covariates

– Fitted values from logistic regression model are estimated propensity scores

– Match or subclassify based on estimated propensity scores and examine resulting balance

– Iterate, choosing the model and matching process that give the best balance, as shown by diagnostics
Randomly order SET patients
For each SET patient, create a set of potential matches:
   - Same clinic
   - Same year
Randomly order SET patients
For each SET patient, create a set of potential matches:
- Same clinic
- Same year
- Same category of number of days between egg retrieval and embryo transfer (2-3 days or 4-7 days)

Number of days: 2 3 4 5 6 7
Randomly order SET patients
For each SET patient, create a set of potential matches:
- Same clinic
- Same year
- Same category of number of days between egg retrieval and embryo transfer (2-3 days or 4-7 days)
- Within fixed distance on logit of estimated propensity score

Select the potential DET match with the estimated propensity score logit closest to that of the SET patient, if it has not already been matched.
When a satisfactory match did not exist within the year, matched across years.

Each DET patient was matched to no more than one SET patient.

Using the criteria above, we identified matches for 923 of the 1025 SET patients; the omitted SET patients were those who were not similar to any of the DET patients.
Measures

• Entire distribution, graphically
• Difference in means (standardized for continuous covariates)
• Odds ratio (for binary covariates)
• Variances (for continuous covariates)
• Extremes: minimum and maximum
Difference in Means for Primary Binary Covariates

-0.05 -0.04 -0.03 -0.02 -0.01 0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08

RFAENDO

RFAOTHERonly

RFAMALEonly

RFATUB

GESTATIO.1

HighFSH

HighFSHUnknown
Difference in Means for Primary Binary Covariates

-0.05 -0.04 -0.03 -0.02 -0.01 0.00 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08

- difference in means

Initial
Final Matches

RFAENDO
RFAPCO
RFAUTERI
RAUNEXP
RFAMultFemaleonly
RFAMultMaleFemale
RFADIMOVonly
RFOTHERonly
RFAMALEonly
RFATUB
GESTATIO.1
HighFSH
HighFSHUnknown

Initial
Final Matches
Difference in Means for Primary Binary Covariates

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- difference in means

- Initial
- Final Matches

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- RFAOTHERonly
- RFAMALEonly
- RFATUB
- GESTATIO.1
- HighFSH
- HighFSHUnknown
Difference in Means for Primary Binary Cov

-0.038 0.005
Absolute Difference in Means
Primary and Secondary Binary Co-
<table>
<thead>
<tr>
<th>Initial Match</th>
<th>Final Match</th>
<th>Absolute Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.05</td>
<td>+0.038</td>
</tr>
<tr>
<td>0.10</td>
<td>0.15</td>
<td>0.005</td>
</tr>
<tr>
<td>0.20</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>
Absolute Difference in Means
Primary and Secondary Binary Confidence
Absolute Difference in Means
Primary and Secondary Binary Co...

Initial Match
Final Match

- 37 decreased
- 10 increased
Absolute Difference in Means
Primary and Secondary Binary C

Initial

Final
Difference in Means
Primary and Secondary Binary C
Why these matches?

Why this propensity score model?

Why this matching protocol?
Choose the model leading to best balance, as shown by diagnostics, emphasizing the most important covariates:

Not necessarily the best-fitting model

Not necessarily the model that best reflects reality

Not necessarily the model that creates best balance overall
Difference in Means for Primary Binary Covariates

- RFAENDO
- RFAPCO
- RFAUTERI
- RFAUNEXP
- RFAMultFemaleonly
- RFAMultMaleFemale
- RFADIMOVonly
- RFAOTHERonly
- RFAMALEonly
- RFATUB
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- HighFSH
- HighFSHUnknown

difference in means

- Initial
- Final Matches
Difference in Means for Primary Binary Covariates

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- RFOTHERonly
- RFAMALEonly
- RFATUB
- GESTATIO.1
- HighFSH
- HighFSHUnknown

Legend:
- Initial
- MatchYear
- MatchYear.Day

difference in means

-0.08 -0.06 -0.04 -0.02 0.00 0.02 0.04 0.06 0.08
Difference in Means for Primary Binary Covariates

-0.08 -0.06 -0.04 -0.02 0.00 0.02 0.04 0.06 0.08

difference in means

- Initial
- Matches
- WithinYear (OrigModel)
- WithinYear (SepModels)
For data through 2008:

Matched based on continuous time instead of within year

Included transfers on days 3 and 5 only

Exact matched within age groups: <35, 35+
• SART clinicians reviewed and approved proposed matches

• Protocol for outcome analysis approved

Outcome analysis currently underway