

## How Infertility and Treatments Can Affect Human Placenta Function



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## Disclosures

- Ferring
- Natara

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## Infertility And Treatment Options

Infertility affects up to 15% of couples




**Ovarian Stimulation/IUI**




4.6% live births in US

**In Vitro Fertilization**



1.9% live births in US  
8 million babies born worldwide

 Cedars Sinai Pisarska, et al. J Clin Endocrinol Metab. 2018  
National Health Statistics Reports 2018  
CDC, National Center for Health Statistics 2017

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### Outcomes based on fertility diagnosis

- Significant difference in maternal age and race
- Infertility increases risk for cesarean section
- Conceptions from infertile couples deliver earlier

|                            | Infertile<br>N=277 | Fertile<br>N=3016 | P-value |
|----------------------------|--------------------|-------------------|---------|
| Maternal Age, years        | 37.4±5.3           | 31.5±5.3          | <0.0001 |
| Maternal Race, n(%)        |                    |                   | 0.023   |
| White                      | 199 (69.9)         | 2066 (68.8)       |         |
| Black- or African-American | 16 (15.8)          | 287 (9.6)         |         |
| Asian or Asian-American    | 49 (17.8)          | 391 (13.0)        |         |
| Other                      | 18 (6.5)           | 260 (8.7)         |         |
| BMI, kg/m <sup>2</sup>     | 23.3±4.6           | 23.0±4.6          | 0.3211  |
| Mode of Conception, n(%)   |                    |                   | <0.0001 |
| IVF                        | 136 (49.1)         | 4 (0.13)          |         |
| NIFT                       | 73 (26.4)          | 4 (0.13)          |         |
| Presumed Spontaneous       | 68 (24.5)          | 3008 (99.7)       |         |
| Cesarean Delivery, n(%)    | 142 (51.8)         | 1078 (36.1)       | <0.001  |
| Gestational age, weeks     | 38.9±2.3           | 39.4±1.7          | <0.0001 |
| Birth weight, grams*       | 3268±634           | 3317±510          | 0.1378  |

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### vAMA

- ART were significantly older
- More likely to be white
- More likely to be nulliparous
- Significantly increased risk for cesarean delivery
- Risk of retained placenta was also significantly higher

**TABLE 1**

Maternal characteristics and maternal and fetal outcomes in singleton gestations conceived either spontaneously or with assisted reproductive technology (ART).

| Variable                       | Spontaneous<br>(n = 193) | ART<br>(n = 185) | P value |
|--------------------------------|--------------------------|------------------|---------|
| <b>Maternal characteristic</b> |                          |                  |         |
| Age (y), mean                  | 45.6 ± 0.1               | 47.0 ± 2.3       | < .05   |
| Race/ethnicity, % white        | 75.6                     | 88.1             | < .002  |
| Parity                         | 1.2 ± 1.8                | 0.4 ± 0.9        | < .001  |
| <b>Maternal outcome</b>        |                          |                  |         |
| Postpartum hemorrhage, %       | 3.1                      | 5.9              | NS      |
| Estimated blood loss (mL)      | 303 ± 104                | 324 ± 116        | NS      |
| Vaginal delivery               | 730 ± 284                | 713 ± 137        | NS      |
| Cesarean delivery              |                          |                  |         |
| Retained placenta, %           | 0                        | 2.7              | < .02   |
| Hysterectomy, %                | 2.1                      | 1.1              | NS      |
| Hysterectomy, %                | 0                        | 0.5              | NS      |
| Rate of ICU admission, %       | 0                        | 1.1              | NS      |
| Length of stay (d), mean       | 3.2 ± 2.2                | 4.2 ± 3.9        | < .01   |
| Total CD, %                    | 49.7                     | 75.1             | < .001  |
| Primary CD                     | 35.3                     | 71.3             |         |
| Repeat CD                      | 22.2                     | 13.5             |         |
| <b>Fetal outcome</b>           |                          |                  |         |
| Gestational age, wk            | 38.9 ± 2.4               | 38.9 ± 2.4       | NS      |
| Birth weight, g                | 3,318 ± 527              | 3,284 ± 567      | NS      |
| NICU admission rate, %         | 1.5                      | 4.3              | NS      |
| Apgar score at 5 min           | 8.8 ± 1                  | 8.9 ± 0.7        | NS      |

Note: CD – cesarean delivery; ICU – intensive care unit; NICU – neonatal intensive care unit; NS – not significant.

Jackson. Pregnancy in very advanced maternal age. Fertil Steril 2015.

Cedars Sinai Jackson, et al Fertil Steril 2015;103:76-80.

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### Risks associated with infertility and fertility treatments

|                                | spontaneous | NIFT | IVF |
|--------------------------------|-------------|------|-----|
| gestational diabetes           |             | ↑    | ↑   |
| pregnancy induced hypertension |             | ↑    | ↑   |
| placenta previa                |             |      | ↑   |
| placental abruption            |             | ↑    | ↑   |
| postpartum hemorrhage          |             |      | ↑   |
| preterm birth                  |             |      | ↑   |
| Low birth weight/SGA           |             | ↑    | ↑   |
| perinatal mortality            |             | ↑    | ↑   |

Cedars Sinai Shevell T. 2005 Obstet Gynecol 106:1039-1045  
Qin J. 2016 Fertil and Steril 2016  
Pisarska M. JCEM 2018

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### Significant maternal morbidity

**Table 2. Rates of Most Commonly Reported and Statistically Significant Severe Maternal Morbidity Indicators and Overall Rate of Any Indicator During Delivery Hospitalizations or Postpartum Readmissions Per 10,000 Deliveries by Assisted Reproductive Technology Status, 2008–2012**

| Indicator  | Singleton Pregnancies |            |                 | Multiple Pregnancies |            |             |
|--|-----------------------|------------|-----------------|----------------------|------------|-------------|
|  | Non-ART               | ART        | P*              | Non-ART              | ART        | P*          |
| Blood transfusion                                | 36                    | 77         | <.001           | 215                  | 200        | .567        |
| Disseminated intravascular coagulation           | 20                    | 46         | <.001           | 68                   | 98         | .042        |
| Mechanical ventilation                           | 18                    | 33         | .001            | 105                  | 143        | .034        |
| Adult respiratory distress syndrome              | 12                    | 21         | .009            | 49                   | 48         | 1           |
| Eclampsia  | 11                    | 13         | .656            | 34                   | 41         | .488        |
| Heart failure during procedure or surgery        | 11                    | 23         | .001            | 26                   | 25         | 1           |
| Hysterectomy                                     | 9                     | 27         | <.001           | 38                   | 34         | .892        |
| Sepsis   | 7                     | 15         | .004            | 22                   | 32         | .227        |
| Acute renal failure                              | 6                     | 18         | <.001           | 30                   | 32         | .681        |
| Puerperal cerebrovascular disorders              | 6                     | 9          | .324            | 19                   | 18         | 1           |
| Operations on heart and pericardium              | 6                     | 12         | .041            | 21                   | 23         | .720        |
| Internal injuries of thorax, abdomen, and pelvis | 3                     | 14         | <.001           | 10                   | 25         | .016        |
| Shock  | 4                     | 14         | <.001           | 22                   | 16         | .585        |
| <b>Overall</b>                                   | <b>126</b>            | <b>273</b> | <b>&lt;.001</b> | <b>539</b>           | <b>604</b> | <b>.089</b> |

ART, assisted reproductive technology.  
Data are n unless otherwise specified.  
\* Helm-Kortmann corrected P<.001 denotes statistical significance of Pearson  $\chi^2$  and Fisher exact tests.

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Martin AS, Obstet Gynecol 2016;127:59-66 7

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### Significant Maternal Morbidity (SMM)

**TABLE 1**

**Baseline characteristics of the maternal cohort.**

| Characteristic                       | SMM (n = 69) | No SMM (n = 6,474) | P value |
|--------------------------------------|--------------|--------------------|---------|
| Maternal age (y), n (SD)             | 34.0 (6.7)   | 32.9 (5.30)        | .18     |
| Maternal race                        |              |                    | .001    |
| White                                | 36 (52.2)    | 4,541 (70.5)       |         |
| Black                                | 14 (20.3)    | 590 (9.2)          |         |
| Asian                                | 14 (20.3)    | 798 (12.4)         |         |
| Other                                | 5 (7.2)      | 512 (8.0)          |         |
| Body mass index (kg/m <sup>2</sup> ) |              |                    | .50     |
| 18.5–24.9                            | 9 (13.0)     | 1,220 (18.9)       |         |
| 25–29.9                              | 29 (42.0)    | 3,021 (46.8)       |         |
| ≥30                                  | 28 (40.8)    | 2,012 (30.9)       |         |
| Mode of conception                   | 7 (10.1)     | 1,509 (23.3)       | <.001   |
| IVF                                  | 7 (10.1)     | 239 (3.7)          |         |
| NFT                                  | 3 (4.3)      | 106 (1.6)          |         |
| Spontaneous                          | 59 (85.5)    | 6,129 (94.7)       |         |
| Delivery (n, %)                      |              |                    | <.001   |
| Cesarean delivery                    | 25 (36.2)    | 2,470 (38.1)       |         |
| Vaginal delivery                     | 44 (63.8)    | 3,984 (61.9)       |         |
| Health insurance                     |              |                    | <.001   |
| Government                           | 20 (29)      | 831 (13)           |         |
| Private                              | 49 (71)      | 5,583 (87)         |         |
| Comorbidities                        |              |                    |         |
| Coronary heart disease               | 5 (7)        | 26 (0.4)           | <.001   |
| Diabetes mellitus                    | 10 (15)      | 455 (7)            | 0.03    |
| Hypertension                         | 3 (4)        | 57 (1)             | 0.03    |

Note: Data presented as n (%), unless stated otherwise. IVF = in vitro fertilization; NFT = non-IVF fertility treatment; SMM = severe maternal morbidity.  
Wang, Fertility treatment and SMM. Fertil Steril 2016.

Cedars Sinai  
Wang et al. Fertil and Steril 2016 8

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### Inferfertility Diagnosis and Maternal Morbidity

**TABLE 3**  
**Risk of severe maternal morbidity by infertility group\***

| Severe maternal morbidity indicator                 | Age (95% CI)         |                         |                    |                          |
|---|----------------------|-------------------------|--------------------|--------------------------|
|   | Treatment vs fertile | Diagnosis vs fertile    | Tending vs fertile | All infertile vs fertile |
| Any severe maternal morbidity indicator             | 1.24 (1.13–1.35)     | <b>1.22 (1.13–1.33)</b> | 1.09 (0.81–1.49)   | 1.22 (1.14–1.31)         |
| Acute myocardial infarction                         | 1.08 (0.52–2.40)     | 0.96 (0.22–3.66)        | †                  | 1.33 (0.52–3.36)         |
| Acute renal failure                                 | 1.03 (0.53–2.02)     | 0.86 (0.47–1.57)        | †                  | 0.84 (0.51–1.38)         |
| Acute respiratory distress                          | 1.57 (1.03–2.38)     | 1.14 (0.76–1.71)        | †                  | 1.26 (0.83–1.92)         |
| Anesthetic fatal embolism                           | 1.61 (0.59–5.18)     | 1.10 (0.35–3.49)        | †                  | 1.21 (0.57–3.02)         |
| Aneurysm  | †                    | †                       | †                  | †                        |
| Cardiac arrest or ventricular fibrillation          | 1.22 (0.29–5.04)     | 2.68 (1.16–6.20)        | †                  | 1.94 (0.88–4.31)         |
| Disseminated intravascular coagulation              | 1.67 (1.33–2.08)     | <b>1.34 (1.08–1.66)</b> | 1.57 (0.81–3.06)   | 1.48 (1.28–1.72)         |
| Eclampsia   | 1.46 (1.02–2.12)     | 1.39 (0.95–1.98)        | 1.41 (0.86–2.31)   | 1.27 (1.05–1.51)         |
| Heart failure during procedure or surgery           | 1.27 (0.85–1.93)     | <b>1.75 (1.3–2.36)</b>  | 0.89 (0.22–3.57)   | 1.54 (1.21–1.97)         |
| Internal injuries of the thorax, abdomen, or pelvis | 1.61 (0.92–2.84)     | 1.52 (0.95–2.42)        | 0.89 (0.14–7.06)   | 1.77 (1.20–2.61)         |
| Intrauterine injuries                               | 1.27 (0.31–5.28)     | <b>2.64 (1.14–6.10)</b> | †                  | 2.05 (0.97–4.32)         |
| Puerperal cerebrovascular disorders                 | 1.05 (0.71–1.45)     | <b>1.41 (1.03–1.92)</b> | 1.65 (0.81–3.39)   | 0.91 (0.68–1.23)         |
| Pulmonary edema                                     | 1.05 (1.09–3.14)     | <b>2.05 (1.36–3.06)</b> | †                  | 2.18 (1.54–3.10)         |
| Severe anesthesia complications                     | 0.33 (0.08–1.32)     | 0.85 (0.42–1.71)        | †                  | 1.13 (0.49–2.60)         |
| Sepsis  | 1.04 (0.59–1.82)     | 0.79 (0.40–1.21)        | 1.37 (0.34–5.51)   | 0.90 (0.59–1.36)         |
| Shock   | 1.76 (1.02–3.02)     | 1.06 (0.58–1.92)        | †                  | 1.14 (0.72–1.80)         |
| Sickle cell anemia with crisis                      | †                    | †                       | †                  | †                        |
| Thrombotic embolism                                 | 1.35 (0.86–2.13)     | <b>1.77 (1.27–2.46)</b> | 1.21 (0.30–4.86)   | 1.58 (1.14–2.17)         |
| Blood transfusion                                   | 1.69 (1.39–2.03)     | <b>1.32 (1.08–1.60)</b> | 1.44 (0.79–2.62)   | 1.50 (1.30–1.72)         |
| Eclampsia   | 1.01 (0.87–1.18)     | <b>1.41 (1.03–1.92)</b> | 1.65 (0.81–3.29)   | 1.29 (0.90–1.82)         |
| Conversion of cardiac rhythm                        | 0.72 (0.10–5.28)     | 0.95 (0.23–3.88)        | †                  | 0.83 (0.26–2.68)         |
| Hysterectomy  | 1.61 (1.03–2.52)     | 1.10 (0.69–1.77)        | 1.53 (0.38–6.16)   | 1.35 (0.97–1.88)         |
| Operations on the heart and pericardium             | 1.44 (0.86–2.38)     | 1.09 (0.67–1.77)        | 2.23 (0.74–6.96)   | 1.52 (1.07–2.14)         |
| Temporary tracheostomy                              | †                    | †                       | †                  | †                        |
| Ventilation   | 0.95 (0.61–1.47)     | 1.08 (0.78–1.51)        | †                  | 0.91 (0.69–1.20)         |
| Intubation  | 0.92 (0.29–2.82)     | 0.98 (0.40–2.36)        | †                  | 0.84 (0.39–1.85)         |

95% adjusted odds ratio. CI, confidence interval.  
\* Adjusted odds ratio (OR) values were used to estimate the odds ratios of the disease between infertile and control groups, adjusted for maternal age, year of delivery, ethnicity, delivery status, internal genital procedure, and other variables. † Calculated OR and 95% CI are not possible because of small numbers.  
† Single study for the disease endpoint. ‡ Calculated OR and 95% CI are not possible because of small numbers.  
†† Single study for all maternal morbidity among infertile women. ††† OR (95% CI) (OR).

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Murugappan, et al. AJOG 2020

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Preterm, late preterm, early term, and term deliveries between infertile and fertile women

|                 | Infertile<br>N=277 | Fertile<br>N=3016 | P value            |
|-----------------|--------------------|-------------------|--------------------|
| <34 weeks       | 8 (2.9)            | 39 (1.3)          | 0.032 <sup>1</sup> |
| 34-36 6/7 weeks | 23 (8.3)           | 130 (4.3)         | 0.003 <sup>2</sup> |
| 37-38 6/7 weeks | 58 (20.9)          | 536 (17.8)        | 0.19 <sup>3</sup>  |
| ≥39 weeks       | 188 (67.9)         | 2311(76.6)        | 0.001 <sup>4</sup> |

Adjusted for maternal age and race

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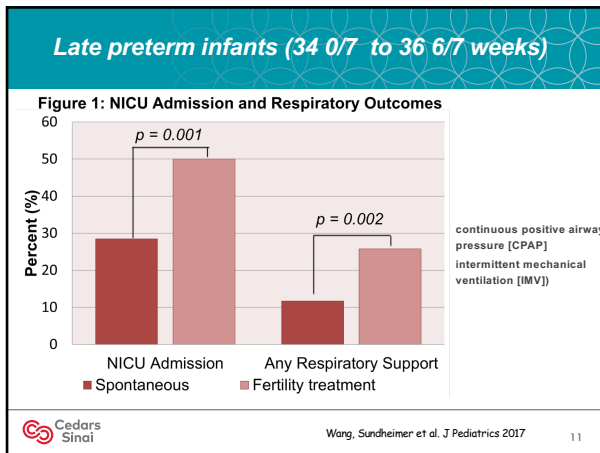
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Table 4. Odds Ratio for Any Birth Defects According to Type of Assisted Conception and Multiplicity.<sup>a</sup>

| Type of Assisted Conception   | Defect<br>no. of births with defect/<br>total no. of births | Singleton Births      |                                  |
|---|---|-----------------------|----------------------------------|
|   |   | Unadjusted Odds Ratio | Adjusted Odds Ratio <sup>b</sup> |
| Any   | 361/4333  | 1.45 (1.30-1.63)      | 1.28 (1.14-1.43)                 |
| IVF   |   |                       |                                  |
| Fresh- or frozen-embryo cycles  | 105/1484  | 1.25 (1.02-1.52)      | 1.06 (0.87-1.30)                 |
| Fresh-embryo cycles   | 71/1005   | 1.25 (0.98-1.59)      | 1.05 (0.82-1.35)                 |
| Frozen-embryo cycles  | 34/479  | 1.24 (0.88-1.76)      | 1.08 (0.76-1.53)                 |
| ICSI  |   |                       |                                  |
| Fresh- or frozen-embryo cycles  | 91/939  | 1.72 (1.38-2.15)      | 1.55 (1.24-1.94)                 |
| Fresh-embryo cycles   | 76/713  | 1.95 (1.53-2.48)      | 1.73 (1.35-2.21)                 |
| Frozen-embryo cycles  | 15/226  | 1.17 (0.70-1.97)      | 1.10 (0.65-1.85)                 |
| GIFT  | 34/319  | 1.98 (1.40-2.80)      | 1.73 (1.21-2.47)                 |
| Intrauterine insemination   | 54/580  | 1.67 (1.25-2.23)      | 1.46 (1.09-1.95)                 |
| Donor insemination  | 36/428  | 1.51 (1.08-2.11)      | 1.37 (0.98-1.92)                 |
| Ovulation induction   | 19/306  | 1.08 (0.68-1.74)      | 0.99 (0.62-1.59)                 |
| Clomiphene citrate at home  | 7/36  | 3.87 (1.58-9.51)      | 3.19 (1.32-7.69)                 |
| Other <sup>c</sup>  | 15/241  | 1.07 (0.63-1.82)      | 0.96 (0.56-1.63)                 |
| Spontaneous conception after previous birth from assisted reproductive technology | 96/1306   | 1.27 (1.02-1.59)      | 1.26 (1.01-1.57)                 |
| Infertile but no history of treatment with assisted reproductive technology       | 52/600  | 1.54 (1.15-2.05)      | 1.37 (1.02-1.83)                 |
| No use of assisted reproductive technology and fertile                            | 16,841/293,314  | 1.00                  | 1.00                             |

Cedars Sinai Davies, et al. NEJM 2012; 366:1803-13

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### Risks of Birth Defects

Table III Risk of birth defects among singletons by maternal characteristics and mode of conception.<sup>a</sup>

| Group <sup>b</sup>              | Major birth defect <sup>c</sup> |            | Blastogenesis |            | Cardiovascular |            | Musculoskeletal |            | Genitourinary-male |            | Chromosomal |              | Any birth defect |            |
|---------------------------------|---------------------------------|------------|---------------|------------|----------------|------------|-----------------|------------|--------------------|------------|-------------|--------------|------------------|------------|
|                                 | AOR                             | 95% CI     | AOR           | 95% CI     | AOR            | 95% CI     | AOR             | 95% CI     | AOR                | 95% CI     | AOR         | 95% CI       | AOR              | 95% CI     |
| Naturally conceived             | 1.00                            | Reference  | 1.00          | Reference  | 1.00           | Reference  | 1.00            | Reference  | 1.00               | Reference  | 1.00        | Reference    | 1.00             | Reference  |
| CU/IVF conceived                | 1.16                            | 0.97, 1.38 | 1.11          | 0.66, 1.85 | 0.96           | 0.74, 1.24 | 1.29            | 0.86, 1.94 | 1.25               | 0.90, 1.73 | 1.00        | 0.60, 1.68   | 1.12             | 0.99, 1.26 |
| ART siblings                    | 1.08                            | 0.95, 1.19 | 1.19          | 0.90, 1.58 | 1.10           | 0.96, 1.26 | 1.32            | 1.04, 1.67 | 0.96               | 0.78, 1.19 | 0.94        | 0.69, 1.27   | 1.15             | 1.08, 1.23 |
| ART solo-fresh, no ICSI         | 1.18                            | 1.05, 1.32 | 0.99          | 0.69, 1.42 | 1.20           | 1.02, 1.40 | 1.19            | 0.95, 1.57 | 1.11               | 0.88, 1.41 | 0.65        | 0.44, 0.95   | 1.18             | 1.09, 1.27 |
| ART solo-fresh, yes ICSI no PF  | 1.30                            | 1.16, 1.45 | 1.49          | 1.08, 2.05 | 1.28           | 1.10, 1.48 | 1.34            | 1.01, 1.78 | 1.09               | 0.85, 1.39 | 0.89        | 0.63, 1.26   | 1.22             | 1.12, 1.32 |
| ART solo-fresh, yes ICSI yes PF | 1.42                            | 1.28, 1.57 | 1.56          | 1.17, 2.08 | 1.45           | 1.27, 1.66 | 1.25            | 0.96, 1.64 | 1.33               | 1.08, 1.65 | 0.93        | 0.66, 1.33   | 1.38             | 1.29, 1.48 |
| Maternal                        | 1.00                            | Reference  | 1.00          | Reference  | 1.00           | Reference  | 1.00            | Reference  | 1.00               | Reference  | 1.00        | Reference    | 1.00             | Reference  |
| Age (years)                     |                                 |            |               |            |                |            |                 |            |                    |            |             |              |                  |            |
| 30-34                           | 1.09                            | 1.05, 1.12 | 0.92          | 0.83, 1.02 | 1.17           | 1.11, 1.23 | 0.97            | 0.89, 1.06 | 1.08               | 1.00, 1.17 | 1.76        | 1.52, 2.03   | 1.07             | 1.05, 1.10 |
| 35-37                           | 1.11                            | 1.06, 1.16 | 0.83          | 0.72, 0.96 | 1.34           | 1.26, 1.43 | 0.91            | 0.81, 1.04 | 1.11               | 1.00, 1.23 | 3.46        | 2.95, 4.05   | 1.13             | 1.10, 1.17 |
| 38-40                           | 1.18                            | 1.03, 1.37 | 0.76          | 0.60, 1.14 | 1.32           | 1.46, 1.44 | 0.97            | 0.83, 1.14 | 1.03               | 0.90, 1.18 | 6.79        | 5.00, 9.06   | 1.23             | 1.19, 1.28 |
| 41-43                           | 1.12                            | 1.03, 1.24 | 1.10          | 0.83, 1.43 | 1.77           | 1.59, 1.97 | 1.12            | 0.89, 1.42 | 1.19               | 0.96, 1.45 | 15.4        | 12.99, 18.25 | 1.43             | 1.34, 1.51 |
| ≥44                             | 1.30                            | 1.07, 1.59 | 1.80          | 1.12, 2.88 | 2.58           | 2.11, 3.16 | 1.42            | 0.89, 2.26 | 1.32               | 0.87, 2.00 | 28.7        | 22.47, 36.67 | 1.68             | 1.49, 1.90 |
| BMI (kg/m <sup>2</sup> )        |                                 |            |               |            |                |            |                 |            |                    |            |             |              |                  |            |
| 18-24                           | 1.00                            | Reference  | 1.00          | Reference  | 1.00           | Reference  | 1.00            | Reference  | 1.00               | Reference  | 1.00        | Reference    | 1.00             | Reference  |
| 25-29                           | 1.01                            | 0.97, 1.06 | 1.00          | 0.88, 1.14 | 1.03           | 0.96, 1.09 | 1.04            | 0.93, 1.17 | 0.99               | 0.89, 1.09 | 1.10        | 0.94, 1.30   | 1.00             | 0.97, 1.04 |
| 30-39                           | 1.18                            | 1.12, 1.24 | 1.10          | 0.96, 1.26 | 1.23           | 1.16, 1.31 | 1.25            | 1.11, 1.41 | 0.96               | 0.86, 1.08 | 1.09        | 0.92, 1.29   | 1.13             | 1.10, 1.17 |
| Diabetes                        |                                 |            |               |            |                |            |                 |            |                    |            |             |              |                  |            |
| None                            | 1.00                            | Reference  | 1.00          | Reference  | 1.00           | Reference  | 1.00            | Reference  | 1.00               | Reference  | 1.00        | Reference    | 1.00             | Reference  |
| Pre- or gestational             | 1.24                            | 1.17, 1.41 | 1.48          | 1.25, 1.69 | 1.47           | 1.37, 1.57 | 1.55            | 0.90, 1.22 | 1.14               | 1.01, 1.30 | 1.11        | 0.93, 1.32   | 1.28             | 1.21, 1.36 |
| Hypertension                    |                                 |            |               |            |                |            |                 |            |                    |            |             |              |                  |            |
| None                            | 1.00                            | Reference  | 1.00          | Reference  | 1.00           | Reference  | 1.00            | Reference  | 1.00               | Reference  | 1.00        | Reference    | 1.00             | Reference  |
| Pre- or gestational             | 1.43                            | 1.36, 1.51 | 1.13          | 0.96, 1.33 | 1.49           | 1.40, 1.60 | 1.04            | 0.90, 1.21 | 1.71               | 1.54, 1.91 | 1.00        | 0.83, 1.21   | 1.34             | 1.29, 1.39 |
| Infant sex                      |                                 |            |               |            |                |            |                 |            |                    |            |             |              |                  |            |
| Female                          | 1.00                            | Reference  | 1.00          | Reference  | 1.00           | Reference  | 1.00            | Reference  | 1.00               | Reference  | 1.00        | Reference    | 1.00             | Reference  |
| Male                            | 1.03                            | 1.00, 1.08 | 1.17          | 1.06, 1.27 | 0.96           | 0.92, 1.00 | 1.44            | 1.26, 1.64 | —                  | —          | 1.01        | 0.92, 1.11   | 1.05             | 1.02, 1.08 |

<sup>a</sup>Models adjusted for all factors listed above, as well as maternal race and ethnicity, education, parity, and State and year of birth. ART births limited to singleton fresh with partner ejaculated sperm. Bolded values are significantly increased.

<sup>b</sup>Major defects are limited to nonchromosomal only.

<sup>c</sup>Major defects include naturally conceived (1,584,522), CU/IVF conceived (89,765), non-ART siblings (2,821), ART solo-fresh, no ICSI (all infertility diagnoses, no ICSI) (6,433), ART solo-fresh, yes ICSI no PF (yes ICSI, no male factor diagnosis, no ICSI) (14,011), ART solo-fresh, yes ICSI yes PF (yes ICSI, yes male factor diagnosis, 18,429), AOR, adjusted odds ratio.

<sup>d</sup>Major birth defects as defined by the National Birth Defects Prevention Network (see Supplemental Table S1).

Any birth defect is any ICD-9 code with the first 3 digits 760-795 and any ICD-10 code inclusive of Q000-07X, 10-18X, 20-28X, 30-43X, 55-56A, 60-67B and 89-99X.

Cedars Sinai Luke B, Brown ML, Wantman E... Hum Reprod 2021 13

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### Risk Assessment

Table 1. Risks Associated With In Vitro Fertilization-Conceived Pregnancies Compared With Naturally Conceived Counterparts—Singleton, Twin, and Nonstratified Gestations

| Risk  | Absolute Risk  |
|---|--|
| Among singleton pregnancies   |  |
| Preterm delivery <sup>20</sup>  | Half day earlier IVF-ICSI vs SC<br>9.7% IVF-ICSI vs 7.9% SC      |
| Low birth weight delivery <sup>20</sup>                                 | 33 g less IVF-ICSI vs SC   |
| Severe maternal morbidity (blood transfusion most common) <sup>15</sup> | 6.8% IVF-ICSI vs 4.9% SC<br>273/10,000 IVF-ICSI vs 126/10,000 SC |
| Among twin pregnancies  |  |
| Monozygotic twins <sup>31,32</sup>                                      | 1.2–2.5% IVF-ICSI vs 0.4% SC                                     |
| Preterm delivery <sup>26–28</sup>                                       | Comparable   |
| Low birth weight delivery <sup>26–28</sup>                              | Comparable   |
| Not stratified  |  |
| DNA methylation <sup>21,22</sup>  | Comparable   |
| Imprinting disorder <sup>21,22</sup>                                    | 0.15% IVF-ICSI vs 0.02% SC                                       |
| Any cardiac defect including ASD, VSD <sup>20</sup>                     | 1.30% IVF-ICSI vs 0.68% SC                                       |

IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; SC, spontaneous conception; ASD, atrial septal defect; VSD, ventricular septal defect.

Cedars Sinai Kawwass, et al Obstet Gynecol 2018;132:763–72

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### Infertility is the contributor to outcomes associated with placentation

- Maternal morbidity is associated with diagnosis of infertility regardless of treatment
- Adverse outcomes are associated with both IVF and NIFT
- Congenital anomalies are associated with underlying infertility
- Time to pregnancy increases risk of congenital malformations

- Models to study the effect of IVF need to include an infertile cohort

- Outcomes are related to placentation defects
  - Mother - diabetes, hypertension, preeclampsia, placenta previa and accreta, retained placenta and abruption as well as SMM
  - Child- prematurity, growth restriction, and birth defects

Cedars Sinai Munuggapan AJOG 2020; Shevell T 2005 Obstet Gynecol ; Davies NEJM 2012; Zhu J, Br Med J 2006; Qin J Fertil and Steril 2016; Jackson Fertil Steril 2015; Wang Fertil and Steril 2016; Pisarska M, JCEM 2018

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Are the adverse outcomes associated with ART due to the in vitro fertilization process, the treatments or the inherent infertility we are trying to overcome?

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Prevalence of ART in patients with BWS

**TABLE 3**  
Prevalence of ART in patients with BWS.

| Reference no.   | Type of study | No. of BWS cases | Prevalence of ART in BWS cohort (cases) | Prevalence of ART in reference population | Type of ART               | Association between BWS and ART |
|-----------------|---------------|------------------|---|---|---------------------------|---------------------------------|
| 62 <sup>a</sup> | Case series   | 65 <sup>b</sup>  | 4.6% (3 <sup>c</sup> )                  | 0.8%                                      | IVF/ICSI                  | Suggestive                      |
| 63              | Case series   | 149              | 4% (6 <sup>c</sup> )                    | 1.2%                                      | 3 IVF/3 ICSI              | Suggestive                      |
| 64              | Case series   | 149              | 4% (6 <sup>c</sup> )                    | 1.3%                                      | 4 IVF/2 ICSI              | Suggestive                      |
| 65              | Case-control  | 37               | 10.81% <sup>d</sup> (4)                 | 0.67% <sup>d</sup>                        | 3 IVF/1 ICSI              | Suggestive                      |
| 66 <sup>a</sup> | Case-series   | 341              | 5.6%(19)                                | NA  | 5 IVF/5 ICSI <sup>e</sup> | NA                              |
| 67              | Survey        | 209              | 2.9% (6 <sup>c</sup> )                  | 0.8%                                      | 1 IVF/5 ICSI              | Suggestive                      |
| 71              | Survey        | 71               | 5.6% (4)                                | 0.92%                                     | IVF/ICSI                  | Suggestive                      |

<sup>a</sup> Data from the same BWS registry (NCI BWS registry and Washington University BWS registry).  
<sup>b</sup> Only BWS cohorts beginning in 2001 were used to calculate prevalence.  
<sup>c</sup> The frequency of children born after ART in BWS cohort was significantly higher than the expected ART cases based on the ART prevalence in the general population.  
<sup>d</sup> Fisher's exact test, two-sided, P=0.006.  
<sup>e</sup> Data on type of ART obtained from 12 patients (two patients had only ovarian stimulation with intrauterine insemination).

Manipalviratan, *Imprinting disorders and ART*, Fertil Steril 2009.

Cedars Sinai  
Manipalviratan, et al, Fertil Steril 2009;91:305-15 17

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Cohort studies of children

**TABLE 4**  
Number of cases of BWS in a cohort study of children conceived naturally and after ART.

| Reference no. | No. of cases of BWS in children born after ART | Number of children born after ART | No. of cases BWS in children conceived naturally | Number of children conceived naturally |
|---------------|--|-----------------------------------|--|--|
| 68            | 0  | 6,052                             | 0  | 442,349                                |
| 69            | 0  | 16,280                            | NA   | 2,039,943                              |
| 70            | 1  | 1,524                             | NA   | NA                                     |

NA = Not available.

Manipalviratan, *Imprinting disorders and ART*, Fertil Steril 2009.

Cedars Sinai  
Manipalviratan, et al, Fertil Steril 2009;91:305-15 18

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### Adverse pregnancy outcomes: methylation

*Differences in DNA methylation and gene expression in term placenta from children conceived in vitro versus in vivo*

*Term placenta and cord blood and may not reflect the early changes that occur as a direct result of the IVF conditions in ART.*

*Term placenta may reflect changes in the intrauterine environment, which has been associated with an altered fetal epigenome leading to altered gene expression.*


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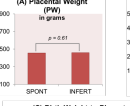
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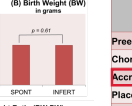
### Placental Weight, Fetal Weight and Fetal Weight to Placenta Weight Ratio

**Figure 1: Placental and Birth Weight Parameters**

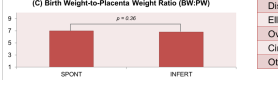
(A) Placental Weight (PW) in grams



(B) Birth Weight (BW) in grams




(C) Birth Weight-to-Placenta Weight Ratio (BW/PW)



**Figure 2: Placental Characteristics**

|                              | SPONT<br>N=1333 | INFERT<br>(NIF+IVF)<br>N=110 | P-<br>value |
|------------------------------|-----------------|------------------------------|-------------|
| Preeclampsia findings, n (%) | 111 (8.3%)      | 9 (8.2%)                     | 0.96        |
| Chorioamnionitis, n (%)      | 392 (29.4%)     | 35 (31.8%)                   | 0.59        |
| Accreta, n (%)               | 16 (1.2%)       | 4 (3.6%)                     | 0.036       |
| Placental Shape, n (%)       |                 |                              | 0.23        |
| Discoid                      | 737 (55.3%)     | 58 (52.7%)                   |             |
| Ellipsoid                    | 202 (15.2%)     | 15 (13.6%)                   |             |
| Ovoid                        | 200 (15%)       | 14 (12.7%)                   |             |
| Circular/Round               | 63 (4.7%)       | 5 (4.5%)                     |             |
| Other                        | 50 (3.8%)       | 9 (8.2%)                     |             |


Sundheimer, et al. J Assist Reprod Genet. 2018

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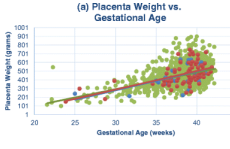
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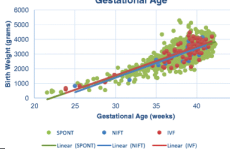
### Placental Weight, Fetal Size and Fetal Size to Placenta Weight Ratio


- Linear regression demonstrates that regardless of gestational age, the placenta weight, fetal weight and fetal size to placenta weight do not vary by mode of conception.*

(a) Placenta Weight vs. Gestational Age



(b) Birth Weight vs. Gestational Age




Sundheimer, et al. J Assist Reprod Genet. 2018

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**Placentation**

*Abnormal placentation is associated with adverse pregnancy outcomes - preeclampsia, PIH, gestational diabetes, previa, abruption, placental retention*

*Pregnancies conceived with infertility and treatments are at risk of:*

- abnormal placentation*
- abnormal placental morphology and cord insertion*
- abnormal protein profiles*
- increased metabolism and clearance of steroids by the placenta*
- Small for gestational age babies*

 Cedars Sinai Giwilt P, et al 1993 *Pediatr Pathol* 13:453-462  
Zhang Y, et al 2008 *Proteomics* 8:4344-4356  
Collier AC, et al 2009 *J Steroid Biochem Mol Biol* 116:21-28  
Delle Piane L, et al 2008 *Reproductive Sciences* 15:81A-81A 22

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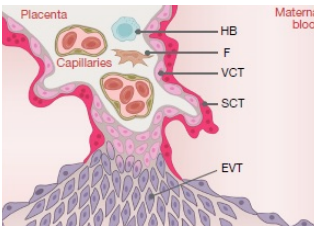
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**Placentation**



**The placenta is made up of important cell types**

- Villous cytotrophoblasts (VCT):** undifferentiated precursor cells
- Extravillous trophoblasts (EVT):** Invade decidua and maternal blood vessels
- Syncytiotrophoblasts (SCT):** Facilitate nutrient exchange and produce hormones
- Endothelial cells:** Line fetal blood vessels
- Immune cells:** stromal fibroblasts (F), dendritic cells, macrophages or Hofbauer cells (HB)

 Cedars Sinai Vento-Tormo et al (2019), *Nature* 23

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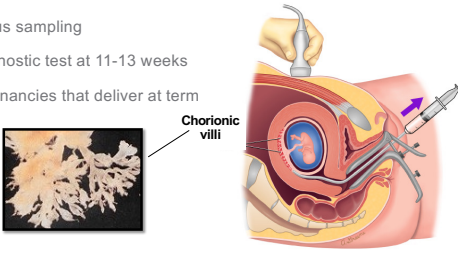
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**Model of Placentation**

- 1<sup>st</sup> trimester placenta tissue

Chorionic villus sampling  
Prenatal diagnostic test at 11-13 weeks  
Ongoing pregnancies that deliver at term



**Chorionic villi**

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**Are the outcomes associated with ART due to the in vitro fertilization process, the treatments or the inherent infertility we are trying to overcome?**

**Earliest time point in ongoing pregnancy**

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**Cytogenetic Abnormalities assessed by CVS in Spontaneous vs. Infertile Patients**

- 1,606 women conceived spontaneously
- 559 women conceived through infertility treatment
  - 233 conceived in vivo
  - 326 conceived in vitro

Conway Fertil Steril 2011 Feb;95(2):503-6

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**Spontaneous/ Medical Assisted/ART (SMAART) Cohort**

- a cohort of pregnancies conceived either spontaneously or in couples with infertility conceived either through non-IVF fertility treatment (NIFT) or IVF, that are enrolled in the late first trimester of pregnancy at the time of Chorionic Villus Sampling (CVS) and followed until delivery
  - 208 spontaneous conceptions
  - 201 pregnancies conceived with a history of Infertility
    - 90 conceived with NIFT
    - 111 conceived with IVF

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Sun, et al. JCEM. 2018

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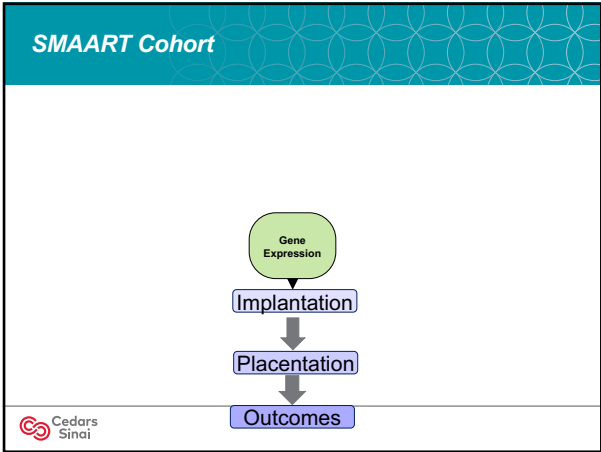
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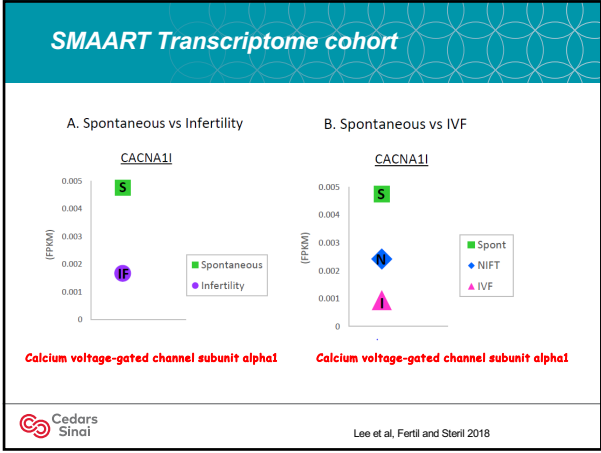
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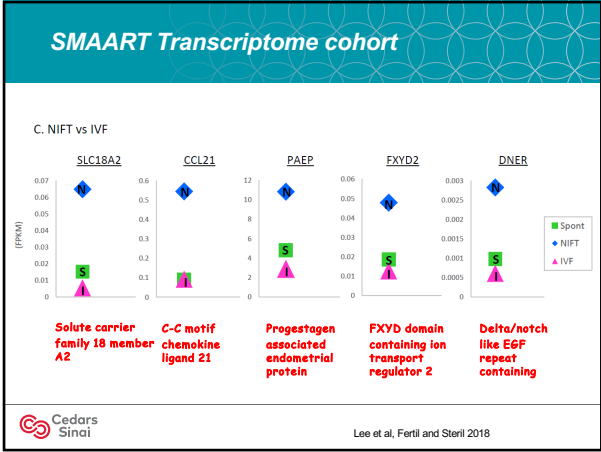
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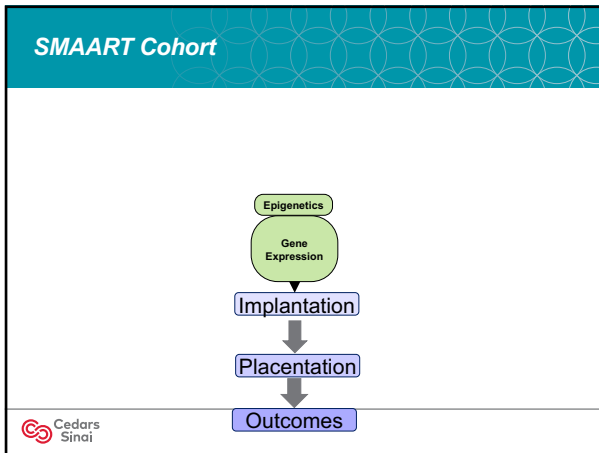
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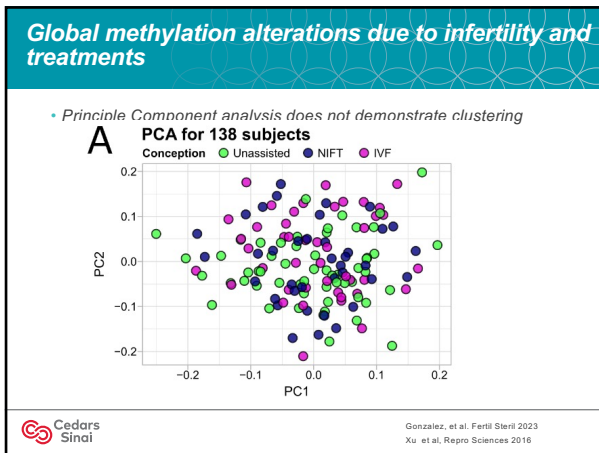
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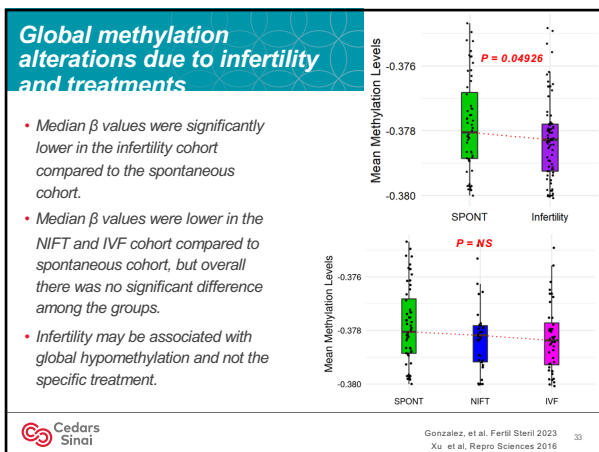
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### Methylation Changes Across the Lifespan A Systematic Review



|  | Trophoblast             | Fetus                 | Pregnancy        | Neonate                                 | Childhood                              | Adult  |
|--|-------------------------|-----------------------|------------------|---|--|--|
|  | T1 Trophoblast Placenta | Fetal Tissue Placenta | Uterine Placenta | Cord Blood                              | Neonatal Urine Blood Spit              | Neonatal Urine Blood Spit                      |
| <b>Inference vs Fertilization</b>  | Domenech (2021)         |                       |                  | Kari (2019)                             |  |  |
| <b>IVF vs IVF vs Unassisted</b>  |                         |                       |                  | Mohamed (2015)<br>Taha (2020)           | Neonatal (2019, **)<br>Domenech (2021) | Novitsky (2019)**<br>Perona, Vassilovic (2021) |
| <b>IVF vs Unassisted</b>   |                         |                       |                  | Hakim (2022)<br>Elking (2017)           | Elkhatib (2016)<br>Young (2022)        |  |
| <b>IVF vs IVF</b>  |                         |                       |                  | Genetha (2018)                          | Elkhatib (2016)                        | Young (2022)                                   |
| <b>Inference IVF vs IVF vs Unassisted with IVF infidelity in Fertilization</b> | Genetha (2022)          |                       |                  | Chouhan (2019)<br>Carmona-Garcia (2021) | Elkhatib (2016)<br>Young (2022)        | Young (2022)                                   |

\*\*p < 0.05 considered this work. Significance of infidelity concerning treatment.  
\*\*p < 0.05 considered this work.



Schaub, et al. Fertil Steril 2023 37

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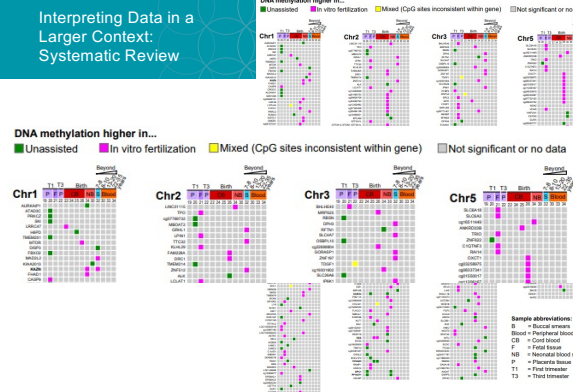
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### Interpreting Data in a Larger Context: Systematic Review




**DNA methylation higher in...**

■ Unassisted ■ In vitro fertilization ■ Mixed (CpG sites inconsistent within gene) □ Not significant or no data

**DNA methylation higher in...**

■ Unassisted ■ In vitro fertilization ■ Mixed (CpG sites inconsistent within gene) □ Not significant or no data

Sample abbreviations:  
B = Buccal swab  
PB = Peripheral blood  
CB = Cord blood  
F = Fetal tissue  
NB = Neonatal blood spots  
P1 = Preimplantation  
T1 = Trophoblast  
T3 = Trophoblast



Schaub, et al. Fertil Steril 2023 38

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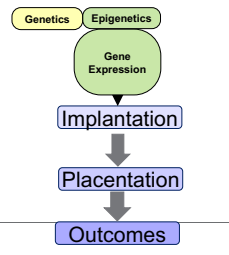
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### SMART Cohort




Genetics Epigenetics

Gene Expression

Implantation

Placental

Outcomes



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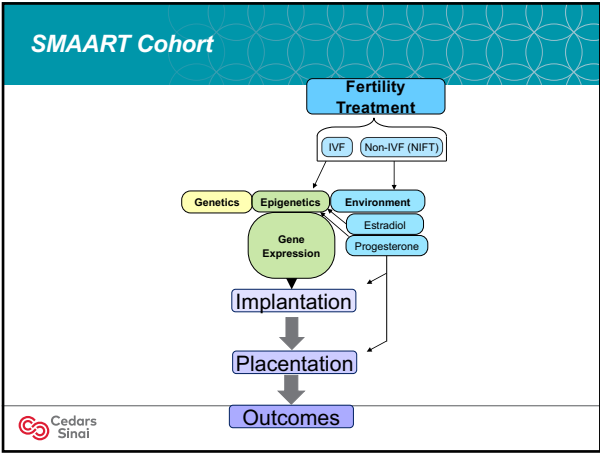
### Single nucleotide variants (SNVs) that associate with infertility – Family associated GWAS

- Most of the SNVs miss the SNVs are associated with variations in the rate of expression of the great risk SNVs passed quality control thresholds of  $5 \times 10^{-8}$
- 2 of the 10 SNVs were identified in SNPs that are for the remaining transcripts AC009495.2, GALNT3 and TTC21B in whole blood and adipose.

| SNP        | Ch | Pos         | allele | allele | freq   | N        | beta     | Pvalue   |
|------------|----|-------------|--------|--------|--------|----------|----------|----------|
| rs966123   | 18 | 72,538,424  | A      | G      | 0.1593 | 219      | 1.883939 | 0.339954 |
| rs1279737  | 18 | 72,443,622  | C      | 0.1420 | 219    | 1.7966   | 0.350161 |          |
| rs9998117  | 18 | 72,441,802  | A      | C      | 0.1416 | 219      | 1.768401 | 0.350115 |
| rs437185   | 18 | 72,443,202  | C      | 0.1416 | 219    | 1.751122 | 0.349388 |          |
| rs8842432  | 3  | 391,465,965 | A      | 0.1814 | 219    | 1.476794 | 0.305644 |          |
| rs3516493  | 3  | 391,465,981 | G      | 0.181  | 219    | 1.351167 | 0.296467 |          |
| rs1560594  | 2  | 166,689,798 | A      | 0.2098 | 219    | 1.372854 | 0.289443 |          |
| rs10930182 | 2  | 166,688,188 | T      | 0.1947 | 219    | 1.260279 | 0.284719 |          |
| rs2062057  | 2  | 166,689,340 | T      | 0.2009 | 219    | 1.290278 | 0.284705 |          |
| rs4899244  | 4  | 5,368,756   | A      | 0.2219 | 219    | 1.229294 | 0.29191  |          |
| rs12461839 | 19 | 48,172,671  | G      | 0.2345 | 219    | 1.21693  | 0.278402 |          |

Cedars Sinai Unpublished Data

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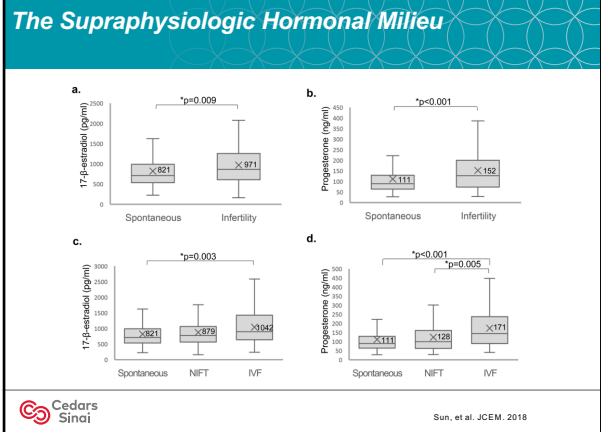
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### Supraphysiologic Hormones

- *Supraphysiologic hormone levels have been implicated in increased rates of low birth weight and small for gestational age babies.*
- *Since pregnancies conceived through fertility treatments are exposed to elevated estradiol and progesterone levels, either endogenously through treatments or exogenously to supplement the pregnancy, we wanted to determine whether previous treatments impact the hormonal milieu of an ongoing pregnancy.*

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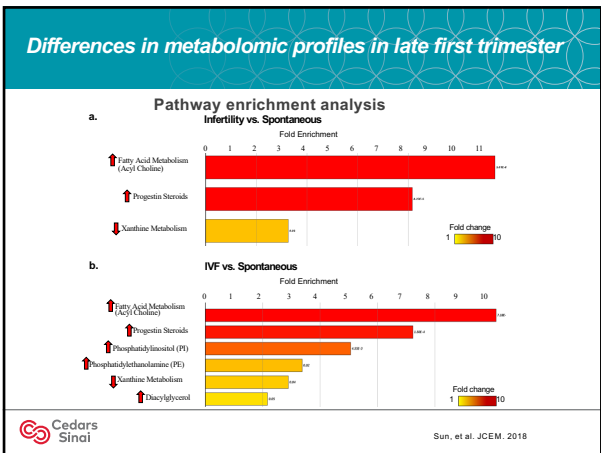
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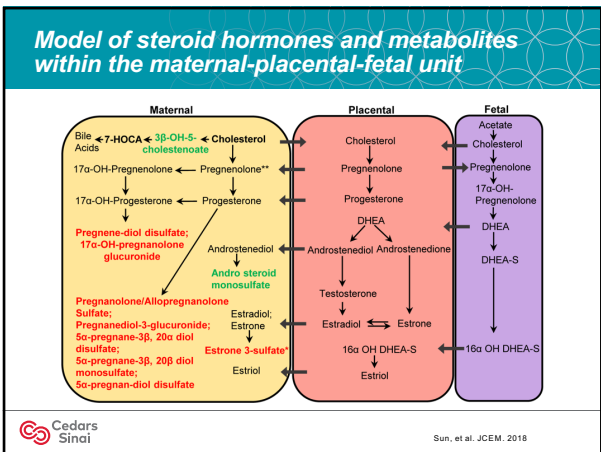
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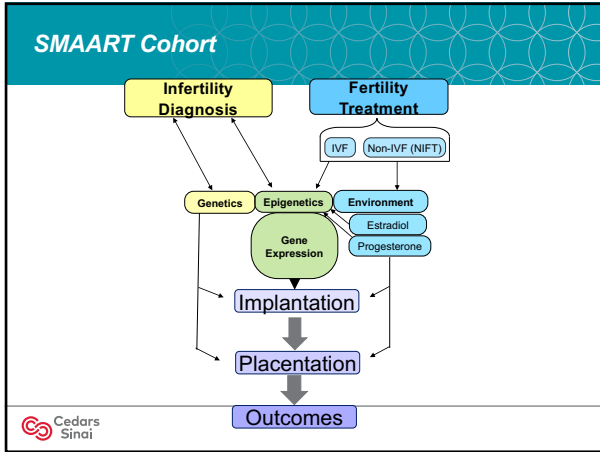
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### Impact of infertility on placentation through a multi-omics analysis

Regularized Canonical Correlation Analysis - Provides correlation across a large data landscape using small sample sizes

| Data  | Features        |
|---|-----------------|
| Phenotypes                                      | 7 traits        |
| Genomics - OmniExpressExome Chip                | 688,534 SNVs    |
| Methylomics - methylation EPIC Array (Illumina) | 865,855 sites   |
| Transcriptomics - Total RNA sequencing          | 61,801 genes    |
| Metabolomics of mother's serum (Metabolon)      | 704 metabolites |

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### Genetic/epigenetic impact of infertility on placentation through a multi-omics analysis

| Correlation Component | Spont  | Infertility | Sex   | Mat Age | Race | CVS age |
|-----------------------|--------|-------------|-------|---------|------|---------|
| 1                     | 0.048  |             |       |         | 0.99 | 0.05    |
| 2                     |        |             |       | -0.11   |      |         |
| 3                     | 0.99   |             | -0.11 |         |      |         |
| 4                     |        |             | 0.11  | 0.99    |      |         |
| 5                     | 0.11   |             | 0.99  |         |      |         |
| 6                     | -0.034 | 0.002       | -0.99 |         |      | 0.06    |

- Component 3 contains the association of infertility with the rest of the data landscape
- Effect of sex, maternal age, race, and CVS age are separated from the effect of infertility

**296 Features Identified in Component 3**

- Genomics: 40 Features (SNVs)
- Methylomics: 40 Features (methylated regions)
- Metabolomics: 8 Features (metabolites)
- Transcriptomics: 209 Features (transcripts)

**Central Theme - Mitochondrial Regulation**

- Mitochondrial Regulatory Genes**
  - ARAF
  - MYOF
  - PRKCZ
  - DNAJC1
  - MTFR1
- Mitochondrial small RNAs**
  - Nuclear encoded
  - Regulators of mitochondrial transcription
    - MTATP6P9,23,31
    - MTCO2P7, MTCYBP42
    - MTND1P2,20,28,31
    - MTND2P15,20
    - MTND4P1,4,8

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**Conclusions**

- Infertility and/or the treatments are associated with some increased risks of adverse outcomes to mother and child including:
  - Mother -diabetes, pregnancy induced hypertension, placenta previa and abruption as well as SMM
  - Child- prematurity, growth restriction, and birth defects
- RISKS ARE SMALL
- Risks are independent of treatment utilized
- Outcomes are related to placentation

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**Conclusions**

- Genetics of infertility appears to be a major contributor that may alter methylation and gene expression
- Supraphysiologic hormonal states may be a contributor
  - Altered methylation
  - Reprogramming the placenta to maintain a high hormonal state
  - Impacting trophoblast invasion and migration
- Multi-omics suggest genetics/epigenetics are impacting mitochondrial genes in the first trimester placenta

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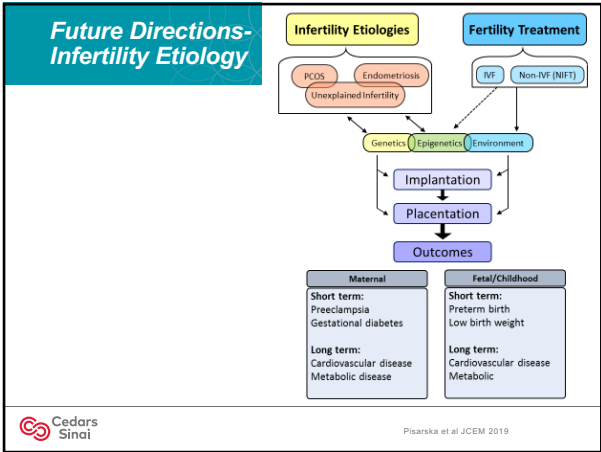
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**Our patients for participating in our studies to improve outcomes!**




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